



DEPARTMENT OF HEALTH & HUMAN SERVICES

JUL 23 2014

Food and Drug Administration
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Re: Docket Nos. FDA-2011-P-0610 and FDA-2013-P-0371

Dear Dr. Del Tito and Messrs. Himmelfarb and Katz:

This letter responds to the citizen petition dated August 18, 2011 (Petition), and the citizen petition supplements dated December 21, 2012 (Teva Supplement), December 11, 2013 (Perrigo Supplement 1), and May 19, 2014 (Perrigo Supplement 2), submitted on behalf of AbbVie Inc. (AbbVie).¹ In the Petition, you request that the Food and Drug Administration (FDA or the Agency) refrain from granting a therapeutic equivalence (TE) rating for any drug approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)) that references AndroGel (testosterone gel) 1% until the Agency has conducted a rulemaking under the Administrative Procedure Act (APA). You state that, at minimum, the rulemaking should:

- Characterize the listing of TE ratings for drug products approved under section 505(b)(2) of the FD&C Act as either orders or substantive rules for purposes of the APA;
- Describe what legal process is available to interested parties for commenting on or challenging a proposed listing; and

¹ The Petition was originally submitted on behalf of Abbott Laboratories, Inc. (Abbott). In the petition supplements, you state that AbbVie is now identified as the holder of new drug application (NDA) 021015 for AndroGel (testosterone gel) 1% products relevant to the Petition. For purposes of this response, we refer to AbbVie as the petitioner and the holder of NDA 021015.

- Establish a coherent set of standards governing such a listing.

This letter also responds, in part, to the citizen petition dated March 26, 2013, submitted by Auxilium Pharmaceuticals, Inc. (Auxilium) (Auxilium Petition), which incorporates by reference the above arguments with respect to its topical testosterone gel product, Testim (NDA 021454).²

As noted, you also submitted citizen petition supplements specific to two 505(b)(2) NDAs for topical testosterone gel products, held by Perrigo Israel Pharmaceuticals Ltd. (Perrigo) (NDA 203098) and Teva Pharmaceuticals USA (Teva) (NDA 202763). Specifically, in these supplements, you request that FDA:

- Assign a “BX” rating to the Perrigo and Teva topical testosterone gel product listings in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book),³ if the Commissioner determines that the Agency will assign a TE rating in the Orange Book to these products. You state that this rating would accurately reflect that the Perrigo and Teva topical testosterone gel products are not therapeutically equivalent to, and cannot safely be substituted for, AndroGel 1%;
- Revise the prescribing information and other relevant labeling for the Perrigo and Teva topical testosterone gel products to remove the abdomen as an approved application site, because Perrigo and Teva have not demonstrated that their products are safe and effective for administration to the abdomen; and
- Require the approved labeling for the Perrigo and Teva topical testosterone gel products to carry the following statement: “The application site and dose of [Product] are not interchangeable with other topical testosterone products.” You assert that this statement is appropriate because the Perrigo and Teva topical testosterone gel products have not been shown to be interchangeable with, or safely substitutable for, any other topical testosterone product, including AndroGel 1%, and also because the statement could reduce the risk of medication errors and inappropriate substitution.

² See Docket No. FDA-2013-P-0371, Auxilium Petition at 2 (requesting “[f]or the reasons set forth in AbbVie’s citizen petition in Docket No. FDA-2011-P-0610, [that FDA] refrain from issuing a [TE] rating to [Upsher-Smith Laboratories, Inc.’s (USL’s)] product and to any other drugs described in section 505(b)(2) [NDAs] referencing Testim until the Agency conducts notice-and-comment rulemaking to establish procedures and standards for these ratings.”) (footnote omitted). We also considered comments submitted to Docket No. FDA-2013-P-0371 on this issue. Auxilium raises two other scientific issues to which the Agency intends to respond in a separate letter. We use the terms “you” and “your(s)” when referring collectively to Auxilium and AbbVie in section II.A. of this response, but otherwise use them only when referring to AbbVie.

³ The Orange Book (at xx) states that “BX” ratings are assigned by FDA for drug products for which the data are insufficient to determine TE.

FDA has carefully considered the petitions, the Teva and Perrigo supplements, comments, and other available information. For the reasons set forth below, your Petition is granted, in part, and denied, in part, and the Auxilium Petition is 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)(1) 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.⁴

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.⁵

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 generic drug approval procedure” with new

⁴ See section 505(b)(1) of the FD&C Act.

⁵ See e.g., sections 505(b)(1), 505(c) and 505(d) of the FD&C Act; and 21 CFR part 314.

incentives for drug development in the form of marketing exclusivity and patent term extensions.⁶

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.⁷ 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.^{8,9} 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*¹⁰ of a listed drug, but which cannot be submitted pursuant to section 505(j) of the FD&C Act because 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

⁶ 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.

⁷ 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"

⁸ 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 [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.").

⁹ 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>.

¹⁰ 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).

and effectiveness information and meet the same statutory standard for safety and effectiveness as a 505(b)(1) NDA.¹¹

An ANDA applicant relies on the Agency's finding of safety and effectiveness for the reference listed drug (RLD)¹² 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.¹³ An ANDA must also include sufficient information to demonstrate that the proposed product is bioequivalent to the RLD.¹⁴ 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.¹⁵

B. Bioavailability and Bioequivalence

A demonstration of bioequivalence 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.¹⁶

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 Perrigo and Teva relied on AndroGel 1%), 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.¹⁷ These types of bioavailability studies are referred to hereinafter as "pivotal comparative bioavailability studies."

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

¹¹ 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.

¹² 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].").

¹³ See e.g., sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act; see also 21 CFR 314.94.

¹⁴ See e.g., sections 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act.

¹⁵ See e.g., sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act; see also 21 CFR 314.94.

¹⁶ 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.

¹⁷ See 505(b)(2) Guidance, at 8-9.

action.”¹⁸ Bioavailability data provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug.¹⁹

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 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....”²⁰

FDA regulations in part 320 (21 CFR part 320) establish acceptable methodologies for determining the bioavailability and bioequivalence of drug products.²¹ 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.²²

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.²³ 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.²⁴ FDA considers products bioequivalent when the 90 percent confidence intervals (CIs) for

¹⁸ See section 505(j)(8)(A)(i) of the FD&C Act; *see also* 21 CFR 320.1(a).

¹⁹ See e.g., BA/BE NDA/IND Guidance, at 3.

²⁰ See section 505(j)(8)(B)(i) of the FD&C Act; 21 CFR 320.1(e); 21 CFR 320.23(b).

²¹ Courts have expressly upheld FDA’s regulatory 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).

²² See e.g., BA/BE NDA/IND Guidance, at 4.

²³ 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.

²⁴ Id.

test/reference AUC and C_{max} parameter ratios are within an 80 to 125 percent acceptance interval.²⁵

C. TE Evaluations

Drug products are considered to be therapeutically equivalent only if they are pharmaceutical equivalents²⁶ 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.²⁷ 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 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.²⁸ 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.²⁹ We use the term “1979-1980 notice-and-comment rulemaking” when referring collectively to the proposed and final rules in this response.

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.³⁰ 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

²⁵ 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>.

²⁶ See 21 CFR 320.1(c) (defining pharmaceutical equivalents); see also Orange Book Preface at vi-vii.

²⁷ See Orange Book Preface at vii.

²⁸ Id.

²⁹ 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.”).

³⁰ 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.

considers not to be therapeutically equivalent to other pharmaceutically equivalent products.³¹ 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.³² 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.³³

D. Factual Background

1. Topical Testosterone Gel Products

On February 28, 2000, FDA approved the NDA for AndroGel (testosterone gel) 1% (NDA 021015), held by AbbVie. AndroGel 1% is indicated for 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).³⁴ AndroGel 1% is approved for topical application to the upper arms and shoulders and/or abdomen.³⁵

On February 14, 2012, FDA approved the 505(b)(2) NDA for topical testosterone gel (NDA 202763), held by Teva. On January 31, 2013, FDA approved the 505(b)(2) NDA for topical testosterone gel (NDA 203098), held by Perrigo. The Perrigo and Teva 505(b)(2) NDAs included, among other things, studies supporting effectiveness (pivotal comparative bioavailability studies) and safety (e.g., irritation and sensitization, hand-washing, transfer potential studies), and relied, in part, on FDA's findings of safety and effectiveness for the listed drug, AndroGel 1%.³⁶

Like AndroGel 1%, the Perrigo and Teva topical testosterone gel products are approved for 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).³⁷ Like AndroGel 1%, they are both approved for topical application to the upper arms and shoulders and/or abdomen.³⁸ The Perrigo and Teva topical testosterone gel products also share the following characteristics in common with AndroGel 1%: the same active ingredient (testosterone), dosage form (gel), route of administration (transdermal), and strength (25

³¹ See Orange Book Preface at xiii-xx.

³² Id.

³³ See e.g., Orange Book Preface at iv-v, xi; see also 44 FR 2932; 45 FR 72582.

³⁴ See Currently Approved Product Labeling for AndroGel 1% (June 19, 2014).

³⁵ Id.

³⁶ See e.g., Teva Medical Officer's NDA Filing Memorandum dated February 25, 2011 (Teva Medical Officer Review (Feb. 25, 2011)) available at

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000MedR.pdf; and Perrigo Cross Discipline Team Leader Review dated January 31, 2013 (Perrigo CDTL Review (Jan. 31, 2013)) available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203098Orig1s000SumR.pdf.

³⁷ See Currently Approved Product Labeling for AndroGel 1% (June 19, 2014); Currently Approved Product Labeling for the Perrigo Topical Testosterone Gel Product (June 19, 2014); Currently Approved Product Labeling for the Teva Topical Testosterone Gel Product (June 19, 2014).

³⁸ Id.

mg of testosterone in 2.5 g of gel; and 50 mg of testosterone in 5 g of gel).^{39,40} The Perrigo and Teva topical testosterone gel products differ from AndroGel 1% in that they have different inactive ingredients commonly referred to as penetration enhancers.

After their respective approvals, the Perrigo and Teva topical testosterone gel products were listed in the Orange Book. Today, FDA assigned an “AB” TE rating to the Perrigo topical testosterone gel product, and a “BX” TE rating to the Teva topical testosterone gel product.⁴¹

2. Risk of Secondary Transfer (Transfer Potential)⁴²

Testosterone is the active ingredient in AndroGel 1% and the Perrigo and Teva topical testosterone gel products. 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.⁴³ 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.⁴⁴ 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 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.⁴⁵

³⁹ Id.

⁴⁰ We note that AndroGel 1% and the Perrigo topical testosterone gel product also are available in metered dose pumps supplying 60 doses of 12.5 mg testosterone per dose.

⁴¹ The “AB” rating for the Perrigo topical testosterone gel product means that FDA has determined that the product has been demonstrated to be therapeutically equivalent to AndroGel 1%. The “BX” rating for the Teva topical testosterone gel product means that the data that have been reviewed by the Agency are insufficient to determine TE to AndroGel 1%. See Orange Book xiii-xx.

⁴² 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.

⁴³ See also Currently Approved Product Labeling for AndroGel 1% (June 19, 2014); Currently Approved Product Labeling for the Teva Topical Testosterone Gel Product (June 19, 2014); and Currently Approved Product Labeling for the Perrigo Topical Testosterone Gel Product (June 19, 2014).

⁴⁴ FDA addressed this risk 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.

⁴⁵ See e.g., Mazer, N., Fisher, D., Fischer, J., Cosgrove, M., Bell, D., Eilers, B., “Transfer of transdermally applied testosterone to clothing: A comparison of a testosterone patch versus a testosterone gel,” Journal of

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 handwashing study to determine whether handwashing affects the amount of residual product on the skin.⁴⁶ FDA therefore concluded that any application submitted for a proposed topical testosterone gel product that uses a different penetration enhancer than the RLD must include transfer potential and handwashing 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, Perrigo and Teva, which had originally submitted ANDAs for proposed topical testosterone gel products with different penetration enhancers from the RLD, received letters from FDA's Office of Generic Drugs (OGD) regarding the use of the different inactive ingredients and risk of secondary transfer of testosterone.^{47,48} Accordingly, Perrigo and Teva resubmitted their applications as 505(b)(2) NDAs and included the appropriate studies and information consistent with the Agency's determination and applicable standards for approval.

II. DISCUSSION

We discuss below your requests that: (a) FDA refrain from issuing TE ratings for products approved pursuant to 505(b)(2) NDAs referencing AndroGel 1% until FDA conducts notice-and-comment rulemaking; and (b) FDA make certain decisions regarding the Perrigo and Teva topical testosterone gel products.

Sexual Medicine, 2005, 2, Pp. 227-234; de Ronde, W., "Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies," Human Reproduction, 2008, Pp. 1-4; Rolf, C., Knie, U., Lemmitz, G., Nieschlag, E., "Interpersonal testosterone transfer after topical application of a newly developed testosterone gel preparation," Clinical Endocrinology, 2002, 56, Pp. 637-641.

⁴⁶ While differences in inactive ingredients other than penetration enhancers may also trigger the need for transfer and hand-washing studies, your Petition and supplements only address penetration enhancers. Accordingly, this response only addresses penetration enhancers.

⁴⁷ See e.g., Perrigo CDTL Review, at 2-3 and Teva Acting Deputy Division Director Summary Review dated February 14, 2012 (Teva ADDD Summary Review (Feb. 14, 2012)), at 4 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000SumRedt.pdf.

⁴⁸ This policy subsequently was embodied in the FDA guidance for industry *Draft Guidance on Testosterone* (2013) (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/UCM347047.pdf>.

A. Request That FDA Refrain from Issuing TE Ratings for Products Approved Pursuant to 505(b)(2) NDAs Referencing AndroGel 1% Until FDA Conducts Notice-and-Comment Rulemaking⁴⁹

You acknowledge that “FDA employed the notice-and-comment procedures” in conducting the 1979-1980 notice-and-comment rulemaking, which added a provision to the Code of Federal Regulations announcing that FDA would publish a list of TE evaluations.⁵⁰ You state, however, that the provision did not prescribe standards or a process for making such evaluations; nor did it afford any procedural right to those with an interest in such listings.⁵¹

You further state that FDA reasoned that the listing process was nonregulatory, and therefore the listings were not an order or rule, because such listings: (1) were solely advisory and (2) entailed merely the application of FDA’s TE criteria to information that was already contained in FDA files based on findings the Agency was statutorily authorized to make in the course of the approval process.⁵² You contend that, even if FDA’s reasoning was correct at the time, it is no longer correct because: (1) FDA’s TE listings are far more than advisory because they have been expressly incorporated into state pharmacy practice statutes, affect insurance reimbursement schemes, and are relied upon in other federal laws (*e.g.*, Medicare Part B); and (2) TE listings for 505(b)(2) NDAs cannot be characterized as merely the product of information already contained in FDA files that is based upon findings made in the course of the 505(b)(2) approval process.⁵³ You further state that FDA must remedy the “legal infirmity” by treating the TE listing process for products approved pursuant to 505(b)(2) NDAs as either a substantive rulemaking or an informal adjudication.⁵⁴

You therefore request that FDA refrain from granting TE ratings for products approved pursuant to 505(b)(2) NDAs referencing AndroGel 1% unless and until the Agency has conducted a notice-and-comment rulemaking that, at minimum: (1) characterizes FDA’s listing of TE ratings for such products as either orders or substantive rules; (2) establishes the procedures available to interested parties in connection with the listings; and (3) establishes a coherent set of standards governing the listings.⁵⁵

⁴⁹ Your Petition addresses TE evaluations as they relate to products pursuant to 505(b)(2) NDAs. Accordingly, this response only addresses TE evaluations for such products.

⁵⁰ Petition at 10. A complete discussion of the background and basis of FDA’s TE policy was published in the Federal Register on January 12, 1979 (44 FR 2932). The final rule, which includes FDA’s responses to the public comments on the proposal, was published in the Federal Register on October 31, 1980 (45 FR 72582). The topics FDA extensively considered in this rulemaking procedure include, but are not limited, to the following: statutory authority, *see e.g.*, 44 FR 2936-37; 45 FR 72584-89; criteria for TE evaluations, including pharmaceutical equivalence and bioequivalence, *see e.g.*, 44 FR 2937-52; 45 FR 72589-72602; legal status of listing TE ratings, *see e.g.*, 44 FR 2937; 45 FR 72584-89; incorporation of TE ratings into drug substitution laws, reimbursements, and related matters, *see e.g.*, 44 FR 2932-34, 2948; 45 FR 72583, 72598-99, 72604; and procedural requirements, *see e.g.*, 44 FR 2937; 45 FR 72586-87.

⁵¹ Petition at 2.

⁵² Id.

⁵³ Id.

⁵⁴ Id.

⁵⁵ Id. at 3.

We do not believe that any additional rulemaking is necessary or appropriate at this time for the reasons below. For ease of discussion, we address your assertions in a different order than you have presented them.

1. *The Agency's reasoning in the 1979-1980 notice-and-comment rulemaking remains sound as it relates to TE evaluations for products approved pursuant to 505(b)(2) NDAs.*
 - a. TE listings for 505(b)(2) NDAs are the product of information already contained in FDA files based on findings the Agency is statutorily authorized to make in the course of the 505(b)(2) approval process.

You state that the Agency reasoned, in the 1979-1980 notice-and-comment rulemaking, that TE evaluations entailed merely the application of FDA's TE criteria to information that was already contained in FDA files based on findings the Agency was statutorily authorized to make in the course of the approval process.⁵⁶ You take issue with this rationale and state that neither the approval process for 505(b)(2) NDAs, nor any other statutory provision applicable to such drugs, provides an adequate statutory basis for TE evaluations.⁵⁷ You further state that, although the constituent findings (bioequivalence, pharmaceutical equivalence, and adequate labeling) that are needed for a TE evaluation are necessarily entailed by the findings FDA must make when it approves an ANDA under section 505(j) of the FD&C Act, those findings are not statutory components of the 505(b)(2) approval process.⁵⁸

Your assertions are without merit. Indeed, the Agency considered and rejected, in the context of the 1979-1980 notice-and-comment rulemaking, these same types of arguments, including those related to the statutory basis for TE ratings.⁵⁹ Through that rulemaking process, FDA provided detailed notice of its statutory authority for TE evaluations, and extensively considered comments regarding that authority.⁶⁰ For instance, FDA carefully considered and responded to numerous comments, which are similar to your arguments, asserting that it was beyond FDA's "regulatory authority" to make a judgment of TE.⁶¹ The Agency explained that the evaluation of TE is based on determinations that FDA is statutorily authorized to make with respect to drug products.⁶²

⁵⁶ Petition at 1-2.

⁵⁷ Petition at 9. We note that your assertion that FDA lacks a statutory basis for TE evaluations is contradicted by another requested action in your Petition and supplements. That is, you request that FDA require that all topical testosterone gel products approved under section 505(b)(2) carry the following labeling statement: "The application site and dose of [Product] are not interchangeable with other topical testosterone products." See Teva Supplement at 2; see also Perrigo Supplement 1 at 2-3.

⁵⁸ Petition at 16-19.

⁵⁹ See e.g., 44 FR 2936-37; 45 FR 72584-89.

⁶⁰ See e.g., 44 FR 2936-37; 45 FR 72584-89.

⁶¹ 45 FR 72584.

⁶² See e.g., 45 FR 72584.

Furthermore, contrary to your argument, the criteria for evaluating TE—safety and effectiveness, pharmaceutical equivalence, bioequivalence, adequate labeling, and compliance with CGMP—encompass *the same* type of information FDA assesses under relevant statutory authorities to ensure that products submitted pursuant to 505(b)(2) NDAs meet applicable standards for approval and marketing. Although there is no statutory requirement *per se* that 505(b)(2) NDAs, like ANDAs, show that proposed products meet certain TE criteria for approval (*i.e.*, that they are pharmaceutically equivalent to and bioequivalent to the listed drugs they reference), the statute does not foreclose that certain 505(b)(2) NDAs may include information to support such findings and that the Agency is authorized to review such information to support TE evaluations.⁶³ As noted in section I.A.2., in certain instances, a 505(b)(2) NDA may describe a drug product that is essentially a duplicate of a listed drug.

To illustrate, in addition to being approved by FDA as safe and effective,⁶⁴ to be classified as therapeutically equivalent to another drug product, FDA determines whether two drug products are bioequivalent. As discussed in section I.B., bioequivalence can be integral to supporting the statutory requirement of safety and effectiveness for 505(b)(2) NDAs, such as in cases where a 505(b)(2) NDA seeks to rely for approval on the Agency’s finding of safety and/or effectiveness for a listed drug.⁶⁵

In addition, as discussed in section I.C., FDA determines whether two products are pharmaceutically equivalent for purposes of TE by considering the active ingredient and amount of active ingredient in a product, the product’s dosage form and route of administration, and whether the product meets compendial or other applicable standards of identity, strength, quality, and purity.⁶⁶ 505(b)(2) NDAs, as with stand-alone 501(b)(1) NDAs and ANDAs, must include information regarding the active drug ingredient, dosage form, route of administration, and identity, strength, quality, and purity.⁶⁷ In fact, certain statutory provisions regarding ANDAs incorporate by reference or track NDA requirements regarding certain chemistry and manufacturing information.⁶⁸ Furthermore, the Agency is authorized by section 501(b) of the FD&C Act to consider whether drugs meet standards for identity, strength, quality, and purity, and compendial standards.⁶⁹

⁶³ See sections 505(b)(2), 505(c), and 505(d) of the FD&C Act; 21 CFR 314.54; and 505(b)(2) Guidance.

⁶⁴ See Orange Book Preface at vii. As described above in section I.A., 505(b)(2) NDAs must include full reports of investigations of safety and effectiveness and a determination of safety and effectiveness by FDA is central to the standard of approval for 505(b)(2) NDAs. See section 505(b)(2), 505(c), and 505(d) of the FD&C Act.

⁶⁵ See also 201(p), 502, and 701(a) of the FD&C Act for additional authorities regarding bioequivalence.

⁶⁶ See Orange Book Preface at vi-vii.

⁶⁷ See sections 505(b)(1), 505(b)(2), 505(c), 505(d), 505(j) of the FD&C Act; see also 21 CFR 314.50 and 21 CFR 314.94.

⁶⁸ See sections 505(j)(2)(A)(vi) of the FD&C Act (incorporating by reference clauses (B) through (F) of section 505(b)(1) of the FD&C Act) and 505(d) and 505(j)(4)(A) of the FD&C Act (including parallel text on identity, strength, quality, and purity); see also 21 CFR 314.94(a)(9) (cross-referencing 314.50(d)(1) with certain exceptions).

⁶⁹ See section 501(b) of the FD&C Act (providing that a drug shall be deemed to be adulterated if it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium).

Finally, to be classified by FDA as therapeutically equivalent, drug products also must be adequately labeled and manufactured in compliance with CGMP.⁷⁰ FDA is authorized to evaluate this type of information, in the context of drug approvals under section 505 of the FD&C Act, and also under section 502 of the FD&C Act (to determine adequate labeling) and section 501(a)(2)(B) of the FD&C Act (to assess compliance with CGMP). Under section 505(b) of the FD&C Act, a stand-alone 505(b)(1) NDA or 505(b)(2) NDA must include, among other information, proposed labeling and “full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug.”⁷¹ Likewise, under section 505(j) of the FD&C Act, an ANDA must contain similar information.⁷²

Accordingly, the information needed to evaluate TE for products approved pursuant to 505(b)(2) NDAs stems from the approval process for such products. In many cases, the differences between products approved pursuant to 505(b)(2) NDAs and their respective listed drugs foreclose a finding that the products are therapeutically equivalent. In other cases, however, drug products approved pursuant to 505(b)(2) NDAs and their respective listed drug(s) may satisfy the TE criteria – such as when a 505(b)(2) NDA describes a drug product that is essentially a duplicate of a listed drug – and a finding by the Agency that the products have been demonstrated to be TE is appropriate. When the Agency makes a TE finding for a particular product approved pursuant to a 505(b)(2) NDA, it may convey that “public information and advice” in the form of TE ratings.^{73,74}

Therefore, the Agency’s reasoning in the 1979-1980 notice-and-comment rulemaking regarding its statutory authorities for TE ratings continues to be sound as it relates to products approved pursuant to 505(b)(2) NDAs.

⁷⁰ See Orange Book Preface at vii.

⁷¹ See section 505(b)(1), 505(b)(2), 505(c), and 505(d) of the FD&C Act.

⁷² See section 505(j)(2)(A)(v), 505(j)(4)(G), and 505(j)(4)(A) of the FD&C Act.

⁷³ See e.g., Orange Book Preface at xi.

⁷⁴ In addition to the above authorities, the Agency has the authority to publish TE ratings under sections 310 and 311(a) of the Public Health Service Act (PHS Act) and section 705(b) of the FD&C Act. FDA’s authority to issue TE evaluations has been cited with approval during judicial review of FDA’s TE program. *Pharm. Mfrs. Ass’n v. Kennedy*, 471 F. Supp. 1224 (D. Md. 1979). In dismissing a challenge to FDA’s 1979 proposed list of TE drugs (the “Drug List”), the court in *Pharmaceutical Manufacturer’s Association v. Kennedy* explained that:

The legal authority to issue the Drug List may be found in section 310 of the Public Health Service Act, (“PHSA”), which directs the Secretary of HEW to issue “information related to public health, in the form of publications or otherwise, for the use of the public,” and to publish “other pertinent health information for the use of persons and institutions concerned with health services.” Section 311(a) of the PHSA also directs the Secretary of HEW to advise the several states as to public health matters, as well as under section 705(b) [of the FD&C Act], to provide information to the public concerning drugs in situations posing “imminent danger to health, or gross deception of the consumer.”

Id. at 1229 n.7 (citations omitted).

b. TE listings are advisory.

In addition, you state that the Agency reasoned, in the 1979-1980 notice-and-comment rulemaking, that TE evaluations are nonregulatory, and therefore not an order or rule, because such listings were solely advisory.⁷⁵ You state that this reasoning is no longer correct because FDA's TE listings are far more than advisory because they have been expressly incorporated into state pharmacy practice statutes, affect insurance reimbursement schemes, and are relied upon in other federal laws (e.g., Medicare Part B).⁷⁶ You therefore state that these listings materially impact the economic rights of competing drug sponsors.⁷⁷ Thus, you state that TE listings have automatic and significant binding legal consequences under the law.⁷⁸

We disagree. The Agency's reasoning in the 1979-1980 notice-and-comment rulemaking, that TE ratings are advisory and the listing is not binding, still stands. As in 1979-1980, the listing today neither determines the legal rights of any drug manufacturer or distributor, nor imposes any requirement or restriction upon any person.⁷⁹ Since the first publication of the Orange Book, FDA has consistently considered TE ratings to be advisory and nonbinding and has repeatedly advised the public of that position.⁸⁰ As discussed above, FDA's TE ratings provide "public information and advice" that FDA is authorized to release to the public and merely inform the public of whether one product is, in fact, therapeutically equivalent to another based on scientific findings made during the approval process.⁸¹ Indeed, you do not appear to contest that TE ratings for products approved pursuant to ANDAs (505(j)) are advisory because, as even you admit, they arguably can be considered to "have no legal effect beyond that already resulting from FDA's decision to approve the drug."⁸² As explained in detail in section II.A.1., contrary to your contentions, the same is true for 505(b)(2) NDAs because the Agency considers the same type of information to support TE evaluations for products approved pursuant to 505(b)(2) NDAs as for ANDAs.

Furthermore, incorporation of FDA's advisory TE ratings into other laws and reimbursement schemes, which are not administered by FDA, does not make TE ratings binding for purposes of determining whether any additional process, such as notice-and-

⁷⁵ Petition at 1-2.

⁷⁶ Id.

⁷⁷ Id.

⁷⁸ Id.

⁷⁹ See e.g., Orange Book Preface at xi, xii-xiii; 45 FR 72584-89; see also *Pharm. Mfrs. Ass'n*, 471 F. Supp. at 1231 (affirming that TE ratings were advisory).

⁸⁰ Id.

⁸¹ See e.g., Orange Book Preface at xi; 45 FR 72587.

⁸² Petition at 16 (also admitting that "[t]he task of consolidating the pharmaceutical equivalence, bioequivalence, and same-labeling analyses made in the course of the ANDA approval process into a TE evaluation arguably is merely ministerial"). We note that, regardless of whether the TE evaluation is made in a manner that is ministerial or otherwise, any collateral effects of the decision that you say make it other than advisory and non-binding for products approved pursuant to 505(b)(2) NDAs are the same for both ANDAs and 505(b)(2) NDAs, i.e., increased incorporation of TE ratings into drug substitution laws and reimbursement schemes, and incorporation of TE ratings into other laws (e.g., Medicare Part B). Thus, your own argument appears to be logically inconsistent.

comment rulemaking, is required under the APA. The case law you rely on for your argument that TE ratings create a binding legal effect is not directly relevant to the question of whether the process available in a given context is sufficient. You rely on *Tozzi v. HHS*, in which the court examined an agency's inclusion of a substance on a statutorily mandated list of known carcinogens.⁸³ In *Tozzi*, however, the court did not address the question of whether the agency's process for listing the substance was deficient; rather, the court examined the effect of the listing to determine whether the listing was judicially reviewable under the APA.⁸⁴ Furthermore, another, more recent case held that materials promulgated by a Federal agency did *not* create a binding effect, even though the materials were adopted by local governments as part of a permitting process.^{85,86}

Moreover, while you assert that there are certain changed circumstances, such as increased incorporation of TE ratings into drug substitution laws and reimbursement schemes, and incorporation of TE ratings into other laws (*e.g.*, Medicare Part B), these trends were anticipated and the types of arguments you raise were addressed by FDA in the 1979-1980 notice-and-comment rulemaking.⁸⁷ Your assertions that any such reliance may have increased does not alter the Agency's fundamental conclusion that TE ratings are advisory and not binding.

To the extent you are arguing that additional process, whether rulemaking or adjudicative, is necessary for each particular drug prior to listing a TE rating, nothing you have cited supports such a position. In addition, FDA addressed comments related to the process available to interested parties in the TE listing context in the 1979-1980 notice-and-comment rulemaking.⁸⁸ As in 1979-1980, sufficient processes (described in section II.A.2.) are currently available to interested parties who wish to comment on particular TE ratings.

Accordingly, your assertions do not call into question FDA's scientifically sound TE criteria or justify the need for additional notice and process beyond that already provided through the 1979-1980 notice-and-comment rulemaking and that continues to be provided through other processes described below, for products approved pursuant to 505(b)(2) NDAs.⁸⁹

⁸³ 271 F.3d 301, 304 (D.C. Cir. 2002).

⁸⁴ *Id.* at 310-11.

⁸⁵ See *Nat'l Ass'n of Home Builders v. Norton*, 415 F.3d 8, 14-16 (D.C. Cir. 2005); see also *Pharm. Mfrs. Ass'n*, 471 F. Supp. at 1231 (reasoning, in the context of FDA's TE ratings, that "no agency is ordering any PMA [association] member to engage in or refrain from any action. Nor is any agency doing anything which is binding on the parties.").

⁸⁶ We note that, even in the unpublished case you cite, where the court, in dicta, theorized that an Orange Book designation may constitute final agency action, the court stated that it need not ultimately resolve that issue and determined that the Orange Book listing with TE rating was not arbitrary and capricious without requiring FDA to undergo notice-and-comment rulemaking or other additional processes. *Zeneca Inc. v. Shalala*, No. Civ. A. WMN-99-307, 1999 WL 728104 (D.Md. Aug. 11, 1999).

⁸⁷ See *e.g.*, 44 FR 2932-34, 2948; 45 FR 72583.

⁸⁸ See *e.g.*, 45 FR 72586-87.

⁸⁹ We also note that there is no statute that expressly requires FDA to promulgate regulations or hold individual hearings before issuing TE ratings for products approved pursuant to 505(b)(2) NDAs. As noted

2. *The Agency has already set forth clear, long-standing, and scientifically sound criteria for TE ratings and related procedures to enable interested parties to comment on or challenge TE ratings for products approved pursuant to 505(b)(2) NDAs.*

Finally, your contention that the 1979-1980 notice-and-comment rulemaking did not prescribe standards or a process for making TE evaluations and that there are not sufficient procedural protections to those with an interest in listings is without merit. Contrary to your assertions, the Agency has already clearly stated, in the context of the 1979-1980 notice-and-comment rulemaking, the criteria we use for TE evaluations. Through that rulemaking, the Agency provided an extensive discussion and analysis of the appropriate criteria to apply in evaluating TE.⁹⁰ These same TE criteria were published in the first edition of the Orange Book in 1980, and have now been used by the Agency for over 30 years.⁹¹ Although FDA's TE evaluation is done on a case-by-case basis to accommodate the different types of data and literature that may be submitted to support approval of 505(b)(2) NDAs, the criteria FDA uses are clear, long-standing, and offer a scientifically sound basis on which to evaluate TE.

You offer no alternative criteria for TE ratings in your Petition, nor do you offer any evidence to call into question any of the TE criteria as they apply to products approved pursuant to 505(b)(2) NDAs.

in section I.C., the Agency's TE criteria were first published in 1980. Congress has passed numerous laws amending the FD&C Act since that time, including the Hatch-Waxman Amendments (Pub. L. 98-417), which created the abbreviated drug approval pathways; the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115); the Food and Drug Amendments Act of 2007 (Pub. L. 110-85); and in 2012, the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144). Congress has not, through these amendments, or any other statute, questioned or reversed FDA's longstanding practice or expressly directed FDA to issue additional regulations to modify the TE listing process that is in place.

⁹⁰ See e.g., 44 FR 2937-52; 45 FR 72589-72602. We note that during the 1979-1980 notice-and-comment rulemaking, FDA considered and addressed public commentary on the central issue raised by your Petition: the evaluation of therapeutic equivalence among products which differ in the composition of their inactive ingredients. See 45 FR 72591 (responding, in the context of rulemaking, to comment stating that "the definition of 'pharmaceutical equivalents' should require that the products contain the same inactive ingredients or that they be produced by the same manufacturing methodology or technique." In responding to this comment, FDA noted:

"[T]he agency's experience with reviewing inactive ingredients does not support the statement that it is necessary and appropriate for 'pharmaceutical equivalents' to contain the same inactive ingredients or to be produced under the same manufacturing method or technique. Inactive ingredients and manufacturing methodology are extremely important. Through the new drug approval process, FDA has the opportunity to review the proposed formulation and manufacturing procedures. ... The agency reviews inactive ingredients through a variety of mechanisms including the evaluation of individual inactive ingredients to ensure safety and the review of formulation information in new drug applications to ensure that appropriate ingredients are used. In addition, the agency imposes bioequivalence study requirements on drugs where there is reason to believe different formulations (of inactive ingredients) would pose bioequivalence problems.").

⁹¹ See Orange Book Preface at vii (listing same criteria as those listed in the preambles to the 1979-1980 notice-and-comment rulemaking and first edition of the Orange Book, except making more explicit the criteria that products must be approved as safe and effective).

Furthermore, in response to your assertion that there is insufficient process available in the context of TE listings, we note that FDA has already established, through other notice-and-comment rulemakings, procedures available to interested parties who wish to comment on or contest FDA's evaluation and listing of TE ratings, including for products approved pursuant to 505(b)(2) NDAs.⁹² For example, one important administrative procedure available to interested parties is the citizen petition process described in FDA's regulations.⁹³ This process allows interested parties to submit requests, comments, and information for FDA to consider in the context of TE ratings or other matters. FDA's regulations also describe important procedural aspects of the citizen process.⁹⁴ As your Petition illustrates, interested parties can and do comment on or contest putative TE ratings prospectively, before a TE rating is issued.⁹⁵ The citizen petition procedure is also available to parties who may wish to comment on or contest previously issued TE ratings.⁹⁶

In addition, as described in the Orange Book Preface, FDA provides a process by which interested parties may submit comments on the Orange Book itself or related Agency procedures.⁹⁷ The Agency specifically states in the Orange Book that application holders are requested to inform the Agency if any changes or corrections are needed.⁹⁸ Thus, FDA already anticipates and solicits comments from interested parties related to TE ratings or to the Agency's process and criteria for the evaluation and listing of TE ratings.

In light of the above, additional notice-and-comment rulemaking to revisit the Agency's long-established approach to TE ratings is not necessary or appropriate at this time.

B. Requests Related to the Perrigo and Teva Topical Testosterone Gel Products

You also raise three main arguments specific to the Perrigo and Teva 505(b)(2) NDAs. We address them below, but, for ease of discussion, present them in a different order.

⁹² Although you describe, in your Petition, procedures you believe may be required in the TE context, you fail to explain why FDA's current procedures are insufficient for interested parties to comment on or contest FDA's evaluation and listing of TE ratings. *See Petition at 19-25.*

⁹³ *See* 21 CFR 10.30.

⁹⁴ *Id.*

⁹⁵ For example, your citizen petition supplement dated December 21, 2012, (submitted pursuant to 21 CFR 10.30(g)) requests, among other things, that FDA assign NDA 202763, referencing AndroGel 1%, a TE rating of BX.

⁹⁶ *See* citizen petition and supplements in Docket No. FDA-2002-P-0071 requesting, among other things, that FDA change the TE rating of an estradiol transdermal system (NDA 020375) from A-rated to B-rated.

⁹⁷ *See* Orange Book Preface at v (stating that the Agency intends to use "this publication to further its objective obtaining input and comment on the publication itself and related Agency procedures.")

⁹⁸ *See e.g.*, Orange Book, at xxii-xxiii.

1. *The Perrigo and Teva Topical Testosterone Gel Products are Safe and Effective for Use when Applied to the Shoulders and Upper Arms and/or Abdomen.*

You request that FDA revise the prescribing information and other relevant labeling for the Perrigo and Teva topical testosterone gel products to remove the abdomen as an approved application site.⁹⁹ You state that AndroGel 1% is approved for topical application to the upper arms/shoulders and the abdomen, based on clinical data in the NDA from studies of the product for both application sites.¹⁰⁰ You assert that although the Perrigo and Teva topical testosterone gel products are approved for application to the upper arms/shoulders and the abdomen, the abdomen site was not studied by either applicant in effectiveness studies (*i.e.*, pivotal comparative bioavailability studies) or safety studies (*e.g.*, transfer studies).¹⁰¹ Thus, you state that there is no basis upon which to conclude that these products are safe and effective for topical application to the abdomen.¹⁰²

- a. The Perrigo and Teva topical testosterone gel products are effective when applied to the shoulders and upper arms and/or abdomen.

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 AndroGel 1%, 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.¹⁰³ The Agency's findings for AndroGel 1% include, among others, those pertaining to two studies (Study UMD-96-017¹⁰⁴ and Study UMD-96-012¹⁰⁵), which are reflected in the approved labeling for AndroGel 1%. For example, the *Dosage and Administration* section of the approved

⁹⁹ See e.g., Teva Supplement at 2; Perrigo Supplement 1 at 2.

¹⁰⁰ See e.g., Teva Supplement at 10; Perrigo Supplement 1 at 8.

¹⁰¹ See e.g., Teva Supplement at 10; Perrigo Supplement 1 at 8-9.

¹⁰² See e.g., Teva Supplement at 10; Perrigo Supplement 1 at 9-10.

¹⁰³ See 21 CFR 314.54, 505(b)(2) Guidance, 505(b)(2) Response Letter.

¹⁰⁴ AbbVie's Study UMD-96-017 was a randomized, multi-center, active-controlled, parallel-group study that compared two doses of the AbbVie topical testosterone gel product with a marketed testosterone patch. See e.g., AbbVie Clinical Pharmacology & Biopharmaceutics Review dated February 25, 2000 (AbbVie Clinical Pharmacology Review (Feb. 25, 2000)) at 6 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-015_AndoGel_BioPharmr.pdf. This study was the pivotal efficacy study for AndroGel 1%, which involved application of the product daily to the left and right upper arm and shoulders and/or the left and right sides of the abdomen, depending on the dosage. Id. at 7. Study UMD-96-017 did not address comparative efficacy at different application sites, and such a showing was not required by FDA to support approval of AndroGel 1%.

¹⁰⁵ Study UMD-96-012 was a single-center, open-label, multiple-dose, crossover study. See e.g., AbbVie Clinical Pharmacology Review (Feb. 25, 2000), at 16. Study UMD-96-012 was a supportive study investigating the impact of application surface area (*i.e.*, whether the number of application sites would affect bioavailability). Study UMD-96-012 demonstrated that there were no statistically significant differences in the PK parameters of testosterone following application to one site (left upper arm/shoulder) or four sites (left upper arm/shoulder, the right upper arm/shoulder, the left abdomen and the right abdomen). Id. At 16-18. (We note that it appears that Study UMD-96-012 is sometimes referenced in the reviews as Study UMD-98-012.)

labeling for AndroGel 1% states: “The recommended starting dose of AndroGel 1% is 50 mg of testosterone . . . applied topically once daily in the morning to the *shoulders and upper arms and/or abdomen*....” (emphasis added).¹⁰⁶ The *Pharmacokinetics* section of the approved labeling for AndroGel 1% states: “AndroGel provides continuous transdermal delivery of testosterone for 24 hours following a single application to intact, clean, dry skin of the *shoulders, upper arms and/or abdomen*” (emphasis added).¹⁰⁷ This approved labeling reflects FDA’s finding that, for AndroGel 1%, neither the site of application (upper arms/shoulders versus abdomen) nor the number of application sites (upper arms/shoulders and abdomen versus upper arms/shoulders or abdomen) significantly affect bioavailability. In other words, FDA found AndroGel 1% to be effective when the product is applied to the shoulders and upper arms only, the abdomen only, or the shoulders and upper arms and abdomen.¹⁰⁸

Perrigo’s Study 03-0415-001 was a randomized, single-dose, three-way crossover comparative bioavailability study comparing the Perrigo topical testosterone gel product to AndroGel 1%.¹⁰⁹ In each treatment period, each subject received a 100 mg application of the test formulation or AndroGel 1% applied to the shoulders and upper arms.¹¹⁰ A series of blood samples were collected before and after dosing to measure testosterone concentration.¹¹¹ The AUC results satisfied the criteria for bioequivalence with a 90 percent CI of 83.2 to 110.3 percent, and the C_{max} results satisfied the criteria for

¹⁰⁶ See Currently Approved Product Labeling for AndroGel 1% (June 19, 2014); see also Approved Product Labeling for AndroGel 1% (January 30, 2011) (approved labeling for AndroGel 1% available at the time of approval of the Teva topical testosterone gel product containing substantially the same text); Approved Product Labeling for AndroGel 1% (September 20, 2012) (approved labeling for AndroGel 1% available at the time of approval of the Perrigo topical testosterone gel product containing substantially the same text).

¹⁰⁷ Id.

¹⁰⁸ You state that the safety and effectiveness conclusion for the Teva 505(b)(2) NDA was based on manipulation of data from a study in the AndroGel 1% NDA (Study UMD-96-012) to reach new conclusions not evident from the AndroGel 1% approval, and you speculate that the Agency did the same for the Perrigo 505(b)(2) NDA. See e.g., Teva Supplement 10-13; Perrigo Supplement 1, at 10. You state that such repurposing of the AndroGel data is unlawful and does not support the Agency’s conclusion regarding safety and effectiveness. See e.g., Teva Supplement 10-13. Although the Clinical Pharmacology Reviewers for the Teva 505(b)(2) NDA in their review summarize the findings of the supportive AndroGel 1% study (Study UMD-96-012) and refer to the review of Study UMD-96-012, the Agency did not as you suggest rely for approval on manipulated data from Study UMD-96-012 to support approval of the Teva 505(b)(2) NDA. See e.g., Teva Office of Clinical Pharmacology Review dated January 19, 2012 (Teva Clinical Pharmacology Review (Jan. 19, 2012)) at 12, 20-21 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000ClinPharmR.pdf.

Rather, as may be the case with any thorough review, the reviewers merely described in a few sentences the findings of the study that supported the Agency’s findings as reflected in the approved labeling for AndroGel 1%. It was not necessary for the reviewers to summarize the findings of Study UMD-96-012 or refer to the review of that study, to support approval of the Teva 505(b)(2) NDA or the Perrigo 505(b)(2) NDA. The information and conclusions supporting the effective use of the Teva and Perrigo topical testosterone gel products are described above in section II.B.1.

¹⁰⁹ See e.g., Perrigo Clinical Pharmacology Review dated December 20, 2012 (Perrigo Clinical Pharmacology Review (Dec. 20. 2012)) at 7, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203098Orig1s000ClinpharmR.pdf.

¹¹⁰ Id.

¹¹¹ Id.

bioequivalence with a 90 percent CI of 80.5 to 115.7 percent.¹¹² FDA determined, and you do not dispute, that the results were adequate to demonstrate bioequivalence between the Perrigo topical testosterone gel product and AndroGel 1%.¹¹³

Teva's Study 70343 was a multicenter, randomized, single-dose, two way-crossover comparative bioavailability study comparing the Teva topical testosterone gel product to AndroGel 1%.¹¹⁴ A single topical dose of the test formulation or AndroGel 1% was administered as 2x5 packets of testosterone gel (each packet corresponding to 50 mg of testosterone for a total of 100 mg and one packet applied on each shoulder and upper arm).¹¹⁵ A series of blood samples were collected before and after dosing to measure testosterone concentration.¹¹⁶ The AUC results satisfied the criteria for bioequivalence with a 90 percent CI of 95.82 to 115.67 percent.¹¹⁷ The 90 percent CI for C_{max} was 105.95 to 126.4 percent. Although the C_{max} results were outside the range for demonstrating bioequivalence in the context of ANDAs (90 percent CI of 80 to 125 percent),¹¹⁸ a showing of bioequivalence is not necessarily required to support approval of 505(b)(2) NDAs. In fact, FDA determined, as you acknowledge, that the bioavailability of the Teva topical testosterone gel product was sufficiently comparable to AndroGel 1% and acceptable for approval.¹¹⁹

Because the Perrigo and Teva topical testosterone gel products share characteristics in common with AndroGel 1%, such as same active ingredient, dosage form, strength, route of administration, and the products were adequately bridged to AndroGel 1% through the pivotal comparable bioavailability studies (Study 03-0415-001 and Study 70343, respectively), it is scientifically appropriate to rely on the Agency's findings of efficacy for the listed drug, AndroGel 1%, to support the conclusion that the Perrigo and Teva topical testosterone gel products are effective when applied to the shoulders and upper arms and/or abdomen.

You assert that it cannot be assumed that the Perrigo and Teva topical testosterone gel products have the same effectiveness when applied to the abdomen as when applied to the upper arms/shoulders because the use of different penetration enhancers in the products may lead to different rates of absorption than observed with AndroGel 1%.¹²⁰

¹¹² The FDA reviewer conducted her own analysis of the data and confirmed that the products were bioequivalent in that the AUC results satisfied the criteria with a 90 percent CI of 81.1 to 108.5 percent, and the C_{max} results satisfied the criteria with a 90 percent CI of 80.7 to 116.8 percent. See Perrigo Clinical Pharmacology Review (Dec. 20, 2012) at 7-8.

¹¹³ Id.; see also Current Approved Product Labeling for the Perrigo Topical Testosterone Gel Product (June 19, 2014).

¹¹⁴ See e.g., Teva Clinical Review dated January 26, 2012 (Teva Clinical Review (Jan. 26, 2012)) at 9, 27-28, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000MedRedt.pdf.

¹¹⁵ Id.

¹¹⁶ Id.

¹¹⁷ Id. at 33.

¹¹⁸ Id. at 43.

¹¹⁹ Id.; see also Teva Supplement at 10.

¹²⁰ See e.g., Teva Supplement at 14.

The Agency's concerns regarding different penetration enhancers were related to safety (not efficacy), and these concerns were addressed by Perrigo and Teva in transfer potential studies, among other safety studies (discussed below). The potential of different penetration enhancers to impact effectiveness was directly measured in the pivotal comparative bioavailability studies conducted by each applicant. These studies were designed to detect whether the proposed formulations released the drug (testosterone) at a comparable rate and extent to AndroGel 1%. These studies demonstrate directly that the differences in penetration enhancers do not result in significantly different release of the drug from the formulations and thus do not significantly affect bioavailability when applied to the upper arms/shoulders. If there were a significant impact on the absorption or distribution of testosterone due to the use of different penetration enhancers in the Perrigo and Teva topical testosterone gel products, it would have been evident in the results of the comparative bioavailability studies. If the differences in penetration enhancers do not significantly affect bioavailability when applied to the upper arms/shoulders, it is scientifically appropriate to conclude that such differences also would not be expected to significantly affect bioavailability when applied to the abdomen.^{121,122} We note that you have not provided reasonable evidence to the contrary, as discussed below.

You cite one article involving a *different* product (Testim) for the proposition that testosterone is generally absorbed less on the abdomen than on the upper arms/shoulders.¹²³ The publication you refer to by Guay *et al.* refers specifically to Testim, and does not generalize to all testosterone products. The Perrigo and Teva topical testosterone gel products have comparable bioavailability profiles to AndroGel 1%. Even assuming *arguendo* that it is reasonable to conclude that the amount of testosterone absorbed from one particular product at different sites may be different, it is still reasonable to conclude that the absorption of two formulations with comparable bioavailability profiles shown at one site would remain similar, relative to each other, across different sites of application. You have not provided reasonable evidence to the contrary.

You also state that, because the Perrigo pivotal effectiveness study was conducted with the entire dose applied to one upper arm/shoulder, those data may be unreliable for demonstrating that the PK of the Perrigo topical testosterone gel product is comparable to AndroGel 1%.¹²⁴ You state that cutting the surface area in half likely biased the study in

¹²¹ We note that the Agency's conclusion is consistent with the Agency's current thinking regarding bioequivalence for ANDAs for topical testosterone gel 1%. See *Draft Guidance on Testosterone* (2013) (recommending that testosterone should be applied to clean, dry, intact skin of the shoulders and/or upper arms; and noting that concerns precluding submission of ANDAs for proposed formulations that differ from the RLD relate to the 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).

¹²² We note that the *Dosage and Administration (Dosing and Dose Adjustment)* section of the approved labeling for the Teva topical testosterone gel products states that: "To ensure proper dosing, the serum testosterone concentrations should be measured periodically and dose should be adjusted so that serum testosterone concentrations remain in the normal range (298 ng/dL to 1043 ng/dL)." The approved labeling for the Perrigo topical testosterone gel product also includes statements regarding dose adjustment.

¹²³ See e.g., Teva Supplement at 14; Perrigo Supplement 1 at 9.

¹²⁴ See e.g., Perrigo Supplement 1 at 12-13.

favor of Perrigo's desired result.¹²⁵ You state that, because the test and reference products were applied to the upper arm/shoulder at the highest dose, each formulation was likely absorbed at a rate that markedly exceeds what occurs under the approved conditions of use, thus reducing the potential to detect differences in bioavailability.¹²⁶ You state further that data on AndroGel 1.62% (NDA 022309) suggest that PK is not dose proportional and that surface area is an important factor influencing absorption of the active ingredient.¹²⁷

First, in Perrigo's comparative bioavailability study, the Perrigo topical testosterone gel product and AndroGel 1% were applied in the same manner to compare the bioavailability profiles, therefore, there is no reasonable basis upon which to conclude that the study is not reliable as you suggest.¹²⁸ Second, your assertion regarding AndroGel 1.62% is misplaced, in part, because it is a different product with a different and higher strength. In fact, your assertions are inconsistent with your own study for AndroGel 1% (Study UMD-96-012), which demonstrated that there were no statistically significant differences in the PK parameters of testosterone following application to one site (left upper arm/shoulder) or four sites (left upper arm/shoulder, the right upper arm/shoulder, the left abdomen and the right abdomen).

You state that FDA raised immediate concerns about Teva's failure to test the abdomen in its pivotal efficacy study.¹²⁹ Specifically, you state that the issue was noted by FDA during the filing review and communicated to Teva in the Day 74 letter, as well as in individual reviews.¹³⁰ The Medical Officer Review merely noted and FDA conveyed in the Day 74 letter the following: "The BE study was conducted using the arms/shoulders only as the application site for all 100 mg of testosterone. Users of AndroGel 1% apply 100 mg of testosterone to both arms/shoulders and both sides of the abdomen. The Sponsor should comment on whether this has any impact on the final determination of bioequivalence to the reference listed drug."¹³¹ The statements you characterize as concerns were observations noted and conveyed during the NDA filing period upon submission of the NDA (*i.e.*, the period during which FDA makes a threshold determination regarding whether the NDA is sufficiently complete to permit a substantive review). Although the abdomen site was not studied, the Agency ultimately concluded that the effective use of the product under the conditions of use for which it is approved is

¹²⁵ Id.

¹²⁶ Id.

¹²⁷ Id.

¹²⁸ We also note that although the approved product labeling for the Perrigo topical testosterone gel product refers to the "shoulder/upper arm," the FDA reviews state that the application site involved the "shoulders and upper arms." *See e.g.*, Currently Approved Product Labeling for the Perrigo Topical Testosterone Gel Product (June 19, 2014); Perrigo Clinical Pharmacology Review (Dec. 20, 2012) at 7; Perrigo Clinical Pharmacology Review (May 1, 2012) at 14, 17, 38.

¹²⁹ *See e.g.*, Teva Supplement at 11.

¹³⁰ Id.

¹³¹ *See* Teva Medical Officer's NDA Filing Memorandum dated February 25, 2011 (Teva NDA Filing Memo (Feb. 25, 2011)) at 4, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000MedR.pdf; Day 74 letter from FDA to Teva dated March 28, 2011, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000Admincorres.pdf.

supported by results of the pivotal comparative bioavailability study and the Agency's previous findings of effectiveness for AndroGel 1%, as reflected in the approved labeling.

- b. The Perrigo and Teva topical testosterone gel products are safe for use on the abdomen.

The Agency recognizes, as discussed above in section I.D.2., that testosterone may transfer in significant amounts when untreated skin comes in direct contact with gel-treated skin, thereby creating a risk of secondary exposure. Consequently, when a proposed topical testosterone gel product uses a different penetration enhancer than the listed drug, FDA expects submission of data from transfer studies to evaluate the potential for transfer of the proposed product. The Agency believes that transfer can be affected by novel penetration enhancers in certain ways. The rate and extent of absorption of testosterone from the skin surface through the stratum corneum and into the deeper epithelial and dermal layers may be affected. This could alter the concentration of testosterone on the skin surface and the resulting concentration gradient between the testosterone-treated skin of the patient and the untreated skin of the individual with whom they have contact. Transfer potential studies are important because they allow FDA to assess, in particular, whether a clothing barrier provides an adequate level of protection from transfer. This, in turn, allows FDA to evaluate the safety of the product and determine appropriate labeling for the product.

Perrigo conducted a single-dose, open-label, 4-way crossover study involving 20 male-female couples to assess the interpersonal transfer potential of its product (Study M1IU09001).¹³² In Study M1IU09001, a single 10 g dose of either the Perrigo topical testosterone gel product or AndroGel 1% was applied to the upper arm/shoulder of one side of male subjects either wearing or not wearing a long-sleeved T-shirt.¹³³ A series of blood samples were collected in female subjects prior to dosing to establish a testosterone baseline and then post-dosing, after contact with male partners.¹³⁴ Study M1IU09001 found that direct skin-to-skin contact between male and female partners following dosing with the Perrigo topical testosterone gel product resulted in a 136 percent increase in testosterone AUC for the female partners and a 250 percent increase in testosterone C_{max} (compared to the baseline measurement).¹³⁵ In contrast, when males wore T-shirts following dosing with the Perrigo topical testosterone gel product, the female partners exhibited a 16 percent increase in testosterone AUC and a 48 percent increase in testosterone C_{max}.¹³⁶

Teva conducted a single-dose, 4-period, 4-treatment, crossover study involving 48 male-female couples designed to assess the interpersonal transfer potential of its product

¹³² See e.g., Perrigo Clinical Pharmacology Review (May 1, 2012) at 8.

¹³³ Id.

¹³⁴ Id.

¹³⁵ Id.

¹³⁶ Id.

(Study MIFX10001).¹³⁷ In Study MIFX10001, a single 10 g topical dose of either the Teva topical testosterone gel product or AndroGel 1% was applied to the upper arm/shoulder of one side of male subjects either wearing or not wearing a cotton long-sleeved T-shirt.¹³⁸ 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.¹³⁹ Study MIFX10001 showed that direct skin-to-skin contact between the male and female partners following dosing with the Teva testosterone gel resulted in a 198 percent increase in testosterone AUC for the female partners and a 271 percent increase in testosterone C_{max} (compared to the baseline measurement).¹⁴⁰ In contrast, when males wore T-shirts following dosing with the Teva topical testosterone gel product, the female partners exhibited approximately an 11 percent increase in testosterone AUC and a 16 percent increase in testosterone C_{max}.¹⁴¹

These results show that for the Perrigo and Teva topical testosterone gel products, as with AndroGel 1% and other topical testosterone gel products, there is potential for significant transfer of testosterone with direct, post-dosing skin-to-skin contact. Although the Perrigo and Teva studies showed increases over baseline in mean total testosterone concentrations in females following secondary exposure with a clothing barrier, as with AndroGel 1%, the serum concentrations of testosterone remained within normal ranges for females, which is approximately 10-80 ng/dL.¹⁴² The Agency concluded, based on the transfer potential study results, that the risk of transfer of the Perrigo and Teva topical testosterone gel products is sufficiently mitigated when the application site is covered with clothing.¹⁴³ Although the Perrigo and Teva studies, Study M1IU09001 and Study MIFX10001, respectively, involved application of the products only to the upper arm/shoulder, the purpose of these types of studies is to assess the ability of a clothing barrier to prevent transfer of the formulation. Accordingly, it is reasonable to conclude that if the clothing barrier mitigates transfer at the upper arms/shoulders, it will likewise

¹³⁷ See e.g., Teva Clinical Pharmacology Review (Jan. 19, 2012) at 15.

¹³⁸ Id.

¹³⁹ Id.

¹⁴⁰ Id.

¹⁴¹ Id.

¹⁴² See e.g., Perrigo Acting Deputy Division Director Summary Review dated May 3, 2012 (Perrigo ADDD Summary Review (May 3, 2012)) at 16 (stating that Study M1U09001 indicated that use of a clothing barrier resulted in a mean maximal increase from baseline testosterone level at any time during the 24 hours following contact of 0.043 ng/ml (4.3 ng/dl). This level compares to a mean maximal increase from baseline of 0.313 ng/ml (31.3 ng/dl) when contact occurs without clothing barrier), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203098Orig1s000MedR.pdf; see also Teva Clinical Pharmacology Review (Jan. 19, 2012) at 44.

¹⁴³ See e.g., Perrigo Clinical Pharmacology Review (May 1, 2012) at 8 (stating the results of the study (M1IU09001) indicate that covering the application site with a clothing barrier such as a T-shirt may significantly reduce the testosterone transfer to others); Perrigo CDTL Review (May 2, 2012) at 26 (stating that a clothing barrier was shown to be effective in preventing clinically significant transfer); Teva Clinical Pharmacology Review (Jan. 19, 2012) at 15-16 (stating that the overall percent difference of the PK parameters for females was much lower when males were wearing a T-shirt during the transfer procedure than without a T-shirt, indicating that there is less exposure to testosterone when a T-shirt is covering the application site); Teva Clinical Review (Jan. 26, 2012) at 13 (stating that it was determined through the study that transfer of testosterone to women and children can be effectively mitigated by a T-shirt for both the test and reference products).

mitigate such transfer at the abdomen.¹⁴⁴ There is no reasonable basis upon which to conclude otherwise, as discussed below.

You state that, for the Teva 505(b)(2) NDA, the Agency's Clinical Pharmacology Reviewer concluded that the absence of data regarding application to the abdomen was critical.¹⁴⁵ To support your claim, you selectively excerpt from the reviews the following sentence: “[I]t should be noted that the interpersonal transfer potential of topical [testosterone] applied on the abdomen was not assessed and therefore, the same conclusion cannot be extrapolated to when [testosterone gel] 1% is applied to the abdomen.”¹⁴⁶ However, you omit the Clinical Pharmacology Reviewer’s recommendation that immediately follows which is that: “[t]his should be clearly reflected on the product label.”¹⁴⁷ The *Clinical Pharmacology (Pharmacokinetics; Potential for testosterone transfer)* section of the approved labeling reflects this recommendation and includes the following statement: “The potential for dermal testosterone transfer following testosterone gel application on the abdomen has not been evaluated.”¹⁴⁸ This statement does not expressly state or even imply that the secondary transfer potential when testosterone gel is applied to the abdomen would be different than when applied to the upper arms and shoulders. The statement merely conveys the fact that the abdomen site was not studied in the transfer potential study.

Furthermore, based on the transfer potential study using the upper arm and shoulder, the Agency concluded that the transfer potential could be adequately mitigated by covering the application site with a clothing barrier. This conclusion is reflected in the *Dosage and Administration (Administration Instructions)* section of the approved product labeling. First, this section states: “Testosterone gel should be applied to . . . the upper arms and shoulders and/or abdomen.” Second, this section includes the mitigation strategy of using a clothing barrier. These conclusions are amply supported in the reviews.

Specifically, the Clinical Pharmacology Reviewer in the same section of the review you cite states: “The overall percent difference of the PK parameters for females was much lower when males were wearing a T-shirt during the transfer procedure than without a T-shirt, indicating that there is less exposure to [testosterone] when a T-shirt is covering the application site.”¹⁴⁹ Further, the Medical Officer indicated that: (1) “The main purpose of the transfer study is to determine whether the secondary exposure (“transfer”) of testosterone to women and children can be effectively mitigated by a [T]-shirt and this appears to be the case for both products”; and (2) “The study’s design, execution and the

¹⁴⁴ See e.g., Currently Approved Product Labeling for the Perrigo Topical Testosterone Gel Product (June 19, 2014); Currently Approved Product Labeling for the Teva Topical Testosterone Gel Product (June 19, 2014).

¹⁴⁵ See Teva Supplement at 15.

¹⁴⁶ See Teva Office of Clinical Pharmacology Review (Jan 19, 2012), at 4, 15-16.

¹⁴⁷ Id.

¹⁴⁸ See Currently Approved Product Labeling for the Teva Topical Testosterone Gel Product (June 19, 2014).

¹⁴⁹ Id.

results appear generally acceptable.”¹⁵⁰ The Acting Deputy Division Director also concurred with this assessment stating, in part, that “clothing over the application site appears to mitigate the risk of transfer.”¹⁵¹ These conclusions relate to the potential for different penetration enhancers to affect the ability of a clothing barrier to block transfer. Based on the Agency’s experience and expertise, this potential is not expected to be site specific. The scientific conclusions regarding transfer potential could be appropriately applied to the abdomen for purposes of approval from a clinical perspective and the reviews and approved labeling reflect that determination.

You state that Perrigo’s study is flawed in a way that likely understates the rate of testosterone transfer to female partners.¹⁵² You state that, in Study M1IU09001, the entire 10g dose of testosterone gel was applied to an upper arm and shoulder on just one side of the body.¹⁵³ You assert that this does not reflect actual use conditions because the instructions for administration direct patients to apply the product so it is evenly distributed between the right and left upper arms/shoulders.¹⁵⁴ You state that application to just one upper arm/shoulder means the surface area for transfer to the female partner is reduced by half.¹⁵⁵

The Agency’s primary interest in evaluating transfer potential of testosterone is determining whether a clothing barrier is adequately protective. Contrary to your assertions, application of the entire dose to one area (even if it is a smaller surface area) maximizes the concentration of drug at the site. If the clothing barrier is protective when there is a maximum concentration gradient, it is reasonable to conclude that it would be protective with a lesser gradient.

Furthermore, as long as there are adequate data demonstrating that the product exhibits acceptable transfer properties, as is the case here, the Agency has not required that all testosterone gel products be evaluated for transfer with respect to all approved application methods reflected in the *Dosage and Administration (Administration Instructions)* section of the approved product labeling (referred hereinafter as “application methods”). In fact, for AndroGel 1%, although the product labeling states that it may be applied to “shoulders and upper arms and/or abdomen area,” the Agency did not require an evaluation of transfer when the entire dose was applied only to the abdomen or only to the upper arms and shoulders. The Agency determined that the transfer data obtained when the dose was distributed across the abdomen and upper arms/shoulders were adequate to demonstrate that AndroGel 1% exhibited acceptable transfer properties and were adequate to support the administration instructions in the approved labeling. Likewise, with the Perrigo and Teva topical testosterone gel products, the Agency found that the studies adequately demonstrated that the formulations using different penetration enhancers resulted in acceptable transfer properties and therefore concluded that the

¹⁵⁰ See e.g., Teva Medical Officer Review (Feb. 25, 2011), at 10; Teva Clinical Review (Jan. 26, 2012) at 78.

¹⁵¹ See e.g., Teva ADDD Summary Review (Feb. 14, 2012), at 18.

¹⁵² See e.g., Perrigo Supplement 1 at 12.

¹⁵³ Id.

¹⁵⁴ Id.

¹⁵⁵ Id.

product is safe for use on the abdomen when applied according to the administration instructions in the approved labeling. It was not necessary for Perrigo and Teva to evaluate all application methods for their topical testosterone gel products, just as it was not necessary for AbbVie to evaluate all application methods for AndroGel 1%.

c. Other testosterone gel approvals do not support your conclusions and are not relevant here.

You state that it appears that more than one topical testosterone product was approved for one application site, and not the other, because of different safety or efficacy at the different sites.¹⁵⁶ You state that, for AndroGel 1.62%, “[t]estosterone exposure is 30-40% lower when applied to the abdomen compared to the shoulders/upper arms.”¹⁵⁷ You state that AndroGel 1.62% (NDA 022309) was studied at both application sites, but approved for administration on the upper arms/shoulders only, and not the abdomen, because the risk of skin transfer was unacceptably higher when the product was applied to the abdomen.¹⁵⁸ You also state that Testim was approved only for application at the upper arms/shoulders, apparently because of transfer risk at the abdomen.¹⁵⁹

Although the Agency approved AndroGel 1.62%, Testim, and the Perrigo and Teva topical testosterone gel products through the 505(b)(2) pathway, the nature of the evidence submitted to support approval of the respective topical testosterone gel products is different and it follows that the conclusions that can be drawn from the data to support approval are different. Perrigo and Teva submitted, in support of their 505(b)(2) NDAs, the results of pivotal comparative bioavailability studies and safety studies, and relied on the Agency’s findings for the listed drug, AndroGel 1%. Unlike Perrigo and Teva, AbbVie and Auxilium did not seek to extrapolate to additional sites based on the Agency’s previous findings of safety and/or effectiveness for another listed drug. Rather, AbbVie and Auxilium submitted, in support of their 505(b)(2) NDAs, results of pivotal clinical endpoint studies to demonstrate effectiveness and safety which involved specific dosing regimens and application instructions, and relied on literature to support certain aspects of the approval. In sum, the sponsors used different approaches to support approval of their products and, therefore, it is reasonable to draw different conclusions based on them.¹⁶⁰

You also state that every other topical testosterone product approved for the abdomen has directly demonstrated effectiveness at that application site through clinical trials on the abdomen.¹⁶¹ As you recognize, the Perrigo and Teva topical testosterone gel products

¹⁵⁶ See e.g., Teva Supplement at 11; Perrigo Supplement 1 at 9.

¹⁵⁷ See e.g., Perrigo Supplement 1 at 9.

¹⁵⁸ See e.g., Teva Supplement at 11; 15-16; Perrigo Supplement 1 at 9.

¹⁵⁹ See e.g., Teva Supplement at 11; Perrigo Supplement 1 at 9.

¹⁶⁰ You also state that every other topical testosterone product has conducted skin transfer studies at each of the application sites for which the product is approved. See e.g., Teva Supplement at 11. As noted above in section II.B.1.b., as long as there are adequate data demonstrating that the topical testosterone gel product exhibits acceptable transfer properties, as is the case here, the Agency has not required that all testosterone gel products be evaluated for transfer with respect to all approved application methods.

¹⁶¹ See e.g., Teva Supplement at 11.

were submitted and approved under the 505(b)(2) abbreviated approval pathway and reference AndroGel 1% as a listed drug.¹⁶² Because the Perrigo and Teva topical testosterone gel products share characteristics in common with AndroGel 1%, such as same active ingredient, dosage form, strength, route of administration, and the products were adequately bridged to AndroGel 1% through the pivotal comparable bioavailability studies (Study 03-0415-001 and Study 70343, respectively), it is scientifically appropriate to rely on the Agency's findings of efficacy for the listed drug, AndroGel 1%, to support the conclusion that the Perrigo and Teva topical testosterone gel products are effective when applied to the shoulders and upper arms and/or abdomen. As discussed above in section I.A., there are three pathways for approval of drug applications. The approval pathways have different statutory requirements for approval and the nature and extent of information submitted by applicants may differ accordingly.

2. *The Perrigo Topical Testosterone Gel Product Has Been Demonstrated to be Therapeutically Equivalent to AndroGel 1% and The Teva Topical Testosterone Gel Product Has Not Been Demonstrated to be Therapeutically Equivalent to AndroGel 1%.*

You request that FDA assign a BX rating to the Perrigo and Teva topical testosterone gel product listings in the Orange Book, if the Commissioner determines that the Agency will assign a TE rating in the Orange Book to these products.¹⁶³ You state that this rating would accurately reflect that the Perrigo and Teva topical testosterone gel products are not therapeutically equivalent to, and cannot safely be substituted for, AndroGel 1%.¹⁶⁴

a. *The Perrigo Testosterone Gel Product Has Been Demonstrated to be Therapeutically Equivalent to AndroGel 1%.*

FDA has determined that the Perrigo topical testosterone gel product is therapeutically equivalent to AndroGel 1%. The Perrigo topical testosterone gel product is: (1) approved as safe and effective; (2) pharmaceutically equivalent to AndroGel 1% in that the products (a) contain identical amounts of the same active ingredient in the same dosage form and route of administration, and (b) meet applicable standards of strength, quality, purity, and identity; (3) bioequivalent to AndroGel 1%; (4) adequately labeled; and (5) manufactured in compliance with CGMP regulations.¹⁶⁵

Your request that FDA assign a BX rating to the Perrigo topical testosterone gel product rests primarily on your assertion that the product has not been demonstrated to have the same clinical effect and safety profile as AndroGel 1% under the approved conditions of use.¹⁶⁶ Contrary to your assertion, the Perrigo topical testosterone gel product and

¹⁶² See e.g., Teva Supplement at 11.

¹⁶³ See e.g., Teva Supplement at 1-2; Perrigo Supplement 1 at 2.

¹⁶⁴ See e.g., Teva Supplement at 1-2; Perrigo Supplement 1 at 2.

¹⁶⁵ You do not take issue in your Petition with the application of the TE criteria to the Perrigo topical testosterone gel product with respect to pharmaceutical equivalence, labeling, and CGMP. Your assertions regarding safety and effectiveness and bioequivalence are addressed elsewhere in this response.

¹⁶⁶ See e.g., Perrigo Supplement 1 at 8.

AndroGel 1% can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

As discussed above in section II.B.1.a., Perrigo's pivotal comparative bioavailability study, together with FDA's findings of effectiveness for AndroGel 1% as reflected in the approved labeling, support the conclusion that the Perrigo topical testosterone gel product and AndroGel 1% can be expected to have the same clinical effect when used under the conditions specified in the labeling.

You assert that the approved labeling for the Perrigo testosterone gel product states that “[t]he potential for dermal testosterone transfer following testosterone gel application on the abdomen has not been evaluated.”¹⁶⁷ You assert that this statement indicates FDA's recognition that nothing is known about skin transfer risk from the abdomen as well as the Agency's determination that the absence of such data is important for healthcare providers to know.¹⁶⁸ You state that this distinguishes the Perrigo topical testosterone gel product from AndroGel 1% in a way that precludes a finding that the products are therapeutically equivalent.¹⁶⁹ The labeling statement to which you refer appears as part of the description of the transfer potential study in the approved labeling for the Perrigo topical testosterone gel product.¹⁷⁰ The labeling statement is completely neutral and informs practitioners of the fact that the abdomen was not evaluated in the study conducted by Perrigo. The approved labeling does not contraindicate or otherwise counsel against use at the abdomen site. As discussed above, it is reasonable to conclude that if a clothing barrier mitigates transfer at the upper arms/shoulders, it will likewise mitigate such transfer at the abdomen. The Agency concluded that the Perrigo topical testosterone gel product exhibits acceptable transfer properties that make it safe for application to the abdomen when used according to the approved labeling.

You also claim that the data regarding transfer risk for the Perrigo topical testosterone gel product demonstrates that there is greater risk of transfer for the Perrigo topical testosterone gel product than for AndroGel 1%,¹⁷¹ necessitating a “BX” rating in the Orange Book.¹⁷² The Agency concluded, as with AndroGel 1%, that the risk of transfer of the Perrigo topical testosterone gel product is sufficiently mitigated when the application site is covered with a clothing barrier.¹⁷³ Although the Perrigo transfer potential study showed increases over baseline in mean total testosterone concentrations in females following secondary exposure when the application site was covered with a

¹⁶⁷ See e.g., Perrigo Supplement 1 at 9.

¹⁶⁸ See e.g., Perrigo Supplement 1 at 9.

¹⁶⁹ See e.g., Perrigo Supplement 1 at 9.

¹⁷⁰ See e.g., Currently Approved Product Labeling for the Perrigo Topical Testosterone Gel Product (June 19, 2014).

¹⁷¹ See e.g. Perrigo Supplement 1 at 11-12.

¹⁷² See e.g., Perrigo Supplement 1 at 8.

¹⁷³ See e.g., Perrigo Clinical Pharmacology Review (May 1, 2012) at 8 (stating the results of the study (M1IU09001) indicate that covering the application site with a clothing barrier such as a T-shirt may significantly reduce the testosterone transfer to others.); Perrigo CDTL Review (May 2, 2012) at 26 (stating that a clothing barrier was shown to be effective in preventing clinically significant transfer).

clothing barrier, the serum levels of testosterone, as with AndroGel 1%, remained within normal ranges for females.¹⁷⁴

Furthermore, although FDA does not require a comparative study to evaluate the risk of secondary transfer of testosterone, Perrigo included AndroGel 1% in a head-to-head comparison of the potential risk of secondary transfer of testosterone. In this comparison, the Perrigo topical testosterone gel product and AndroGel 1% were applied to the same application site (*i.e.*, one side of the upper arm/shoulder). We do not agree with your assertion that the results regarding the Perrigo topical testosterone gel product compare unfavorably with AndroGel 1%.¹⁷⁵ In Perrigo's head-to-head study, the results showed different trends and did not favor a specific product. Numerically higher transfer potential (% increase from baseline) was observed for AndroGel 1% without a T-shirt barrier, while numerically higher transfer potential was observed for Perrigo's testosterone gel with a T-shirt barrier.¹⁷⁶ Despite these numerical differences, FDA concluded that the transfer risk can be mitigated through use of a clothing barrier for the Perrigo topical testosterone gel product and AndroGel 1%.¹⁷⁷

In addition, the Perrigo topical testosterone gel product and AndroGel 1% are both approved with substantially the same labeling with respect to *Contraindications*, *Warnings and Precautions*, *Adverse Reactions*, and *Drug Interactions*, among other sections. The approved product labeling reflects FDA's conclusion that the Perrigo topical testosterone gel product poses substantially the same risks as AndroGel 1%.

Therefore, Perrigo's topical testosterone gel product is appropriately assigned an "AB" rating. The Perrigo topical testosterone gel product is therapeutically equivalent to AndroGel 1% and can be substituted with the full expectation that it will produce the same clinical effect and safety profile as AndroGel 1%.

b. The Teva Topical Testosterone Gel Product Has Not Been Demonstrated to be Therapeutically Equivalent to AndroGel 1%.

You state that FDA must assign a BX rating to the Teva topical testosterone gel product because it is not bioequivalent to AndroGel 1% and the product has not been

¹⁷⁴ See e.g., Perrigo ADDD Summary Review (May 3, 2012) at 16 (stating that Study M1U09001 indicated that use of a clothing barrier resulted in a mean maximal increase from baseline testosterone level at any time during the 24 hours following contact of 0.043 ng/ml (4.3 ng/dl). This level compares to a mean maximal increase from baseline of 0.313 ng/ml (31.3 ng/dl) when contact occurs without clothing barrier).

¹⁷⁵ See e.g., Perrigo Supplement at 11-12.

¹⁷⁶ It should be noted, however, that there is intra-subject variability associated with the baseline measurement and baseline-adjusted PK parameters were also provided.

¹⁷⁷ The other safety studies demonstrate that the Perrigo topical testosterone gel product is safe with respect to skin irritation and sensitization, that handwashing is an effective method for removing most residual testosterone from the hand after application, and that skin-to-skin transfer can be effectively mitigated by washing the site of application after the drug is applied. See e.g., Perrigo CDTL Review (Jan. 31, 2013) at 8-10 for overview of the safety studies. You do not raise any arguments in support of your position with respect to these studies.

demonstrated to have the same clinical effect and safety profile as AndroGel 1% under the approved conditions of use.¹⁷⁸

As discussed above in section II.B.1.a., the Teva topical testosterone gel product has not been demonstrated to be bioequivalent to AndroGel 1% because the study results fall outside the range for demonstrating bioequivalence. Thus, FDA has assigned a TE rating of “BX” to the Teva topical testosterone gel product because the data that have been reviewed by the Agency are insufficient to determine TE to AndroGel 1%.¹⁷⁹

3. It Is Not Necessary or Appropriate, At This Time, To Require the Perrigo and Teva Topical Testosterone Gel Products to Bear the Labeling Statement You Request.

You state that the labeling for all topical testosterone products, including the Perrigo and Teva topical testosterone gel products, should clearly state that they are not interchangeable with other topical testosterone products to avoid the risk of inappropriate substitution with AndroGel 1%.¹⁸⁰ Specifically, you state that, like AndroGel 1% and 1.62%, the Perrigo and Teva topical testosterone gel products should bear the following two statements:

- “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).^{181,182}

The approved labeling for the Perrigo and Teva topical testosterone gel products, as you acknowledge, already bears the limitation-of-use statement.¹⁸³

The addition of the non-interchangeability statement to the Perrigo topical testosterone gel product labeling would be misleading because it would incorrectly suggest that the

¹⁷⁸ See e.g., Teva Supplement at 8.

¹⁷⁹ Because FDA finds that the Teva topical testosterone gel product has not been demonstrated to be therapeutically equivalent at this time based on the failure to demonstrate bioequivalence, it is not necessary to address here your assertion that the Teva topical testosterone gel product should be assigned a “BX” rating because it cannot be expected to have the same clinical effect and safety profile as AndroGel 1%. See Teva Supplement at 10-17.

¹⁸⁰ See e.g., Teva Supplement at 18; Perrigo Supplement 1 at 14-15.

¹⁸¹ See e.g., Teva Supplement at 18; Perrigo Supplement 1 at 15.

¹⁸² You also state that Axiron (topical testosterone solution), Fortesta (topical testosterone gel), AndroGel (testosterone gel) 1.62%, and Testim (testosterone gel) incorporate in their approved labeling substantially the same non-interchangeability statement. See e.g., Teva Supplement at 18; Perrigo Supplement at 15. FDA notes that Vogelxo (topical testosterone gel) does not include a non-interchangeability statement. See Currently Approved Product Labeling for Vogelxo (June 4, 2014).

¹⁸³ See e.g., Teva Supplement at 18; Perrigo Supplement 1 at 15-16; Current Approved Labeling for the Perrigo Topical Testosterone Gel Product (June 19, 2014); Approved Labeling for the Teva Topical Testosterone Gel Product (June 19, 2014).

Perrigo topical testosterone gel product is not interchangeable with other topical testosterone products, including AndroGel 1%. FDA has determined, however, as discussed above, that the Perrigo topical testosterone gel product is therapeutically equivalent to AndroGel 1% and, therefore, the two products are interchangeable. Accordingly, it would not be appropriate to add the non-interchangeability statement to the approved labeling for the Perrigo topical testosterone gel product.

The Agency specifically considered and rejected during review of the Teva 505(b)(2) NDA different types of interchangeability statements (also taking into account the lack of tradename) and ultimately decided on the limitation-of-use statement as reflected in the approved labeling for the Teva topical testosterone gel product.¹⁸⁴ Further, at this time, we have concluded that the limitation-of-use-statement by itself is appropriate and not misleading, as you suggest.

Finally, 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.

For the above reasons, it is not necessary or appropriate, at this time, to require that the Perrigo and Teva topical testosterone gel products bear the non-interchangeability statement you request. We recognize, however, that it is possible that variation in the approved labeling for the 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.

III. CONCLUSION

Your Petition is granted, in part, and denied, in part, and the Auxilium petition is denied, in part, for the reasons explained above.

Sincerely,



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

¹⁸⁴ See e.g., Label and Labeling Review dated November 2, 2011, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000OtherR.pdf; Memorandum dated February 14, 2012 (subject: therapeutic equivalence for Teva's Topical Steroid Androgen), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202763Orig1s000OtherR.pdf; Currently Approved Product Labeling for the Teva Topical Testosterone Gel Product (June 19, 2014).