DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 4 2010

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Philip Katz
Hogan & Hartson LLP
Columbia Square
555 Thirteenth St. NW
Washington, DC 20004

RE: FDA-2010-P-0196

Dear Mr. Katz:

This letter responds to your citizen petition (Petition) submitted on behalf of Abbott Laboratories ("Abbott") and received on April 9, 2010. Your petition concerns the procedural and evidentiary requirements for FDA approval of generic transdermal testosterone gel (TTG) drug products that reference Abbott's product AndroGel, including but not limited to abbreviated new drug applications (ANDAs) submitted by Perrigo Israel Pharmaceuticals (Perrigo). The Petition asks us to act consistently with our August 6, 2009, response to a citizen petition (Testim Petition) submitted by Auxilium Pharmaceuticals in connection with generic versions of Testim testosterone gel (Testim Response).[1] Specifically, you request that we:

- Require any applicant for a product that does not contain the same penetration enhancers as AndroGel to conduct transfer and hand-washing studies (and the other required studies as set forth in the Testim Response), and to seek approval by means of a 505(b)(2) NDA (i.e., a new drug application submitted under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FD&C Act)), not an abbreviated new drug application (ANDA) submitted under section 505(j), unless the applicant has obtained a right of reference from Abbott.

- Require any NDA referencing AndroGel, including a 505(b)(2) NDA for a product that previously had been the subject of an ANDA referencing AndroGel, to contain new certifications to all patents listed with AndroGel in the list of *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), and if any of those certifications assert that the patent is invalid, unenforceable, or will not be infringed, require the applicant to provide timely notification as provided for in section 505(b)(3) of the FD&C Act.

We have carefully reviewed the arguments in your petition. For the reasons stated below, we are granting your request in part and denying it in part with regard TTG products as a whole. Our discussion of the issues you have raised reflects our current views on TTG

[1] Docket No. FDA-2009 P-0123.

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products generally, but makes no comment on the approvability of specific pending or future applications.

I. BACKGROUND

AndroGel and Testim are both drugs that are indicated for testosterone therapy in adult males with a deficiency or absence of endogenous testosterone. Both are designated in the Orange Book as reference listed drugs (RLDs) for potential generic transdermal testosterone gel (TTG) drug products.

Beginning in early 2009, FDA became aware of significant adverse effects in children from secondary exposure to TTG occurring through inadvertent drug transfer from adult male users of transdermal testosterone gels. 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. In a few cases, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age. The risk of secondary exposure is a function of both the amount of residual product that remains on the skin of the patient and the manner in which the product is absorbed and metabolized by another individual in the course of a secondary exposure. FDA addressed this risk in April 2009 by requiring safety related labeling changes for both AndroGel and Testim, 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. These steps were taken to ensure that the benefits of these drugs outweigh the risks of secondary exposure of children to testosterone due to drug transfer from adult male users of the products.[2] The full details of FDA's actions to address this risk are described in the Testim Response (Testim Response at 2-3).

As noted above, your petition relates to the application of our decision in the Testim Petition to the requirements for approval of competing TTG product applications that reference AndroGel, another TTG drug, instead of Testim, as the RLD. The Testim Petition asked FDA (1) not to approve a pending ANDA that listed Testim as the RLD unless the applicant conducted specified safety studies (including but not limited to testosterone transfer and hand-washing studies) to rule out vehicle-related differences in testosterone transfer potential; and (2) to require such products to be approved with NDAs rather than ANDAs because of the need for clinical safety studies.[3] Our response to the Testim Petition declined to address pending applications, but provided a general discussion of issues applicable to all proposed generic TTG products having penetration enhancers different from the RLD (i.e., Testim or AndroGel). The specific requirements identified for such products in the Testim Response were:

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[2] A Medication Guide (MedGuide) is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208 and other applicable regulations.

[3] Section 505(j)(2)(A) of the FD&C Act prohibits FDA from requiring information in an ANDA in addition to the types of information set out in that subsection (21 USC 355(j)(2)(A)).

- Submission as a 505(b)(2) NDA, not an ANDA;[4]
- A body transfer study and hand-washing studies to evaluate secondary transfer potential;[5]
- A standard (single dose, crossover) pharmacokinetic study to establish bioequivalence;[6]
- Skin irritation and sensitization studies;[7] and
- Showering studies in some but not all cases (based on results of the required hand-washing, body transfer, and pharmacokinetic/bioequivalence studies).[8]

Finally, the Testim Response advised that approval requirements for these products "may be reconsidered as new information about the relationship between penetration enhancers and interpersonal transfer of [TTG] products becomes available to the Agency."[9]

II. DISCUSSION

A. Procedural Requirements for Generic TTG Drugs

Your petition asks us to require any applicant seeking to rely on AndroGel as the RLD for a TTG product having different penetration enhancers to seek approval by means of a 505(b)(2) NDA rather than as an ANDA, because of the need for clinical safety studies. The Agency remains concerned about the risk of secondary transfer of TTG products as described in the Testim Response. Accordingly, we continue to believe that TTG products with penetration enhancers that differ from those used in the RLD product will require human safety studies to determine whether the potential absorption of testosterone by secondary transfer is the same as that of the RLD. As we stated in the Testim Response, the practical effect of this determination is that an application for such a product must be submitted as a 505(b)(2) NDA rather than an ANDA.

Your petition also raises a procedural question related to the requirement that TTG drugs with different penetration enhancers must be submitted as 505(b)(2) NDAs rather than ANDAs. You ask us to clarify the patent certification and notification requirements for any applicant submitting a 505(b)(2) application referencing AndroGel if the applicant had previously filed an ANDA referencing AndroGel for approval of the same drug product. Your petition seeks to affirm that the applicant in such a circumstance must submit appropriate patent certifications and notifications to the patent holder as required under FDA regulations for the later-filed 505(b)(2) application, and cannot simply rely on the earlier certifications and notifications submitted for the earlier filed ANDA.[10] We agree that the patent certification and notification requirements apply to a new and

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[4] Testim Response at 5.
[5] *Id.*
[6] *Id.* at 8.
[7] *Id.* at 7.
[8] *Id.* at 6-7.
[9] *Id.* at 5-6.
[10] Requirements for patent certifications and notifications are found in: 21 CFR §§ 314.50(i), 314.52, and 314.54(a)(1)(vi) (applicable to 505(b)(2) NDAs); 21 CFR §§ 314.94(a)(12) and 314.95 (applicable to ANDAs); 21 CFR 314.107 (applicable to 505(b)(2) applications and ANDAs).

distinct application regardless of whether the proposed drug was previously submitted under another application that had proper certifications and notifications. A subsequent 505(b)(2) application cannot rely on or reference the patent certifications and notifications submitted with an earlier ANDA application. Even though the relevant listed patents and patent holder for the RLD may be the same for both applications, the subsequent 505(b)(2) application is a separate application and is required to contain its own, independent patent certification and notification. Moreover, the patent certifications and notifications for each application would be "clocked" for regulatory purposes from the time each was provided. Accordingly, we are granting your petition with respect to this point.

B. Approval Requirements for Proposed TTG Products Whose Penetration Enhancers Differ From the RLD

1. Body Transfer and Hand-Washing Studies

As your petition requests, and as we required in the Testim response, we are continuing to require a body transfer study for proposed TTG products that contain penetration enhancers different from the RLD. Similarly, a hand-washing study is also required for products intended to be applied with the hands. A hand-washing study determines whether or not residual TTG is adequately removed from the hands by hand-washing following application of the product. These studies are necessary because variations in the penetration enhancers might affect the amount of residual product left on the patient's skin. If residual product remains on the skin, there is a greater risk of secondary testosterone exposure and resulting adverse events for persons who come into contact with the patient.

2. Other Required Studies

Your petition also asks (without further discussion) that sponsors of proposed TTG products that reference AndroGel be required to perform "other required studies as set forth in" the Testim Response. These specifically included a standard (single dose, crossover) pharmacokinetic study to establish bioequivalence; skin irritation and sensitization studies; and showering studies in some but not all cases (based on results of the required hand-washing, body transfer, and pharmacokinetic/bioequivalence studies).

To the extent that your petition would require us to apply every aspect of our discussion of such studies in the Testim Response to future generic applications, the petition is denied. We are continuing to require 505(b)(2) applicants for TTG drug products to conduct a standard bioequivalence study, as well as skin irritation and sensitization studies, for products whose penetration enhancers differ from those in the RLD. However, we have refined our thinking about when showering studies will be required, as discussed below.

Showering studies are designed to evaluate the effect of showering or immersion of the application site on TTG product efficacy, as indicated by serum testosterone levels taken

at various time intervals before and after showering.[11] Data from showering studies are used primarily to support labeling recommendations to patients and prescribers about how soon the user can shower, swim, or immerse the application site without affecting drug efficacy. As stated in the Testim Response, we will not routinely require 505(b)(2) applicants to conduct showering studies for proposed TTG products whose penetration enhancers differ from the RLD.[12]

The Testim Response further stated that showering studies would be required if results of the required bioequivalence or hand-washing studies showed a significant difference between a proposed TTG product and the RLD. We are continuing to rely on the results of bioequivalence studies in determining the need for showering studies. In particular, we will not require 505(b)(2) applicants to perform showering studies when the proposed product is shown to be bioequivalent to RLD, provided that (1) the labeling of the RLD contains information on the appropriate interval between product application and showering based on the results of a showering study performed on the RLD; and (2) no change is sought by the applicant in the related time interval recommendations to be included in the proposed drug's labeling.[13] If an NDA applicant has demonstrated bioequivalence, a showering study would be required only if the applicant seeks to shorten the recommended interval between application and wash-off in the proposed drug's labeling. Such a proposed labeling modification would need to be supported by new data from a showering study conducted on the applicant's drug product.

Finally, based on further consideration and our experience with TTG products since the Testim Response was issued, we now believe that the need for a showering study can be adequately assessed based on the results of bioequivalence testing irrespective of hand-washing study results. As described above, hand-washing studies are designed to evaluate the risk of harm to persons who come into contact with residual testosterone on the patient's skin. Consistent with that purpose, they evaluate the amount of testosterone on the user's hands before and after washing. They do not, however, measure serum testosterone levels in the user or otherwise indicate whether or not showering studies should also be required.

We have limited the discussion in this response to the specific requirements discussed in the Testim Response as raised by your petition. The above discussion does not, therefore, preclude the possibility that additional data requirements, such as additional clinical studies, not discussed here or in our Testim Response, may be applicable to any TTG products referencing Testim or AndroGel, including the proposed Perrigo products referred to in your petition. Data requirements will be established in the context of each NDA based on the proposed ingredients and the other specific data and information

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[11] See Testim Response at 3 and 6.

[12] See Testim Response at 6 (showering studies will be necessary in "some instances").

[13] Our response to the Testim Petition was intentionally general and did not discuss the potential implications of a positive bioequivalence showing in connection with showering studies as described above. However, we believe that the position stated above is a logical extension of our established practice for 505(b)(2) applications, and we are therefore providing it here for purposes of clarification.

contained in each application, and will be discussed individually with each applicant, as appropriate.[14]

III. CONCLUSION

For the reasons described in this response, your petition is granted in part and denied in part, without comment on any specific actions we may take in connection with the Perrigo ANDAs or any other application.

Sincerely,

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

[14] Also, as with the Testim response, our views as articulated here may be reconsidered as new information about the relationship between penetration enhancers and interpersonal transfer of [TTG] products becomes available to the Agency.