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HAND DELIVERED

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
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Re: Docket No.2006P-0387, ANDA Suitability Petition
For Clobetasol Propionate Non-Aerosol Foam,
0.05% -- Response To Stiefel Laboratories, Inc.'s Opposition

Dear Food and Drug Administration:

This letter is submitted on behalf of our client Paddock Laboratories, Inc. (Paddock). This letter responds to comments filed by Stiefel Laboratories, Inc. (Stiefel) on behalf of its subsidiary Connetics Corporation (Connetics) on April 13, 2007, in opposition to Paddock's suitability petition filed on September 14, 2006. The suitability petition requests permission from the Commissioner of Food and Drugs to submit an abbreviated new drug application (ANDA) for a proposed drug product that differs in dosage form from the reference listed drug (RLD), Connetics's Olux® (clobetasol propionate) foam, 0.05%. Specifically, the RLD is an aerosol foam using a hydrocarbon

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propellant, while the proposed product is a non-aerosol foam using a mechanical pump. For the reasons discussed below, the Stiefel comment is without merit.

I. A Suitable *In Vivo* Bioequivalency Test Method Is Available

The thrust of Stiefel's comment appears to be that a non-aerosol foam formulation of clobetasol propionate cannot be shown to be bioequivalent to Olux. However, whether the proposed drug product is in fact bioequivalent to the RLD is an issue for the ANDA, not the suitability petition. FDA will decide in the context of any ANDA submitted pursuant to the suitability petition whether bioequivalence has been demonstrated appropriately.

Stiefel also suggests that appropriate criteria for the demonstration of bioequivalence of topical dermatological products are a matter of debate. Paradoxically, as discussed below, Stiefel's own references suggest an appropriate and sensitive test of bioequivalence with a high degree of accuracy, the vasoconstrictor assay.

Stiefel contends that there are no established criteria and that there is no relevant guidance on bioequivalency testing for topical products. Stiefel Comment, p. 10. To the contrary, the FDA has issued such guidance for topical corticosteroid products. In its May 1997 "Guidance for Industry, Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation," Section VIII, In Vivo Bioequivalence Studies, p. 25, FDA stated:

> The bioequivalence study can be a comparative skin blanching study as in glucocorticoids (FDA, *Topical Dermatological Corticosteroids: In Vivo Bioequivalence*,

> June 2, 1995.) or a comparative clinical trial or any other appropriate validated bioequivalence study ... for the topical dermatological drug product.

Additionally, as noted in the quoted language, FDA issued a guidance document in June 1995; that guidance discusses the vasoconstrictor assay at length, and notes that it is also known as the skin blanching assay. *Guidance for Industry, Topical Dermatological Corticosteroids: In Vivo Bioequivalence* (June 1995) at p. 2.

II. FDA May Make A Suitability Determination Based On The Information Provided In The Petition

Stiefel claims that the suitability petition for the proposed drug product should be rejected because additional information is needed. In support of this assertion, Stiefel cites various studies and minutes of FDA meetings. However, as demonstrated below, most of these references are inapposite. Further, to the extent that any of the cited references are relevant, sufficient information has been provided and appropriate *in vivo* testing of the non-aerosol foam formulation of clobetasol propionate against the RLD will be performed.

A. Changes In Dosage Form

On page 4 of its comment, Stiefel claims that an ANDA is not appropriate for any change in dosage form of a drug that can have significant effects on safety and/or efficacy, and that this is "especially the case in topical dermatological drugs." However, this statement is based upon an "expert opinion" touting the attributes of non-alcoholic foams over ethanol-containing foams, such as Olux, and other topical dosage foams in the treatment of dry skin disorders. *See* Stiefel Comment, Ex. A. This distinction is not

relevant to the question at hand, as the instant petition concerns the suitability of an ANDA for a non-aerosol clobetasol propionate foam. Ironically, the "expert opinion" on which the Stiefel comment relies appears to suggest the advantages over ethanol-containing foams (like Olux®) of non-alcoholic foams, of which the proposed product would be a good example.

B. Concentration Of Excipients

Stiefel also cites a meeting with FDA in November 2003 to suggest that "investigations beyond bioequivalence studies are necessary to provide the required proof of safety." Stiefel Comment, p. 4. The statement upon which this claim is based appears to be a discussion regarding an ethanol-free Olux® (clobetasol propionate) foam formulation; namely, that the sponsor should perform an additional toxicity study or "decrease the concentration of these excipients to levels that are found in approved topical drug products." Stiefel Comment, Ex. B, p. 5. Here, however, assuming the excipients used in the proposed drug product are within the range of concentrations used in approved topical products, as noted in the current Inactive Ingredient Guide, such a toxicity study would be unnecessary.

C. Investigations Beyond Bioequivalence

On page 4 of its comment, Stiefel claims that "investigations beyond bioequivalence studies" should be required to demonstrate the safety of the proposed drug product. Stiefel provides several references ostensibly in support of this statement. However, none of these references is consistent with Stiefel's claim.

First, Stiefel cites the Review and Evaluation of Pharmacology and Toxicology Data performed by FDA's Division of Dermatologic and Dental Drug Products of the original Olux application, relative to the topical dosing of clobetasol propionate:

> The potential for systemic toxicity from topical dosing is usually low.... The present foam formulation differs from these other commercial products in some inactive ingredients.
>
> [. . .]
>
> At this time, the most important issue for toxicological safety evaluation is whether the submission could be considered a 505(b)(2) application so all preclinical data generated by Schering could be used for this application. Ms. Elizabeth Dickinson of the General Counsel's Office has assured me that it would be proper to examine other Sponsor's data on BMV for the safety evaluation of this foam product without any authorization letters from them. In such situation, the Sponsor only has to show that the proposed product is bioequivalent to the innovator product. The sponsor has proposed such a study, i.e., a vasoconstriction study in humans.

Stiefel Comment, Ex. C, p. 5. Unfortunately for Stiefel, this discussion does not support their claim that "investigations beyond bioequivalence" would be required. The quoted language does support the conclusion that the aforementioned vasoconstriction assay would be an appropriate means of demonstrating *in vivo* bioequivalency.

In the same vein, Stiefel cites two statements made at an Advisory Committee meeting by a member of the staff of FDA's Center for Drug Evaluation and Research (CDER), Dr. Robert Lionberger:

> Finally, if you go down to products that are Q1 different, which means that they might have a different excipient between test and reference products...but here it seems that you would always want to do some sort of in vitro test to make sure that the new excipients are not having a different effect on the skin barrier process.
>
> [. . .]

> Well, I think we are trying to provide an alternative framework so the idea is that, certainly, you can have products that will give similar efficacy and they won't match at all the in vitro tests. It is certainly possible to come up with products that have different viscosities, different in vitro release rates, especially since that is not a limiting step, and still be bioequivalent in a clinical study. So we are trying to provide sort of an alternative pathway.

Stiefel Comment, Ex. D, pp. 244, 246-47. Again, the cited remarks do not support the Connetics assertion that "investigations beyond bioequivalence" should be required. In fact, Dr. Lionberger expressly stated that products with different excipients and different characteristics can nevertheless be bioequivalent.

D. Formulation Changes

Stiefel suggests that formulation changes can trigger issues that "require investigations into safety and efficacy." Stiefel Comment, p. 4. In support of this statement, Stiefel references a study regarding the percutaneous absorption of drugs. Interestingly, the author of this study states: "With few exceptions, the vasoconstrictor assay can be very accurate in predicting clinical potency and, at this time, must be one of the rare bioassays that will do this for any topical therapeutic drug." Stiefel Comment, Ex. E (internal citations omitted). The referenced vasoconstrictor assay appears to be the method employed in summarizing the differences in the betamethasone dipropionate – not clobetasol propionate – formulations compared and contrasted in Table 1 of this same reference. Rather than providing a recommendation for additional investigations, the study supports the validity of the assay method in determining potency or bioavailability differences in varying formulations of the same active ingredient. This further

undermines Stiefel's claim that there is not an acceptable method for demonstrating bioequivalence.

Stiefel also makes the assertion, "[f]or high potency topical corticosteroids such as clobetasol propionate, safety risks are generally increased when the area to which the drug is applied is occluded." Stiefel Comment, p. 4. This appears to be a well-known precaution to the use of topically applied corticosteroids, in general. However, the current Olux labeling includes the following statement, "Unless directed by a physician, OLUX Foam should not be used with occlusive dressings." Suitability Petition Attachment 2. The proposed drug product would bear labeling with that exact language. Further, were the potency of the proposed drug product to be more or less affected by occlusion than the RLD, such differences would be detectable through the bioequivalence study, as there would be enhanced or decreased penetration, resulting in different bioavailability resulting from such occlusion.

E. Systemic Circulation

Stiefel asserts that "[o]ther safety issues may also be implicated by the addition or subtraction of solvents or other ingredients that affect absorption of the active ingredient into the systemic circulation." Stiefel Comment, p. 5. However, the study cited as a reference for that statement is inappropriate for several reasons. Primarily, the model compound (4-cyanophenol) and the solvents used (water and acetone) in this study, *see* Stiefel Comment, Ex. G., p. 1292, are not germane to the formulation of the proposed drug product. Further, the reference (Exhibit G) does not at all address "absorption of the active ingredient into the systemic circulation," Stiefel Comment, p. 5. The uptake of the

compound into the stratum corneum, as determined by a tape stripping technique, was the procedure upon which the results were based. Thus, this reference only addressed a topical endpoint, not a systemic circulation endpoint.

Stiefel also claims that one of the key risks for topical corticosteroids is HPA axis suppression, "which can occur if too much of the drug reaches the systemic circulation." Stiefel Comment, p. 5. The Stiefel comment cites as support for this claim research presentations made before the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee. Stiefel Comment, Ex. H. The first presentation in the cited reference indeed provides that "the vehicle or base used, that is, whether the preparation is a cream, a lotion, or an ointment, may also be an influencing factor...." Stiefel Comment, Ex. H, p. 43. However, there is no discussion regarding HPA axis suppression as a result of changing excipients within a dosage form type, as the issue at hand is how to best address differences between foam formulations. Moreover, there is no discussion of foaming dosage forms in the text cited. The subsequent presentation in the cited reference also describes differences between a lotion and a cream for a member of the "superpotent" class of topical corticosteroids as they relate to HPA axis suppression. Stiefel Comment, Ex. H, pp. 68-69. Accepting for the sake of discussion that lotions and creams, as distinct dosage forms, may have widely disparate physical properties that alone could influence topical absorption, this reference still fails to support Stiefel's statement, as it lacks any discussion of formulation differences within different types of

form as it relates to HPA axis suppression. It is not clear that such comparisons are relevant as they may relate to differences between foam formulations.[1]

Stiefel claims that "[e]valuation of systemic exposure is of particular importance for a drug intended for the treatment of psoriasis of the scalp, because the scalp may allow for greater penetration than other skin." Stiefel Comment, pp. 5-6. The study cited in support of this statement, Stiefel Comment, Ex. K, is not directly applicable here. First, the study did not examine topical corticosteroids. Further, the flux across human scalp tissue of the lipophilic drugs that were studied was examined in two formulations: a formulation with a known absorption enhancer, and an enhancer-deficient formulation.

In the cases of both melatonin and ketoprofen, the added enhancers NMP (n-methylpyrrolidone) and IPM (isopropyl myristate) only "slightly enhanced" or "slightly increased" the penetration through scalp skin. Stiefel Comment, Ex. K, p. 373. The authors further stated: "The enhancing effect of enhancers such as NMP and IPM was much less than that predicted based on the data (Ogiso *et al*, 1995)." Stiefel Comment, Ex. K, p. 377. The central point of these descriptions of the effect of enhancers incorporated into the study as alternative formulations of the same dosage form is that in this study, their effect was slight.

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[1] Arguably, the fact that aerosol foam and non-aerosol foam are regarded as different dosage forms for ANDA purposes is an artifact of FDA's Uniform Terms in Appendix C of the Orange Book. If FDA regarded all "foams" as a single dosage form regardless of the mechanism used to produce the foam – just as all "patch" products are a single dosage form regardless of drug release mechanism – this entire inquiry would be moot.

F. Effect Of Changes In Product Dosage Form And Vehicle

Stiefel makes several statements regarding the effects of changes in dosage form, excipients, and profile. However, as demonstrated below, these changes are irrelevant, unsupported by the cited references, or easily addressed through the planned bioequivalence testing.

Stiefel claims that changes in dosage form may affect "the spreadability (rheology) of the drug, the rate and extent to which the vehicle releases the active ingredient, the active ingredient's ability to permeate the skin, and the likelihood of its absorption into the systemic circulation." Stiefel Comment, p. 6. In support of this statement, Stiefel references presentations made by CDER staff members, Drs. Robert Lionberger and Ajaz Hussain.[2] However, to the extent that these presentations apply to the proposed drug product, they simply support the intended evaluation of the proposed non-aerosol foam formulation against the RLD.

In his presentation, CDER's Dr. Lionberger states simply: "In vivo test required to demonstrate that the new excipients do not alter permeability." As previously discussed, the bioequivalence of the proposed drug product will be tested *in vivo* against the RLD by appropriate means. Further, the presentation by Dr. Hussain does not appear

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[2] *See* Robert Lionberger, Ph.D., Office of Generic Drugs, Center for Drug Evaluation and Research, *Topical Bioequivalence Update* (Apr. 15, 2004)(available at http://www.fda.gov/ohrms/dockets/ac/04/slides/4034S2_12_Lionberger.ppt); Ajaz Hussain, Ph.D., Acting Director, Office of Testing and Research, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, *Methods for Assessing Bioequivalence of Topical Products: How Should FDA Redirect its Research Program?* (Nov. 17, 2000)(available at http://www.fda.gov/ohrms/dockets/ac/00/slides/slides/3661s1_01.ppt).

to support Stiefel's statement, as it not pertinent to the issue of establishing bioequivalence between two foam formulations of topical corticosteroids. One substantial emphasis of Dr. Hussain's presentation appears to be dermatopharmacokinetic tape stripping methods associated with tretinoin products. It is not clear what Stiefel is suggesting through the inclusion of this information.

Stiefel also claims that differences in the quantities of excipients can result in different effects. Stiefel Comment, p. 7. However, the reference upon which that statement relies is taken out of context.

> If we sort of step down the level one more time and we look at products that are just Q1 identical, they just have the same components but maybe in different amounts, in this case we might be more concerned that the different amounts of, say, excipients in the formulation might have different effects on the skin barrier.

Stiefel Comment, Ex. D, p. 243. This remark was intended to describe potential differences among, or between, formulations that are Q1 identical (same excipients but in different amounts), which does not apply in the case of the proposed drug product, in that it is not intended to be Q1 identical. Further, a later statement in the same reference not only clarifies the intent of its author but also supports the planned bioequivalence testing: "So in these cases [Q1 identical products] we might be more likely to say that in this category you might want to do some sort of in vitro test...." Stiefel Comment, Ex. D, p. 244. As previously stated, the bioequivalence of the proposed drug product will be demonstrated through *in vivo* testing, a higher standard than this quotation calls for.

According to Stiefel, "variability in the source of the excipients, assuming the identity and quantity are constant, also may have a dramatic effect on their physical and chemical nature." Stiefel Comment, p. 7. It is helpful to note that FDA has an established process for addressing changing sources of inactive ingredients, typically through review of technical information contained in excipient suppliers' Drug Master Files. Further, where variations in the quality of the excipients could affect the performance of a finished product, conducting discriminating analyses of incoming excipients from a selected supplier may be important. However, the transcript citation on which Stiefel's statement relies is pertinent only to Q1 and Q2 (same formulation, same amounts) formulation approaches, which do not directly apply to the proposed drug product addressed in the suitability petition.

Stiefel also claims that "clobetasol propionate is one of the drugs whose biological potency is affected by the vehicle." Stiefel Comment, p. 8. In support of its assertion, Stiefel cites data regarding the *in vitro* skin permeation of different dosage forms (foam, solution, emollient cream, cream, lotion) of clobetasol foam. Stiefel Comment, Ex. L. Stiefel's statement is misleading. The important distinction here is that the studied products are truly different dosage forms, not what is in essence the same dosage form employing different vehicles. As such, they would be expected to have substantially different compositions, lipid phase proportions, and physical properties.

III. There Is No Legal Impediment To Granting The Suitability Petition

Finally, Stiefel argues that the suitability petition should be denied because the proposed non-aerosol foam would likely have different instructions for use than the instructions for the RLD:

> [A] likely consequence will be the need for different instructions to the patient in terms of how to apply the product and how much to apply.***But the FDCA does not allow ANDAs, whether pursuant to a suitability petition or not, when the conditions of use for the proposed product are not the same as the conditions of use stated in the label [sic] of the reference listed drug.

Stiefel Comment, pp. 11-12.[3] This contention is without merit. Any ANDA submitted pursuant to the approved suitability petition will have to be for the same indications for use, including the same dosing schedule. Otherwise, FDA would be without statutory authority to approve the ANDA. *See* 21 U.S.C. § 355(j)(4)(G).

FDA has approved many ANDA suitability petitions for changes in dosage form, for example, tablets to capsules or tablets to liquid, with the resulting need to make appropriate corresponding changes in the labeling of the generic product. It is well-recognized that FDA has the authority to permit changes of this type. *See Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000). Taken literally, Stiefel's comment would mean that

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[3] The two examples that Stiefel cites in footnote 33 at page 12 of its comment do not support its contentions. The first example involved testosterone gel and sought a change in strength from 1% to 5%. There is nothing in FDA's letter denying the petition to support Stiefel's characterization that the petition was denied because the requested change "would alter conditions of use." Stiefel's second example involved pentoxifylline (misspelled in Stiefel's comment as "phetoxifyline") extended release tablets. FDA denied a request for change in strength because, among other reasons, the new strength would have resulted in a dosing regimen that is not supported by the approved labeling of the RLD.

FDA could not approve any ANDA suitability petition seeking a change in dosage form, because it would require a labeling change along the lines of, for example, "take two tablespoons" of a liquid version, instead of "take two tablets" of the RLD. Such an interpretation makes no sense and would undermine the purpose of permitting ANDA suitability petitions.

IV. Conclusion

Despite Stiefel's claims to the contrary, sufficient information has been provided for the agency to permit an ANDA to be filed for a non-aerosol clobetasol propionate foam, 0.05%. Therefore, Paddock requests that FDA grant the petition to permit the filing of an ANDA.

Respectfully submitted,

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OFW:jdc