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October 30, 2008

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

Re: FDA-2006-P-0451

Dear Sir or Madaam:

Stiefel Laboratories, Inc. (Stiefel) has acquired Connetics Corporation (Connetics) and is submitting this supplemental information to Citizen Petition FDA-2006-P-0451. Stiefel agrees that the Food and Drug Administration (FDA) should not approve any generic version of acitretin until all of the issues presented in the Citizen Petition have been resolved. Stiefel wishes to take this opportunity to comment specifically on the public health need for an adequate assessment of the risk minimization action plan (RiskMAP) that is currently in place for Soriatane® (acitretin) Capsules before any generic acitretin product is approved.

The Federal Food, Drug, and Cosmetic Act (FDC Act) requires that FDA approve a new drug only after determining that the product is safe and effective for the product's indications in accordance with its labeled conditions of use. The FDC Act's safety requirement for product approval applies equally to innovator and generic drugs. A sponsor generally establishes the safety of an innovator product by way of adequate and well-controlled clinical studies. See FDC Act §§ 505(b), 505(d). The safety of a generic product, on the other hand, generally is established by demonstrating that it is pharmaceutically equivalent and bioequivalent to the reference drug and that the labeling for the generic drug is the same as that of the reference product. See FDC Act §§ 505(j). Recognizing that safety does not imply an absolute absence of risk, FDA has stated that:

> [A] product is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product

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> is considered safe if it has an appropriate benefit-risk balance for the intended population and use.

FDA Guidance for Industry: Development and Use of Risk Minimization Action Plans (March 2005) at 4.

As a means of reducing risk and thereby improving the benefit-risk balance, FDA seeks to supplement the routine risk management mechanisms built into the drug approval process under certain circumstances by requiring a RiskMAP. A RiskMAP is intended to minimize specific known risks of approved products, for example, those unique to certain patient sub-populations, as is the case with the use of Soriatane® Capsules by women of childbearing potential. If FDA requires a RiskMAP for an innovator drug, it will also require risk management plans for generic versions of the product. Thus, it is critical to the public health that the effectiveness of an innovator drug's RiskMAP be demonstrated before FDA approves generic versions of the drug.

The focus of the Soriataine® RiskMAP, which is now known as "Do Your P.A.R.T. (**P**regnancy Prevention **A**ctively **R**equired During & After **T**reatment"), is to continuously educate women of childbearing potential and their healthcare providers about the serious risks associated with acitretin and to help prevent pregnancies from occurring during the use of this drug and for three years after stopping treatment. Components of this plan include:

- Pregnancy testing along with contraceptive counseling prior to initiation of treatment and then each month before receiving the next prescription and every three months for three years after stopping treatment, which are provided at no charge to the patient.

- Warning that women of childbearing potential must not ingest alcohol during Soriatane® Capsules treatment and for two months after stopping treatment as concurrent ingestion has been associated with the formation of etretinate, which has a significantly longer half life than Soriatane® Capsules.

- Women of childbearing potential must sign an informed consent form prior to initiation of Soriatane® Capsules therapy.

- Distribution of various educational publications, including those that test the patient's understanding of the serious risks associated with Soriatane® Capsules.

- A medication guide.
- Letters to physicians and pharmacists.
- Maintaining a 24-hour, toll-free information hotline for patients and healthcare providers.
- Extensive training of sales representatives with emphasis on the indicated use of Soriatane® Capsules in severe psoriasis, and in women of childbearing potential only where there are no other treatment alternatives.
- Actively monitoring reported pregnancies and submitting periodic reports to FDA describing the outcome of such occurrences, as well as the numbers and timing of pregnancies relative to Soriatane® Capsules exposure during or within three years of discontinuation of treatment.

Throughout 2007, the FDA Division of Dermatologic and Dental Drug Products and Stiefel worked closely together to enhance the "Do Your P.A.R.T." program. In addition, Stiefel solicited input from members of the American Academy of Dermatology Association (AADA) to obtain additional feedback on the RiskMAP and patient survey. After considering the comments and suggestions of FDA and AADA, the following improvements in the program have been implemented recently:

- Revised Soriatane® Capsules web site.
- Revised "Do Your P.A.R.T." Patient Brochure.
- Revised Patient Agreement/Informed Consent Form.
- Revised Package Insert and Medication Guide.
- Revised Pregnancy Report Form.
- Voluntary Patient Survey.

The patient survey will provide a critically needed assessment of the effectiveness of the entire "Do Your P.A.R.T." RiskMAP. All physicians who are known to prescribe Soriatane® Capsules in the United States will be provided with the survey materials, and they will be instructed to provide the materials to all women of childbearing potential as part of the process for initiating treatment with Soriatane® Capsules. The specific,

evidence-based performance measures used in the patient survey include calculating the rate of pregnancy among female Soriatane® Capsules users (at the time of prescribing the drug, during use of the drug, and during the three-year period after Soriatane® Capsules are discontinued), measuring compliance with the contraceptive use, pregnancy testing, contraceptive counseling and avoidance of alcohol requirements, and determining female patient awareness of the teratogenic risks of Soriatane® Capsules. Additionally, the survey will also explore how the various communications regarding pregnancy risk (e.g., the medication guide, review of risks and benefits by the physician) are presented to and perceived by female patients upon enrollment into therapy. Developed with extensive input from FDA, the survey results will provide the primary assessment of the "Do Your P.A.R.T." RiskMAP.

Currently, there are limited data available that would help to quantify the effectiveness of these various tools in the reduction or elimination of pregnancies, or to target further possible improvements in the RiskMAP. Accordingly, it is in the interest of the public health to determine whether the enhanced "Do Your P.A.R.T." plan is effective in minimizing or preventing pregnancies from occurring during the use of this drug. As FDA has recognized, risk management is an iterative process and evaluation of the tools and plan performance is an important component of that process. Periodic evaluation of the plan is needed to determine if the goals of the RiskMAP are being met, and whether modifications to the plan are indicated. FDA has recognized the important public health benefit inherent in assessing the performance of any RiskMAP. "As FDA and sponsors seek additional knowledge about the design, effectiveness, burdens, and potential unintended consequences of RiskMAPs, it is important to collect as much information as possible on plan performance." FDA Guidance for Industry: Developing and Use of Risk Minimization Action Plans (March 2005) at 12 (emphasis added). In July of 2007, the Agency for Healthcare Research and Quality (AHRQ) and FDA held a joint public workshop entitled "Implementation of Risk Minimization Action Plans (RiskMAPs) to Support Quality Use of Pharmaceuticals: Opportunities and Challenges." This public workshop collected input from a wide range of stakeholders, including clinicians, pharmacists, patients, third party payers of care, the pharmaceutical and biotechnology industries, researchers, and innovators in health information technology, to help in the development and implementation of RiskMAPs. Several common themes were expressed by workshop participants, including the critical importance of evaluating RiskMAP performance, insisting on a standard of efficacy for RiskMAPs on par with other therapeutic interventions, and sharing the results of such evaluations.

Stiefel agrees with the importance of collecting and analyzing RiskMAP performance data. Consistent with this FDA guidance, Stiefel has designed a survey with

valid performance measures of the "Do Your P.A.R.T." RiskMAP, and will also be evaluating the effectiveness of the different tools used in the plan. Stiefel began enrolling participants in the patient survey in August 2008.

It is not clear what FDA would require in the way of RiskMAPs for generic versions of acitretin, that is, whether FDA would require the sponsor of each approved generic version of the drug to establish its own RiskMAP, thereby creating multiple, parallel RiskMAPs, or instead seek to encourage multiple acitretin sponsors to voluntarily establish a single, unified RiskMAP program. In FDA's own experience, the creation of multiple RiskMAPs for the same drug has proved unworkable and not in the interests of the public health. FDA observed, for example, in assessing the original risk management plans for the innovator and generic versions of isotretinoin that "[t]he multiple programs created confusion and the concern that patients would not receive appropriate counseling and testing to prevent the possibility of birth defects." "FDA Announces Enhancement to Isotretinoin Risk Management Program," FDA Talk Paper (November 23, 2004) (available at gttp://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01328.html).

Stiefel shares FDA's concerns. The introduction of generic acitretin products before Stiefel and FDA have had an opportunity to evaluate the effectiveness of the "Do Your P.A.R.T." program as determined by input from the patient surveys is not in the interest of the public health. The presence of generic products will, at a minimum, delay the collection of this data and greatly complicate the interpretation of the results of the survey. Stiefel will have no control over the quantity or quality of information presented to patients and healthcare professionals receiving any generic product. It would not be in the interest of the public health to assume that the current RiskMAP is adequate to address the unique concerns of patients, pharmacists, and physicians, particularly with respect to a generic drug. Further, the RiskMAP was developed in collaboration with FDA, and both Stiefel and the agency have devoted a tremendous amount of medical and scientific resources to this task. To introduce generic acitretin before the evaluation of the Soriataine® RiskMAP has even begun would essentially nullify those resources, and will require the unnecessary expenditure of additional agency resources in the event the data not yet collected and analyzed from the patient survey suggests the need for revisions to the risk management plan. Most importantly, the presence of generic versions of acitretin will adversely affect the evaluation of the RiskMAP for Soriatane® Capsules, possibly obscuring important risks to patients or areas where further improvement in the RiskMAP could help protect the public health.

In summary, Stiefel requests that approval of generic acitretin await an assessment of the effectiveness of Stiefel's RiskMAP. In that way, FDA and the public can be assured

that the labeling, patient information, web site, and other educational materials for this compound and any subsequent generic entrants provide optimal information to physicians and patients, and that all appropriate risk management tools and measures have been incorporated. Stiefel further requests that FDA not approve any generic version of acitretin until all of the issues presented in the Citizen Petition have been resolved.

* * * * *

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about October 23, 2008. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Stiefel Laboratories, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

David B. Clissold

DBC/jg