DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 18 2013

David B. Clissold
Hyman, Phelps & McNamara, P.C.
700 13th Street, NW, Suite 1200
Washington, DC 20005

Re: Docket No. FDA-2006-P-0451[1]

Dear Mr. Clissold:

This letter responds to the citizen petition (Petition) submitted on behalf of Stiefel Laboratories, Inc. (Stiefel or the Petitioner),[2] which was received by the Food and Drug Administration (FDA or the Agency) on March 24, 2006. The Petition requests that FDA take certain actions with respect to all abbreviated new drug applications (ANDAs) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) for Soriatane (acitretin) Capsules unless certain "sameness" and bioequivalence standards are met. Specifically, the Petitioner requests that FDA require the following for all ANDAs referencing Soriatane:

1. Establish that the generic product is the "same" as Soriatane with regard to: (i) degradation product profile; (ii) polymorph composition; and (iii) manufacturing to a residual solvent specification no greater than that of Soriatane, to control for conversion of acitretin to the teratogen, etretinate (Petition at 1).

2. Demonstrate bioequivalence: (i) of the parent drug as well as the active 13-cis isomer of acitretin according to the specific study design described by the Petitioner; (ii) with regard to the absence of additional or higher levels of metabolites; (iii) in the presence of food; (iv) in the presence of alcohol; and (v) in the elderly (Petition at 1, 6-8).

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[1] The March 27, 2006 citizen petition was originally assigned docket number 2006P-0140/CP1. This number has been changed to FDA-2006-P-0451 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] The Petition was originally submitted by Michael Eison, Ph.D., Vice President, Regulatory Affairs, Connetics Corporation (Connetics). On October 30, 2008, we received a comment from Hyman, Phelps & McNamara, P.C. (Petition Supplement), indicating that the Petitioner (Stiefel Laboratories, Inc.) had acquired Connetics, and emphasizing the continued request to withhold approval of an ANDA referencing Soriatane until the completion of an assessment of the effectiveness of Soriatane's *Do Your P.A.R.T. Program* to minimize pregnancy in patients while on therapy (Petition Supplement at 1).

The Petition further requests that FDA withhold approval of any ANDA referencing Soriatane until after completion of post-implementation assessment of the effectiveness of the Soriatane *Do Your P.A.R.T.* (Pregnancy Prevention Actively Required During & After Treatment) *Program* (formerly the *Pregnancy Prevention Program*) to minimize pregnancies in patients while on therapy and for 3 years after discontinuation of the product (Petition at 1).

FDA has carefully considered the information submitted in the Petition and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, the Petition is granted insofar as an ANDA for which Soriatane is the reference listed drug must include data from bioequivalence testing conducted under fed and fasted conditions and pharmacokinetic measurements of the major metabolite (for use only as supportive evidence).[3] In all other respects, the Petition is denied.

I. BACKGROUND

A. Soriatane

Stiefel holds the new drug application (NDA) 19-821 for Soriatane (acitretin), a retinoid product. FDA approved the NDA for Soriatane Capsules, 10 and 25 milligrams (mg), on October 28, 1996. On August 6, 2009, FDA approved Soriatane Capsules in strengths of 17.5 mg and 22.5 mg. FDA also approved a formulation change for the drug in 2001 and various labeling and packaging changes in 1997, 2003, 2004, 2007, 2009, and 2011.

Soriatane is indicated for the treatment of severe psoriasis in adults. Because of significant adverse effects associated with its use, Soriatane should be prescribed only by those knowledgeable in the systemic use of retinoids. The approved labeling for Soriatane bears extensive information about the potential risks associated with use of the drug, including a lengthy boxed warning and a Medication Guide. Due to a significant risk of birth defects, Soriatane's labeling states that use in females of childbearing potential should be limited to women who are not pregnant and who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Soriatane is approved with the *Do Your P.A.R.T. Program*, which is intended to prevent fetal exposure to Soriatane.

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[3] This response addresses the requests in the Petition generally. It should not be construed as addressing specific issues raised by any pending 505(j) or 505(b)(2) application, nor does it purport to make any final decisions with respect to any such pending application. Those decisions are made in the normal course as part of the review process applicable to any such applications.

B. ANDAs Submitted Under Section 505(j) of the FD&C Act

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA sponsor is not required to submit evidence to establish the clinical safety and effectiveness of the ANDA drug product, as is required for an NDA. Instead, an ANDA relies on FDA's previous finding that the approved, listed drug to which the ANDA refers (reference listed drug or RLD) is safe and effective. To rely on this finding, the ANDA must contain (with certain exceptions) information to show that the proposed drug has the same active ingredient(s), indications, route of administration, dosage form, strength, and labeling as the RLD (FD&C Act § 505(j)(2)(A) and (j)(4)), and is bioequivalent (FD&C Act § 505(j)(2)(A)(iv)). A drug's dosage form refers to the physical form of the drug product and the way in which it is administered, not to its release mechanism.[4] Thus, a generic drug will not necessarily release its drug substance in the same manner as the RLD.

C. "Sameness"

Section 505(j)(2)(A)(ii)(I) of the FD&C Act specifies that an ANDA must contain information to show that the active ingredient is the "same" as that of the RLD. Under section 505(j)(4)(C)(i) of the FD&C Act, FDA may refuse to approve an ANDA referencing a listed drug that has only one active ingredient if the ANDA contains insufficient information to show that the active ingredient is the "same" as that of the RLD. Thus, the ANDA applicant bears the burden of providing sufficient information to show that the active ingredient in the proposed generic drug product is the "same" as the active ingredient in the RLD.

FDA regulations state that the term "same as" means, among other things, "identical in active ingredient(s)" (21 CFR 314.92(a)(1)). However, in the preamble to the 1992 *Abbreviated New Drug Regulations, Final Rule* (1992 Final Rule) (57 FR 17950, Apr. 28, 1992), FDA specifically rejected the notion that an ANDA applicant must demonstrate that the active ingredient in its proposed generic drug product and the active ingredient in the RLD "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process[,] and that the stereochemistry characteristics and solid state forms of the drug have not been altered" (1992 Final Rule, 57 FR at 17958-17959). Instead, FDA adopted a more flexible approach. The Agency will "consider an active ingredient [in a generic drug product] to be the same as that of the reference listed drug if it meets the same standards for identity" (1992 Final Rule, 57 FR at 17959). In most cases, standards of identity are tests or specifications described in the *United States Pharmacopeia* (USP),

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[4] *Pfizer Inc. v. Shalala*, 1 F. Supp 2d 38, 46 (D.D.C. 1998), aff'd in part and rev'd in part, 182 F.3d 975 (D.C. Cir. 1999).

although FDA may prescribe "additional standards that are material to the ingredient's sameness" (1992 Final Rule, 57 FR at 17959).

D. Bioequivalence

A generic drug product is 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" (FD&C Act § 505(j)(8)(B)(i)). FDA regulations further set forth requirements for determining bioequivalence of an ANDA product. In particular, 21 CFR 320.1(e) specifies that two drug products are bioequivalent if there is an:

> absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[5]

The regulations specify various methods of establishing bioequivalence in generally descending order of accuracy, sensitivity, and reproducibility. These include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, in vitro studies, or "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence" (21 CFR 320.24(b)). FDA's decision to allow other approaches to show bioequivalence need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs...."[6] For example, FDA has been given "the discretion to determine whether in vitro, or in vivo bioequivalence studies, or both, are required for the approval of generic drugs under the abbreviated application process."[7] Thus, bioequivalence for different types of drug products can be shown in different ways. Ultimately, under the statute and regulations, the choice of bioequivalence study is based on the ability of the study design to compare the drug delivered by the two products at the particular site of action of the drug.

For systemically acting drug products, such as Soriatane, the concentration over time of either the active ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolite(s), in blood, plasma, serum, or other appropriate biological fluid is usually the most sensitive, accurate, and reliable indicator of bioavailability or bioequivalence (21 CFR 320.24(b)(1)(i)). The determination of bioequivalence usually rests on a pharmacokinetic comparison of drug and/or metabolite

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[5] See also 21 CFR 320.23(b).

[6] *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp 212, 218 (D.D.C. 1996) (quoting *Schering v. Sullivan Corp.*, 782 F. Supp 645, 651 (D.D.C. 1992), vacated as moot sub nom, *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993)).

[7] *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp at 217.

concentrations after administration of a single and identical dose of each drug product to healthy volunteers. Frequently, these pharmacokinetic measures include total exposure to the drug (area under the concentration versus time curve, referred to as AUC) and peak concentration of a drug (Cmax).

1. FDA's Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations

The moieties to be measured in biological fluids collected in bioavailability and bioequivalence studies are either the active drug ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolite(s) (21 CFR 320.24(b)(1)(i)). FDA's guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* (March 2003) (BA/BE Guidance)[8] generally recommends that bioequivalence studies measure only the parent drug. The basis for this recommendation is that the "concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination" (BA/BE Guidance at 18). The BA/BE Guidance describes the following two situations when this general recommendation (i.e., measuring the parent drug only) does not apply:

- Measuring a metabolite may be preferred when the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. In such cases, the metabolite data should be subject to a confidence interval approach for the bioequivalence demonstration.

- Measuring a metabolite may be preferred when a metabolite may be formed as a result of gut wall or other presystemic metabolism and the metabolite contributes meaningfully to safety and/or efficacy. In this instance, the metabolite should be measured in addition to the parent drug, but data regarding the metabolite are only used to provide supportive evidence of comparable therapeutic outcome; the metabolite data *should not* be subject to a confidence interval approach to demonstrate bioequivalence (BA/BE Guidance at 18).

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[8] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf.

2. FDA's Draft Guidance for Industry on Acitretin Bioequivalence

FDA has also issued draft guidance specific to bioequivalence studies for acitretin. The draft guidance on *Acitretin Bioequivalence* (May 2007) (Acitretin BE Draft Guidance)[9] recommends two studies using the 25-mg capsule: one fasting study, and one fed study. Each study should be a single-dose, two-way crossover study measuring all-trans acitretin and, because all-trans acitretin undergoes extensive pre-systemic metabolism, the 13-cis-acitretin metabolite in plasma. The studies should be conducted in normal, healthy males and females (excluding pregnant females). Bioequivalence is based on a two-one-sided t-test criterion with a 90 percent confidence interval of all-trans acitretin.

The metabolite 13-cis-acitretin should be measured for supportive evidence of comparable therapeutic outcome, but its pharmacokinetic measures are not used in the statistical analyses to determine bioequivalence.

II. DISCUSSION

A. Sameness

1. Degradation Product Profile

The Petition requests that FDA refrain from approving any ANDA referencing Soriatane as the RLD unless the ANDA has demonstrated that it is the "same as" Soriatane with respect to its degradation product profile. In support of this request, the Petition states that because it is not known whether the degradation products in Soriatane are teratogenic or might interact with ethanol to form teratogenic substances, any ANDA applicant must demonstrate that the degradation products in the generic version of the drug are qualified by comparison to Soriatane and do not exceed the maximum allowable levels for degradation products permitted for Soriatane (Petition at 5).

Degradation products are a type of impurity caused by the inherent instability of the drug molecule or by an interaction with an excipient. FDA agrees that stringent controls on impurities such as degradation products are essential to ensure the safety, efficacy, and quality of generic drug products, including acitretin capsules. However, as explained previously, a generic drug is not required to have an impurity profile identical to the RLD, nor is a generic drug required to be produced using the same manufacturing process as the RLD (see 1992 Final Rule 57 FR at 17958-17959). The chemistry, manufacturing, and controls (CMC) review for any ANDA referencing Soriatane will carefully evaluate the degradation product profile of the proposed generic acitretin capsule product, and will ensure that the levels of degradation products (including any degradation products that may result from the reaction of acitretin with residual alcohols

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[9] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM082349.pdf).

in the drug product and yield teratogenic etretinate or other esterified acitretin impurities) are appropriately qualified in accordance with the concepts documented in the guidance for industry, *ANDAs: Impurities in Drug Products* (November 2011),[10] and the guidance for industry, International Conference on Harmonization (ICH), *Q3B(R2) Impurities in New Drug Products* (July 2006).[11] These standard processes and criteria are adequate to ensure that degradation product levels in a generic acitretin product are appropriately identified and qualified as safe.

Therefore, the Petitioner's request that FDA not approve an ANDA referencing Soriatane unless its degradation product profile is identical to the RLD is denied.

2. Residual Solvent Specification

The Petition also requests that the Agency require ANDAs referencing Soriatane to be manufactured to a residual solvent specification no greater than that of Soriatane. In support of this request, the Petition indicates that in addition to the teratogen etretinate, which is formed from acitretin in the presence of ethanol, certain other esterified compounds form when acitretin is in the presence of their alcohols (i.e., methanol, ethanol, propane, butanol, or hexanol). The Petitioner argues that because the possibility of teratogenic effects from these other esterified compounds is not known, and because (like etretinate) the known teratogenic effects of these esterified compounds may be long-lasting and/or accumulate in adipose tissue, the levels of organic solvents in any generic acitretin must be demonstrated to be no greater than the levels detected in Soriatane (Petition at 5-6).

We do not agree that any ANDA referencing Soriatane must have residual solvent levels identical to that of Soriatane. FDA has determined that appropriate in-process and/or finished product limits applied to etretinate and any other possible esters that could form during the manufacturing process are sufficient to limit exposure to these solvents to safe levels.[12]

Just as with any other drug, we understand that impurities in this product, whether solvents or compounds created by interactions within the production process, can have known or unknown teratogenic or other toxic effects. FDA requires that the risk from impurities be controlled by standard procedures that will be applied here. In reviewing acitretin ANDAs, FDA will ensure that there are appropriate limits on residual ethanol

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[10] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072861.pdf.

[11] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf.

[12] Larsen F.G. et al., Acitretin is converted to etretinate only during concomitant alcohol intake, British Journal of Dermatology, 2000, 143: 1164-1169.

and other solvents, and on any other impurities that may be present.[13] This review will provide adequate assurance that the potential for exposure to residual solvents, and any potentially teratogenic compounds that may be produced because of interactions with solvents in the generic drug product, will be minimized.

Accordingly, the Petitioner's request that the Agency require that ANDAs referencing Soriatane manufacture the product to a residual solvent specification no greater than that of Soriatane is denied.

3. Polymorph Composition

The Petition requests that FDA refrain from approving any ANDA referencing Soriatane unless the ANDA has demonstrated that it has the same polymorph composition as Soriatane. In support of this request, the Petition states that because it is not known whether different polymorphs of acitretin might have different pharmacological or biochemical properties (potentially increasing the teratogenic risks associated with the product), any ANDA referencing Soriatane as the RLD must contain only the polymorph contained in Soriatane (polymorph A). Alternatively, the Petitioner requests that an ANDA sponsor referencing Soriatane be required to demonstrate that its acitretin product has biological activity (e.g., metabolite formation, interactions with other active moieties, effect of alcohol on etretinate formation) and structural stability equivalent to Soriatane (Petition at 5).

FDA does not agree that an ANDA sponsor referencing Soriatane as the RLD must demonstrate that its acitretin product: (1) contains only the same polymorph as Soriatane; or (2) has equivalent biological activity and structural stability. As described previously in this response, FDA has specifically rejected the argument that a generic applicant should be required to demonstrate that its drug exhibits the same physical and chemical characteristics as the RLD (1992 Final Rule, 57 FR at 17958-17959).

ANDA applicants must demonstrate bioequivalence to the RLD and sufficient stability of the generic product. Although the polymorphic form of a product may affect its performance characteristics and stability, using a polymorphic form of a drug substance that is different from that of the RLD does not preclude an ANDA applicant from formulating a product that is both bioequivalent to the RLD and sufficiently stable. FDA will carefully evaluate the acitretin polymorphs in ANDAs referencing Soriatane to ensure that there are appropriate controls in place.[14] In other words, FDA's standard

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[13] See, e.g., *USP 467, Residual Solvent General Chapter* (March 2007), available at http://www.usp.org/; guidance for industry, *ICH Q3C Impurities: Residual Solvents* (December 1997), available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128317.pdf.

[14] Guidance for industry on *ANDAs: Pharmaceutical Solid Polymorphism – Chemistry, Manufacturing, and Controls Information* (July 2007), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072866.pdf.

processes will ensure that any acitretin ANDA demonstrates acceptable product stability, dissolution, and other performance-related characteristics that are critical to the safety, efficacy, and quality of the generic acitretin product.

Accordingly, the Petitioner's request that an ANDA referencing Soriatane must demonstrate that its acitretin contains only the same polymorph as Soriatane or have equivalent biological activity and structural stability is denied.

B. Bioequivalence

The Petition requests that FDA require any ANDA applicant referencing Soriatane demonstrate that its drug product is bioequivalent to Soriatane based on certain pharmacokinetic standards that exceed those typically required, due to the risk profile for acitretin.

1. Active 13-cis Isomer

The Petition requests that FDA withhold approval of any ANDA for acitretin unless: (1) both acitretin and its major metabolite, the 13-cis isomer, meet the current bioequivalence criteria (80%-125%); and (2) both acitretin and the 13-cis isomer are assayed after achieving steady state plasma concentration through collection of samples (extending out to at least five half-lives) and an adequate washout period (of at least five half-lives or more than 10 days) between treatments in a crossover study to demonstrate bioequivalence (Petition at 6-8).

FDA does not agree that an ANDA sponsor must demonstrate bioequivalence of the 13-cis metabolite within the 80%-120% range. Instead, we recommend measuring the 13-cis-acitretin in plasma during bioequivalence studies as supportive evidence of comparable therapeutic outcome (as recommended in the BA/BE Guidance at 18; see also *Acitretin BE Draft Guidance* at 1). However, the metabolite data are not included in the statistical analyses for purposes of demonstrating bioequivalence; only the parent drug data are used for bioequivalence calculations. Accordingly, the Agency denies the Petitioner's request that any acitretin ANDA demonstrate that the 13-cis isomer of acitretin meets current bioequivalence criteria (80%-125%).

The Agency also does not agree that steady state (multiple dose) studies are needed to characterize either acitretin or 13-cis metabolite bioequivalence pharmacokinetics. As indicated above, FDA recommends two single-dose, two-way crossover studies (one fasting and one fed) using the 25-mg capsule and measuring all-trans acitretin and 13-cis-acitretin in the plasma of healthy adult males and females (excluding pregnant females). Single-dose studies are generally more sensitive in assessing release of the drug substance from the drug product into the systemic circulation than are multiple-dose, steady state studies. FDA believes that it is unlikely that two acitretin products found to

be bioequivalent after single-dose administration would be determined to be bioinequivalent after multiple-dose administration.[15]

Because acitretin is an oral drug with a long half-life, FDA recommends a nonreplicate, single-dose, crossover study with an adequate washout period and an adequate sample collection time to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance (approximately 2 to 3 days). Pharmacokinetic sampling over a 72-hour time period is sufficient because, by 72 hours after administration, the drug from the formulation is generally absorbed and distributed. Unabsorbed formulation (if any) is usually out of the body by this time. Therefore, any pharmacokinetic changes that may manifest after 72 hours generally reflect clearance changes unrelated to comparative product performance. The BA/BE Guidance does indicate that AUC truncation (e.g., at 72 hours) should be used cautiously for drugs with high intra-subject variability in distribution or clearance (BA/BE Guidance at 19), but the Petitioner has provided no evidence in the Petition, nor is the Agency aware of evidence that the intra-subject variability in distribution and clearance for acitretin is too large to use a 72-hour sampling time.

For the reasons discussed above, we deny the Petitioner's request that FDA withhold approval of any ANDA for acitretin unless the application demonstrates bioequivalence based on steady state studies with sample collection and washout times extended out to at least five-half lives or 10 days, as described by the Petitioner.

2. Other Metabolites

The Petition requests that, in addition to demonstrating bioequivalence of both acitretin and the 13-cis isomer of acitretin, a generic applicant should be required to demonstrate that no metabolites other than those detected in Soriatane are present, and that such metabolites are not present at a level exceeding the levels in Soriatane (Petition at 7).

It is not necessary for an ANDA for acitretin to demonstrate that no other metabolites are present, or to show bioequivalence of metabolites that the ANDA product and Soriatane have in common. As described in greater detail in the BA/BE Guidance, metabolite measurement is generally recommended where metabolites are known to form pre-systemically and where they contribute meaningfully to the safety and/or efficacy profile

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[15] See Ahmed A. El-Tahtawy et al., "Evaluation of Bioequivalence of Highly Variable Drugs Using Monte Carlo Simulations. I. Estimation of Rate and Absorption for Single and Multiple Dose Trials Using Cmax," *Pharmaceutical Research,* 11:1634-1641, 1995; Ahmed A. El-Tahtawy et al., "Comparison of Single and Multiple Dose Pharmacokinetics Using Clinical Bioequivalence Data and Monte Carlo Simulations," *Pharmaceutical Research,* 9:1330-1336, 1994; see also Henning H. Blume et al., "Practical Strategies and Design Advantages in Highly Variable Drug Studies: Multiple Dose and Replicate Administration Design," *Bio-International 2: Bioavailability, Bioequivalence and Pharmacokinetic Studies*, International Conference held in Munich, Germany, June 15-17, 1994, pp. 117-122, 1995 (multiple-dose testing dampens intra-subject variability in subjects administered propafenone).

of the drug product (BA/BE Guidance at 18). The Petitioner has not provided evidence that any other metabolites for acitretin are both formed pre-systemically and have significant biological activity (Petition at 7). Consequently, FDA does not recommend that any other metabolite be measured and the Petitioner's request with respect to bioequivalence of other metabolites is denied.

3. Presence of Food

The Petition requests that any ANDA for acitretin be required to demonstrate the bioequivalence of acitretin and the 13-cis isomer in the presence of food, because the effect of food on the bioavailability of acitretin is pronounced (Petition at 7).

FDA currently recommends both fasting and fed bioequivalence studies measuring both acitretin and the 13-cis isomer (Acitretin BE Draft Guidance at 1). Fed bioequivalence studies demonstrate comparable bioavailability between the test and reference products when co-administered with meals. A single-dose, two-period, two-treatment, two-sequence crossover study is recommended for fed bioequivalence studies. Accordingly, the Petitioner's request that FDA require an ANDA to demonstrate bioequivalence in the presence of food is granted. (We emphasize again, however, that only acitretin must be bioequivalent; the plasma concentration of the 13-cis-isomer should be measured as supportive evidence only and should not be included in the bioequivalence calculation).

4. Presence of Alcohol

The Petition requests that any ANDA for acitretin be required to demonstrate bioequivalence of acitretin and its major metabolite in the presence of alcohol, because when acitretin is combined with alcohol, there is potential for formation of etretinate, a retinoid with a longer half-life than acitretin (Petition at 8). The Petition also indicates that because of safety concerns related to the possible teratogenic effects associated with acitretin in the presence of alcohol, any generic applicant must be required to demonstrate a mean elimination half-life, AUC, and time to steady state for both acitretin and 13-cis-acitretin, to ensure that the ANDA product's safety is comparable to that of Soriatane (Petition at 6).

FDA does not agree that a separate bioequivalence study involving alcohol is necessary. If a generic product demonstrates bioequivalence using single-dose fasting and fed studies, additional studies generally are not required to demonstrate bioequivalence. The equivalence of the two formulations with respect to acitretin and similarity with respect to 13-cis-acitretin would ensure that the two products are similar with respect to other metabolites, if any, precluding the need for any studies specifically targeted to monitor such metabolites.

In addition, we note that a determination of bioequivalence of an ANDA for acitretin to Soriatane in the presence of alcohol is unnecessary given that the labeling for any ANDA product would, like the Soriatane label, contain explicit warnings and precautions

regarding alcohol use. Accordingly, the Petitioner's request regarding a demonstration of bioequivalence in the presence of alcohol is denied.

5. Elderly Subjects

The Petition requests that any ANDA for acitretin be required to demonstrate bioequivalence of acitretin and the 13-cis isomer in "elderly patients" due to potential differences in absorption or metabolism of acitretin as compared to other adults (Petition at 8).

FDA does not agree that a requirement to demonstrate bioequivalence of a generic acitretin to Soriatane in elderly subjects is necessary. First, it is not clear whether there is any difference in acitretin plasma concentrations in healthy, elderly subjects compared to healthy, younger subjects. The study cited by the Petitioner as evidence of a difference in concentration included only six younger adults and eight elderly subjects.[16] Given the small numbers, this study cannot adequately predict whether there are differences in acitretin concentration between the two populations.

Second, even if the elderly do experience higher plasma concentrations of acitretin, the general BA/BE Guidance refers to the adult population as 18 years or older, and recommends that bioequivalence studies be conducted in individuals representative of the general population, taking into account age, sex, and race. The BA/BE Guidance further recommends that the total number of subjects in the study provide adequate power to demonstrate bioequivalence. However, the Agency generally does not require demonstration of bioequivalence in specific subpopulations (e.g., the elderly), and, in fact, recommends against statistical analyses of bioequivalence in subpopulations, absent specific guidance to the contrary (BA/BE Guidance at 7-8).

In general, to demonstrate bioequivalence, FDA recommends using a crossover trial with healthy adults (BA/BE Guidance at 7-8). In a crossover trial, bioequivalence is evaluated by giving the same study subject the two products on two separate occasions, and comparing the pharmacokinetic properties of each product in each study subject. Each *pair* of pharmacokinetic data is then analyzed and statistically compared to determine whether the two products are bioequivalent. A cross-over design thus minimizes differences in pharmacokinetic measurements of the drug that may be due to intra-subject variability (e.g., age, race), because the pharmacokinetic profile of both products is measured in each study participant and compared intra-subject. If the two products show bioequivalence in a crossover study, it reflects that the rate and extent of drug release are comparable in vivo in healthy adults, because extraneous variables in study subjects have been minimized by the study design.

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[16] Labeling for Soriatane Capsules, CLINICAL PHARMACOLOGY, Special Populations (current label approved Nov. 25, 2011).

Under these circumstances, the products are also expected to behave similarly and comparably in subpopulations such as the elderly. In other words, if generic acitretin were bioequivalent to Soriatane in a healthy adult population, there is no evidence to suggest it would not be bioequivalent in a subpopulation such as the elderly, even if that meant that elderly subjects had higher plasma concentrations of both products than younger subjects. Bioequivalence testing compares the *relative* bioavailability of two products; it is not intended to assess the absolute bioavailability of a single product. Although the absolute bioavailability of Soriatane may or may not be different in a younger population than in an older population, the issue in an ANDA is whether a generic acitretin product will act in the same manner as Soriatane in both populations.

The Petitioner has not presented a sufficient basis to depart from these recommended bioequivalence assessment methods for acitretin. Therefore, the Petitioner's request with respect to demonstrating bioequivalence in elderly subjects is denied.

C. Soriatane *Do Your P.A.R.T. Program*

The Petition requests that FDA withhold approval of any ANDA referencing Soriatane until a "post-implementation assessment" of the effectiveness of the *Do Your P.A.R.T. Program* has been completed (Petition at 1). The Petitioner contends that the current *Do Your P.A.R.T. Program* is more rigorous than was required by the labeling in effect for Soriatane at the time the Petition was submitted in 2006 and that the approval of a generic acitretin under a less stringent label would undermine the *Do Your P.A.R.T. Program* (Petition at 9).

Furthermore, according to the Petitioner, even if the generic acitretin were required to follow the *Do Your P.A.R.T. Program*, the presence of a generic product on the market would create difficulties for the Petitioner in conducting its observational study to assess risk comprehension and compliance with the *Do Your P.A.R.T. Program* (Petition at 9). The Petition states that, because of the small patient population, a commercially marketed generic product would make it more difficult for the Petitioner to enroll patients in the Soriatane observational study and confound the interpretation of data from the study (because of generic substitution of products at the pharmacy level) (Petition at 9).

Finally, in the supplement to the Petition submitted in 2008, the Petitioner notes that it has designed a patient survey to evaluate the effectiveness of the *Do Your P.A.R.T. Program* (Petition Supplement at 4-5). The Petitioner argues that introduction of a generic acitretin product before FDA and the Petitioner have had an opportunity to evaluate the *Do Your P.A.R.T. Program* based on input from the patient surveys is "not in the interest of public health" (Petition Supplement at 5).

The Agency does not agree that it is necessary to delay approval of an ANDA until additional assessment of the Soriatane *Do Your P.A.R.T. Program* is completed. As the Petitioner notes, FDA worked extensively with the Petitioner to review and improve the *Do Your P.A.R.T. Program* in 2007 (Petition Supplement at 3). The current *Do Your*

P.A.R.T. Program is reflected in the current approved labeling for Soriatane. An approved ANDA referencing Soriatane must, with certain exceptions, have the "same labeling" and conditions of use as Soriatane. In addition, the ANDA will be required to have the same (or a comparable) program to ensure that the benefits of the drug outweigh its risks. The Petitioner's concern that a generic acitretin product would not be required to implement the current *Do Your P.A.R.T. Program* is therefore not supported.

In March 2011, the Agency released the Petitioner from its referenced postmarketing commitment to conduct an observational study to assess risk comprehension and compliance with pregnancy prevention requirements. Therefore, the Petitioner's concern that the availability of generic acitretin will interfere with the conduct of and interpretation of results from this study is moot.

Finally, there is no reason to delay approval of a generic product simply to await results from the Petitioner's patient survey on the effectiveness of the current *Do Your P.A.R.T. Program*. Stiefel has had more than 3 years to gather and analyze data from the patient survey. Moreover, if FDA determines that the conditions of approval of Soriatane are no longer adequate to ensure that its benefits outweigh the risks, FDA can require changes to the characteristics and labeling of the RLD and any ANDAs referencing the RLD (see 21 CFR 314.94(a)). Thus, should ongoing review of Soriatane, including the review of information provided in patient surveys, cause FDA to reconsider the conditions of approval or require changes to the labeling of Soriatane, the ANDA would also be subject to those changes. The Petitioner has not provided sufficient grounds for FDA to depart from this standard process or to require completion of the assessment of the *Do Your P.A.R.T. Program* before approving an ANDA referencing Soriatane. Therefore, the Petitioner's request in this respect is denied.

III. CONCLUSION

For the reasons discussed above, the Petition requesting that FDA take certain actions with respect to ANDAs referencing Soriatane is granted in part and denied in part.

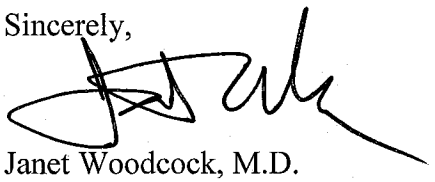
- We do not agree that an ANDA referencing Soriatane as the RLD must demonstrate, in the manner described in the Petition, that it is the "same" as Soriatane with respect to its degradation product profile, residual solvent specification, and polymorph composition. The Petitioner's requests in this regard are denied.

- We agree that bioequivalence of an acitretin ANDA to Soriatane must be demonstrated with respect to acitretin in both fasted and fed subjects and that the major metabolite of acitretin, 13-cis-acitretin, should be measured as supportive evidence of bioequivalence. However, the Petitioner's requests with respect to demonstrating bioequivalence: (1) of the 13-cis-isomer of acitretin; (2) with multiple-dose, steady-state studies of extended

duration; (3) of other metabolites; (4) in the presence of alcohol; and (5) in the elderly, are denied.

- We do not agree that an assessment of the *Do Your P.A.R.T. Program* for Soriatane must be completed before approving an ANDA that references Soriatane and that will incorporate a comparable program to prevent fetal exposure to Soriatane. The Petitioner's request in this regard is denied.

Sincerely,



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