CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202428Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202428 SUPPL # HFD # 540

Trade Name Fabior

Generic Name (tazarotene) Foam, 0.1%

Applicant Name Stiefel Laboratories, Inc.

Approval Date, If Known May 11, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-600 tazarotene gel

NDA# 21-184 tazarotene cream

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1 – W0260-301 – Demonstrate superiority of tazarotene foam versus vehicle

Investigation #2 – W0260-302 – Demonstrate superiority of tazarotene foam versus vehicle

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 (W0260-301) YES ☐ NO ☒

Investigation #2 (W0260-302) YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 (W0260-301) YES ☐ NO ☒

Investigation #2 (W0260-302) YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 – W0260-301 – Demonstrate superiority of tazarotene foam versus vehicle

Investigation #2 – W0260-302 – Demonstrate superiority of tazarotene foam versus vehicle

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 (W0260-301)

IND # 105564 YES ☒ NO ☐

Explain:

Investigation #2 (W0260-302)

IND # 105564 YES ☒ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ NO ☐

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Cristina Attinello
Title: Regulatory Project Manager
Date: 5-11-12

Name of Division Director signing form: Susan Walker
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CRISTINA Petruccelli Attinello
05/11/2012

GORDANA DIGLISIC
05/11/2012

SUSAN J WALKER
05/11/2012

DEBARMENT CERTIFICATION

Stiefel, a GSK company, certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 202428).

Devon Allen

29 JUN 2011

Devon L. Allen, MS, RAC
Sr. Director, Global Clinical Development
Stiefel, a GSK company

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202428		If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Fabior Established/Proper Name: tazarotene 0.1% Dosage Form: Foam		Applicant: Stiefel Laboratories Agent for Applicant (if applicable): n/a
RPM: Cristina Attinello		Division: DDDP

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 5/29/12	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	☒ Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AP 5-11-12
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	5-7-12
• Original applicant-proposed labeling	7-29-11
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	5-7-12
• Original applicant-proposed labeling	7-29-11
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	5-7-12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	2-2-12, 5-2-12 2-2-12, 5-1-12
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 10-4-11 ☒ DMEPA 12-6-11, 5-4-12, 5-8-12 ☒ DMPP/PLT (DRISK) 3-7-12 ☒ ODPD (DDMAC) 3-15-12 ☒ SEALD 5-1-12
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	9-13-11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 5-11-12
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 2/15/12 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	☒ Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 6-15-11
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ 5-11-12
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 4-11-12
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	4-11-12
• Clinical review(s) *(indicate date for each review)*	3-30-12, 5-8-12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	3-30-12, pg. 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[6] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☒ 3-14-12
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 11-28-11, 3-12-12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 2-29-12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☒ 3-19-12, 5-4-12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	3-19-12, pg. 104
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 5-3-12 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/

CRISTINA Petruccelli Attinello
05/11/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202428

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Stiefel Laboratories, Inc.
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

ATTENTION: Brandy L. Muchanic
Associate Director, Regulatory Affairs

Dear Ms. Muchanic:

Please refer to your New Drug Application (NDA) dated July 29, 2011, received July 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tazarotene Foam, 0.1%.

We also refer to your February15, 2012, correspondence, received February15, 2012, requesting review of your proposed proprietary name, Fabior. We have completed our review of the proposed proprietary name, Fabior and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your February 15, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Cristina Attinello at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/02/2012

Attinello, Cristina

From: Attinello, Cristina
Sent: Wednesday, February 15, 2012 1:07 PM
To: 'Brandy Muchanic'
Subject: Draft Label for NDA 202428

Hi Brandy,

I note the following in the draft label for the above product, under Section 7: Drug Interactions:

(b) (4)

To what data are you referring? Can you provide the source of the data or a rationale? Please respond by 2-21-12 via email, but also submit your response officially to the NDA.

Thanks,

Cristina Petruccelli Attinello, MPH
Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology & Dental Products
White Oak, Bldg. 22, Room 5181
Phone: 301-796-3986
Fax: 301-796-9895

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/s/

CRISTINA Petruccelli Attinello
02/15/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202428 **INFORMATION REQUEST**

Stiefel Laboratories, Inc.
Attention: Brandy L. Muchanic
Manager, Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (tazarotene) Foam, 0.1%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by February 21, 2011.

- Remove the word "(b) (4) from the Description section (sec. #11) of the package insert (drug product is described as "aqueous-based (b) (4) foam vehicle"). Alternatively, provide information demonstrating that the drug product continues to be an (b) (4) inside the aerosol can after filling and upon storage.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Cristina Attinello, Regulatory Project Manager the Office of New Drugs (Cristina.Attinello@fda.hhs.gov).

If you have any questions regarding this CMC letter, please contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
02/06/2012
Chief, Branch IV

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 202428

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Stiefel Laboratories, Inc.
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

ATTENTION: Brandy L. Muchanic
Associate Director, Regulatory Affairs

Dear Ms. Muchanic:

Please refer to your New Drug Application (NDA) dated July 29, 2011, received July 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tazarotene Foam 0.1%.

We also refer to your November 15, 2011, correspondence, received November 15, 2011, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

1 page has been withheld in full as B(4) CCI/TS immediately following this page

We note that you have proposed an alternate proprietary name in your submission dated November 15, 2011. In order to initiate the review of the alternate proprietary name, Fabior, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Cristina Attinello at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202428 **INFORMATION REQUEST**

Stiefel Laboratories, Inc.
Attention: Brandy L. Muchanic
Manager, Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (tazarotene) Foam, 0.1%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by January 20, 2011.

1. Address the following issues which concern the proposed analytical procedure for identification and assay of tazarotene and related substances in tazarotene drug substance.

   - Clarify what the composition of the mobile phase gradient is in this analytical procedure. There are two different solvents defined as A/B and C/D, but the gradient is expressed as "%A", "%B", etc. A and B, etc. are not defined.

   - Provide a sequence of injections for this analytical procedure.

   - Describe how Quantitation Limits for (b) (4) were determined for this analytical procedure. Data submitted indicates that recovery for these three compounds was evaluated at the QL, but no information is provided regarding how the QL was determined.

   - Provide a specific list of parameters that were adjusted in the evaluation of Robustness for this analytical procedure. In addition, re-submit figures 7, 8, and 9 in sec. S.4.3 of the submission (Validation of Analytical Procedures), which exhibits the data generated to demonstrate Robustness. The notations on the figures currently in the submission are distorted and unclear and cannot be read.

(b) (4)

[redacted]

3. In the description of Process for Analysis for the analytical procedure for Determination of [redacted] Impurities in Tazarotene Foam, and for the analytical procedure for Determination of Sorbic Acid Content in Tazarotene Foam, a statement should be added indicating how many injections of each sample preparation should be made. At least three (3) such injections are recommended.

4. Explain why [redacted] is listed among the Unrelated Substances that potentially would be determined using the analytical procedure for Determination of Sorbic Acid Content in Tazarotene Foam. [redacted] was not identified as a process impurity, drug substance degradation product, or potential extractable from the packaging.

5. For both the release and stability specifications for the drug product, change the acceptance criterion for Appearance from [redacted] to "Upon collapse, the resulting liquid is white to off-white in color".

6. Submit a certificate of analysis from your suppliers for the reference standards for tazarotene and sorbic acid.

7. Re-write your stability commitments for Tazarotene Foam so that they include the names of each specified impurity [redacted], Any Unidentified Impurity, Total Impurities, Appearance, and Collapsed Foam Appearance. Currently, the stability commitments contain references to "appearance" and "drug related impurities", which is not considered specific.

8. The proposed expiration dating period of [redacted] months is not acceptable because [redacted] At this time, an 18-month expiration period is considered more appropriate until it is demonstrated that acceptance criteria are not breached after storage longer than 18 months.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Cristina Attinello, Regulatory Project Manager the Office of New Drugs (Cristina.Attinello@fda.hhs.gov).

If you have any questions regarding this CMC letter, please contact Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
12/20/2011
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202428

INFORMATION REQUEST

Stiefel Laboratories, Inc.
Attention: Brandy L. Muchanic
Manager, Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (tazarotene) Foam, 0.1%.

We are reviewing the nonclinical section of your submission and have the following information request. We request a prompt written response by November 25, 2011 in order to continue our evaluation of your NDA.

The animal multiples of human exposure in Section 13.1 of the (tazarotene) Foam, 0.1% label were calculated based on (b) (4) instead of from AUC data available from the clinical pharmacokinetic study conducted with (tazarotene) Foam, 0.1%. You should provide an updated (tazarotene) Foam, 0.1% label with the animal multiples of human exposure contained in Section 13.1 calculated based on the AUC data available from the clinical pharmacokinetic study described in Section 12.3 of the (tazarotene) Foam, 0.1% label. You should also provide the systemic exposure levels (i.e., AUC values) for the animal studies contained in Section 13.1 that you used to calculate the animal multiples of human exposure.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GORDANA DIGLISIC
11/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202428

FILING COMMUNICATION

Stiefel Laboratories, Inc.
Attention: Brandy L. Muchanic
Manager, Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your New Drug Application (NDA) dated July 29, 2011, received July 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (tazarotene) Foam, 0.1%.

We also refer to your amendment dated August 29, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 11, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have the following information requests:

1. Submit report # MC09B-0176, titled "Evaluation of extended stability of tazarotene and tazarotenic acid in human plasma using high-performance liquid chromatography with mass spectrometric detection." This report is needed to support your statement within the

bioanalytical report for study W0260-105 that the long-term storage stability has been demonstrated for 196 and 204 days for tazarotene and tazarotenic acid, respectively.

2. We note that you have not proposed a proprietary name for review. Per your telephone message of September 13, 2011 to Janet Anderson, Project Manager in the Office of Surveillance and Epidemiology, we note your intention to have a proprietary name for this product. A separate request for proposed proprietary name review should be submitted as an amendment to this NDA. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

   The review time frame for proprietary name submissions to NDAs and supplemental NDAs is 90 days from date of receipt of the proprietary name submission.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. In Highlights, the Initial U.S. Approval statement must be placed immediately beneath the product title. Delete the (b) (4) between "Initial U.S. Approval…" and the product title.

2. In Highlights, under Contraindications, revise the cross reference to read "Pregnancy (4)".

3. In Highlights, under Adverse Reactions, use the term "adverse reactions." Do not include a (b) (4) for each adverse reaction. Revise this section to include criteria used to determine inclusion of adverse reactions (incidence rate greater than X%).

4. In Highlights, under Drug Interactions, add a cross reference.

5. In Highlights, revise the Patient Counseling Information Statement to **"See 17 for Patient Counseling Information and FDA-approved patient labeling."**

6. In the Table of Contents, delete the (b) (4)

7. Insert a horizontal line to separate the Table of Contents from the Full Prescribing Information.

8. In Section 17, Patient Counseling Information, revise the statement to read *"[See FDA-approved patient labeling (Patient Information).]."*

We request that you resubmit labeling that addresses these issues by October 21, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

SUSAN J WALKER
10/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 050803, NDA 021026, NDA 021738
NDA 021978, NDA 022013, NDA 022484
NDA 022563, (b) (4) NDA 202428

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Stiefel Laboratories, Inc.
Attention: Jeffrey S Troughton, MS, RAC
Associate Director, Regulatory Affairs
20 TW Alexander Drive
Research Triangle Park, NC 27709

Dear Mr. Troughton:

Please refer to your New Drug Applications (NDA) submitted under sections 505(b) and 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for

NDA 050803	Veltin (clindamycin phosphate and tretinoin) Gel, 1.2%/0.025%
NDA 021026	Vusion (0.25% miconazole nitrate, 15% zinc oxide, and 81.35% white petrolatum) Ointment
NDA 021738	Extina® (ketoconazole) Foam, 2%
NDA 021978	Verdeso® (desonide) Foam, 0.05%
NDA 022013	Olux-E (clobetasol priopionate) Foam, 0.05%
NDA 022484	Onmel (itraconazole) Film-Coated Tablets, 200mg
NDA 022563	Sorilux (calcipotriene) Foam, 0.005%
(b) (4)	
NDA 202428	(tazarotene) Foam, 0.1%

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria,

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Barbara Gould, Chief, Project Staff Management, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BARBARA J GOULD
09/15/2011
p.p. DIVISION DIRECTOR Susan J. Walker

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202428

NDA ACKNOWLEDGMENT

Stiefel Laboratories, Inc.
Attention: Salisa Hauptmann, MPH
VP Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Hauptmann:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (tazarotene) Foam, 0.1%

Date of Application: July 29, 2011

Date of Receipt: July 29, 2011

Our Reference Number: NDA 202428

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 27, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Cristina Attinello, MPH
Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

CRISTINA Petruccelli Attinello
08/09/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105564

MEETING MINUTES

Stiefel Laboratories, Inc.
Attention: Brandy Muchanic
Manager, Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazarotene foam, 0.1%.

We also refer to the teleconference between representatives of your firm and the FDA on June 15, 2011. The purpose of the meeting was to discuss information needed to support an NDA submission for tazarotene foam, 0.1%.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Meeting Minutes
Attachment 1
Attachment 2

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 15, 2011, 9AM
Meeting Location: Teleconference

Application Number: IND 105564
Product Name: tazarotene foam, 0.1%
Indication: for the topical treatment of acne vulgaris
Sponsor/Applicant Name: Stiefel Laboratories, Inc.

Meeting Chair: Gordana Diglisic, M.D.
Meeting Recorder: Cristina Attinello, M.P.H.

FDA ATTENDEES

Susan Walker, M.D., F.A.A.D., Director, DDDP
Gordana Diglisic, M.D., Clinical Team Leader, DDDP
Denise Cook, M.D., Clinical Reviewer, DDDP
Jiaqin Yao, Ph.D., Pharmacology Reviewer, DDDP
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Tapash Ghosh, Ph.D., Pharmacologist, OPS/ONDQA
Roy Blay, Ph.D., Regulatory Director, OC/DSI/GCPBII
Douglas Warfield, Regulatory Information Specialist, OPI/OBI/DRRS
Dhananjay Chhatre, Operations Research Analyst, OPI/OBI/DRRS
Cristina Petruccelli Attinello, M.P.H., Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Michele Larussa, Director, Regulatory Affairs Head of Dermatology, Allergan
Frederick Beddingfeld, M.D., V.P., Clinical Dermatology, Allergan
Salisa Hauptmann, M.Ph., V.P., Regulatory Affairs, Stiefel
Brandy Muchanic, Manager, Regulatory Affairs, Stiefel
Tom Brundage, M.S., Director, Data Sciences, Stiefel
Matthew Kersey, Ph.D. ,Director, Analytical Sciences, Stiefel
Gary Lawrence, Manager, CMC, Stiefel
James Lee, M.D., V.P., Project Physician, Clinical Dermatology, Stiefel
Alessandra Alio, M.D., Clinical Manager, Stiefel

Purpose of the Meeting:
The purpose of the meeting is to discuss information needed to support an NDA submission for tazarotene foam, 0.1%.

Regulatory Correspondence History

We have sent the following correspondences:

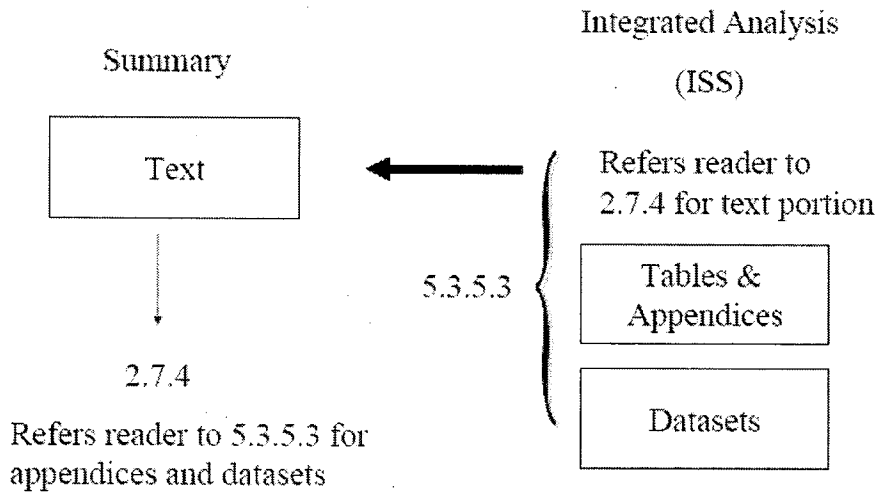
- December 28, 2010: Biostatistics Advice Letter
- August 3, 2010: Nonclinical Advice Letter
- May 25, 2010: Nonclinical Advice Letter
- December 4, 2009: Multidiscipline Advice Letter

Please consider the advice communicated in the above correspondences as you prepare the NDA submission.

Regulatory

Question 10:
In the eCTD structure of the planned NDA, Stiefel intends to incorporate the text for the Integrated Summary of Safety and Integrated Summary of Efficacy into the Clinical Summary in Module 2 and to include related tables, appendices, and datasets in Module 5. This approach is consistent with FDA's draft *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*. The figure below, taken from the draft guidance, provides an illustration:

Figure 4



Does the Agency agree with this approach?

Response:
The above-referenced guidance states that situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2, are rare but can occur if the application is small and consists of a single study or a number of small studies. Based on your description of your development program it does not appear that your application would meet the criteria of a 'small' application suitable for the exception. We recommend using the main approach discussed in the guidance where complete ISS and ISE documents are presented in Module 5 and briefer summary documents are presented in Module 2.

Meeting Discussion:
The sponsor stated that the ISS and ISE information submitted in Module 2 would be under 400 pages and would be consistent with the guidance. The Agency agreed that this would be acceptable.

Question 11:
Stiefel will submit a request for a partial waiver from pediatric studies in patients less than 12 years of age due to the low prevalence of acne vulgaris in this population. A brief summary of the justification is provided Section 10.2.5.

Does the Agency agree with this approach?

Response:
Yes, the waiver should be submitted with a justification.

Chemistry, Manufacturing and Controls (CMC)

Question 7:
The drug product used in the clinical program for tazarotene foam was manufactured at DPT Laboratories Ltd, San Antonio, Texas (DPT). However, to support commercial launch and production, Stiefel intends to qualify (b) (4) (b) (4) as the primary manufacturer. The planned NDA will list both sites as qualified to manufacture commercial tazarotene foam product. At least 12 months of long-term stability data on finished drug product made from 3 bulk batches manufactured at DPT will be provided in the NDA. Also, at least 3 months of accelerated stability data on drug product from 3 bulk batches manufactured at (b) (4) will be provided in the NDA. Details of the qualification strategy for (b) (4) are provided in Section 10.3.3.

A) Does the Agency agree that the stability data on product manufactured at DPT is sufficient to support the filing of the tazarotene foam NDA?

B) Does the Agency agree that the strategy to support qualification of (b) (4) as the primary commercial production site is sufficient?

Response:

(A) Yes, we agree that the data on product manufactured at DPT is sufficient to support the filing of the NDA.

(B) No, we do not agree. [redacted]

Meeting Discussion:

[redacted]

Question 8:

The current drug product specification for tazarotene foam is provided in Table 15 and lists the test attributes proposed for the drug product. Per 04 December 2009 correspondence from the Agency, acceptance criteria for several of the test attributes – including related substances, specified and unspecified impurities, [redacted] delivered amount, pressure and pH – will be either established or [redacted] as appropriate in the NDA based upon stability data that is currently being generated for registration batches manufactured at DPT and [redacted] Refer to Section 10.3.4 for more information.

Does the Agency agree that the test attributes listed in the proposed drug product specification (see Table 15) are sufficient?

Response:

Yes, we agree that they are sufficient to support the filing of the NDA.

Additional CMC Comments:

1. The acceptance criterion for the test on Dispensing Rate should be a range rather than a limit.

2. The acceptance criterion for the test on Delivered Amount should not be lower than the labeled amount.

Pharmacology/Toxicology

Question 1:
To support the overall nonclinical package for tazarotene foam, Stiefel intends to rely on the Agency's previous findings of safety for Tazorac Gel by incorporating by reference the nonclinical data in NDA 020600. Stiefel has reviewed the nonclinical safety data in NDA 020600, which includes single-dose toxicity, repeat-dose toxicity, genotoxicity, reproductive and developmental toxicity, carcinogenicity, and photococarcinogenicity studies, and determined that it adequately supports the tazarotene foam development program. The specific nonclinical studies being referenced from NDA 020600 are summarized in Appendix 1.

In addition to the nonclinical studies in NDA 020600 that are being referenced, Stiefel has conducted the following studies to evaluate the safety of tazarotene in the foam formulation:

- *In vitro* human skin penetration study (Section 10.1.2.1)
- 28-day dermal toxicity study in rats (Section 10.1.2.2)
- 28-day dermal toxicity study in minipigs (Section 10.1.2.4)
- 90-day dermal toxicity study in rats (Section 10.1.2.3)
- Acute ocular irritation study in rabbits (Section 10.1.2.5)
- Acute dermal irritation study in rabbits (Section 10.1.2.6)
- Local lymph node assay (Section 10.1.2.7)

The repeat-dose toxicity studies included Tazorac Gel, 0.1% as a comparator.

In addition, Stiefel conducted a comparative bioavailability (BA) study to establish a clinical bridge between tazarotene foam and Tazorac Gel, 0.1% that will support the ability to reference the information in NDA 020600. Refer to Section 10.2.1 for a summary of the study. The BA study showed that the mean plasma concentrations of tazarotene and tazarotenic acid were lower in the tazarotene foam group compared with the Tazorac Gel, 0.1% group; therefore, systemic exposure to the active ingredient from administration of tazarotene foam is not higher than from administration of Tazorac Gel, 0.1%.

A) Does the Agency agree that an adequate clinical bridge has been established, thereby allowing reference to nonclinical safety data from Tazorac Gel NDA 020600?

Response:
An adequate clinical bridge between tazarotene foam (0.1%) and Tazorac Gel, 0.1% would not be needed since you have obtained full right of reference for NDA 020600 (Tazorac Gel) and NDA 021184 (Tazorac Cream) from Allergan, Inc. The nonclinical safety data available for Tazorac Gel and Tazorac Cream can be used to support a 505(b)(1) NDA submission for tazarotene foam.

B) Does the Agency agree that the nonclinical safety information in NDA 020600 may be used to support filing of the nonclinical package for the tazarotene foam NDA?

Response:
Since you have obtained full right of reference to NDA 020600 for Tazorac Gel, then the nonclinical safety information in NDA 020600 can be used to support submission of the nonclinical package for the tazarotene foam NDA.

C) Does the Agency agree that the nonclinical studies performed by Stiefel, in addition to those being incorporated by reference, are sufficient to meet the nonclinical requirements for an NDA submission?

Response:
It appears that the nonclinical studies performed by Stiefel, in addition to those being incorporated by reference, are sufficient to meet the nonclinical requirements for an NDA submission. However, the adequacy of the 90-day repeat-dose dermal toxicity study in rats will be determined after review of the final study report.

Clinical Pharmacology/Biopharmaceutics

There are no Clinical Pharmacology/Biopharmaceutics questions proposed in this section of the briefing package, however; we have the following comments:

- Confirm that the 7 clinical trials listed in Table 2 of the May 12, 2011 briefing package were conducted with the to-be-marketed formulation of tazarotene foam, 0.1%. The NDA should clearly state the formulation used for each clinical trial.

- The NDA should address absorption, distribution, metabolism, and excretion of tazarotene foam, 0.1% as well as potential for drug-drug interactions. This information may be obtained from studies conducted by you or from the literature.

- Provide in the NDA raw pharmacokinetic data for study W0260-105 in SAS transport format (.XPT).

- Submit in the NDA bioanalysis reports and bioanalytical method validation reports for study W0260-105.

Clinical/Biostatistics

Question 2A:
To demonstrate the clinical safety of tazarotene foam for the topical treatment of acne, Stiefel has conducted 4 dermal safety studies (cumulative irritation, contact sensitization, phototoxicity, and photoallergy) in healthy subjects, a comparative bioavailability study in subjects with acne, and two Phase 3 clinical safety and efficacy studies in subjects with acne. Details of the studies are presented in Section 10.2.

Results from the 4 dermal safety studies with tazarotene foam were consistent with those expected for a topical retinoid (eg, Tazorac Gel, 0.1%).

A) Does the Agency agree that the 4 dermal safety studies meet the clinical safety requirements to support filing of the clinical safety package in the tazarotene foam NDA?

Response:
Dermal safety studies should include contact irritancy, contact sensitization, phototoxicity and photoallergy studies to be performed with the to-be-marketed drug product. It appears from the May 12, 2011 briefing package that you have performed four dermal safety trials. The performance of those trials does support the filing of the clinical safety package under an NDA for tazarotene foam.

Question 2B:
The comparative bioavailability study showed that the mean plasma concentrations of tazarotene and tazarotenic acid were lower in the tazarotene foam group compared with the Tazorac Gel, 0.1% group and, therefore, established a clinical bridge between tazarotene foam and Tazorac Gel, 0.1%.

B) Does the Agency agree that the bioavailability study supports filing of the clinical safety package in the tazarotene foam NDA?

Response:
Yes, this supports filing.

Question 2C:
In the two Phase 3 studies, the majority of treatment-related adverse events were mild to moderate application site reactions, which is not unexpected for a topical retinoid.

C) Does the Agency agree that the two Phase 3 studies complete the clinical safety package for filing in the tazarotene foam NDA?

Response:
The Agency does agree, provided that you have full right of reference to NDA 020600 and NDA 021184, that the two Phase 3 studies with more than 700 subjects on tazarotene foam complete the clinical safety package for filing the tazarotene foam NDA. Evidence of your right of reference should be submitted with the NDA.

Question 3:
Two Phase 3 clinical studies in subjects with acne were performed to determine the efficacy of tazarotene foam in the treatment of acne vulgaris. Both studies met all primary endpoints, thereby demonstrating efficacy. Study results are presented in Section 10.2.

Does the Agency agree that the two Phase 3 studies are adequate to support filing of the tazarotene foam NDA?

Response:
Two Phase 3 trials described in the briefing package appear to be adequate to support the filing of the NDA. The trials are double-blinded, vehicle controlled with what appears to be an adequate number of subjects with appropriate efficacy endpoints as discussed in communications between the Agency and the sponsor.

Question 4:
Stiefel plans to provide subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the studies conducted with tazarotene foam. In addition, Stiefel will provide case report forms (CRFs) in Module 5, Section 5.3.7 for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason.

Does the Agency agree with this approach?

Response:
FDA does not use 537-crf-ipl. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Note that you should just have one stf per study with the appropriate file tags for all of that study's components, including the CRFs.

In addition, please provide the following:

1. Electronic links for:
   a. all serious AEs
   b. all severe AEs
   c. all patients discontinued regardless of reason
   d. all deaths

2. CRFs should be referenced under the study in which it belongs and tagged as "case-report-forms" in that study's stf.xml file.

3. CRFs that are not submitted should be readily available upon request.

Question 5:
Raw datasets (Case Report Tabulations) and analysis datasets, including define.pdf documentation, will be provided for the pivotal Phase 3 clinical studies and integrated

analyses of safety and efficacy. The raw datasets will be modeled in accordance with the CDISC Study Data Tabulation Model Implementation Guide: Human Clinical Trials v1.2, which comprises Version 3.1.2 of the Submission Data Standards. The analysis data sets will be modeled in accordance with the CDISC Analysis Data Model, Version 2.0. Details of the analysis data sets are provided in Section 10.2.4.

Does the Agency agree with this approach?

Response:
The proposal to submit raw datasets in accordance with SDTM and analysis data sets in accordance with ADaM for the Phase 3 studies, ISS, and ISE is acceptable. For additional information on CDER recommendations refer to the *CDER Common Data Standards Issues Document* (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM254113.pdf). In particular note the following:

1. The electronic datasets for clinical studies in should be submitted in SAS transport form (.xpt).

2. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified.

3. The analysis dataset documentation (define.pdf file) should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

4. Definition files for raw datasets modeled according to CDISC/SDTM IG and standards should be submitted as .xml file types (define.xml). Refer to CDISC's Define.XML page for assistance/guidance related to creating define.xml files for CDISC/SDTM data. Also, for ease of viewing by the reviewer and printing, submit corresponding define.pdf files in addition to the define.xml.
5. Statistical programs for non-standard analyses (e.g. ordinary least squares multiple regression model imputation) should be submitted.

6. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

You are encouraged to submit sample electronic datasets to the Agency for testing prior to your NDA submission.

Meeting Discussion:
The Agency described the process for obtaining a test submission number and process for the submission of sample SDTM datasets for analysis and review prior to submission of the NDA.

To arrange a test submission, please refer to the *Submit a Sample eCTD to the FDA* Website for guidance on sending a test submission. The sponsor may request dataset(s) analysis for CDISC specifications compliance as part of a test submission. Please note that the scope of test submissions is limited. The Agency will give priority to testing electronic submissions made in preparation for actual submission for review. If requested, the Agency will provide reports of the dataset(s) CDISC compliance analyses of the eCTD test submission processing to the submitter. Please notify the Agency if you want feedback for SDTM formatted datasets submitted by sending an email to esub@fda.hhs.gov or cder-edata@fda.hhs.gov.

In addition to the electronic data sets, the NDA submission should include the following items for the Phase 3 studies:

- Study protocols including the statistical analysis plan, all protocol amendments (with dates), and an annotated copy of the Case Report Form (which maps variables in the datasets to the CRF).

- The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

Question 6:
Stiefel intends to prepare and submit integrated analyses of efficacy and safety and clinical summaries of efficacy and safety as follows:

- The integrated analysis of efficacy and the integrated analysis of safety will be based on pooled data from the two Phase 3 studies, in which subjects were exposed to tazarotene foam once daily for 12 weeks.

  A) Does the Agency agree with this approach?

- The clinical summary of safety will summarize the integrated analysis of safety as well as provide comprehensive discussions of safety across the entire clinical program, including the dermal safety, bioavailability, and Phase 3 studies.

  B) Does the Agency agree with this approach?

Response:
A) Yes, the Agency does agree with this approach.

B) Yes, the Agency does agree with this approach. In addition, you should provide the following:

a. Adverse event tables ≥ 1% regardless of causality.
b. Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) ≥ 1%.
c. Line listings for all safety data.
d. If the foam formulation is approved in any other jurisdiction, provide a world-wide safety update in addition to the 120 day safety update for the Phase 3 trials.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.

2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).

3. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

4. You are reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

5. Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

   Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

6. To facilitate our inspectional process, the Division of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single*

location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility. Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Attachment 1

This document is enclosed for additional content and format considerations as you prepare the NDA submission.

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:

    a. Site number
    b. Principal investigator
    c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
    d. Current Location of Principle Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

    a. Number of subjects screened for each site by site
    b. Number of subjects randomized for each site by site
    c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

    a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    b. Name, address and contact information of all CROs used in the conduct of the clinical trials
    c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
    d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

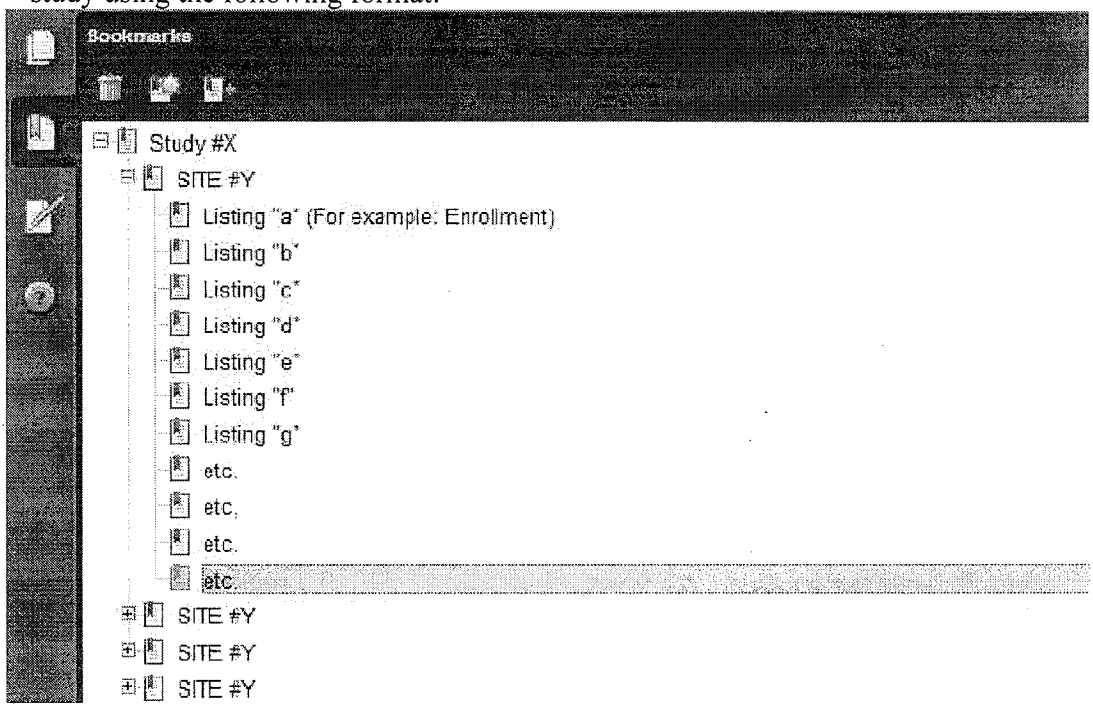
4. For each pivotal trial provide a sample annotated Case Report Form.
5. For each pivotal trial provide original protocol and all amendments.

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:

a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
b. Subject listing for treatment assignment (randomization)
c. Subject listing of drop-outs and subjects that discontinued with date and reason
d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, that includes requested data for each pivotal study submitted in your application.

Attachment 2

This document is enclosed for additional content and format considerations as you prepare the NDA submission.

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR".

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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/s/

GORDANA DIGLISIC
06/20/2011
Signing for Dr. Susan Walker, Division Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105564

ADVICE/INFORMATION REQUEST

Stiefel Laboratories, Inc.
Attention: Brandy Muchanic
Manager, Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazarotene foam, 0.1%.

We also refer to your amendment dated July 6, 2010 containing a statistical analysis plan.

We have the following comments and recommendations regarding your requests for information on amendment two for Protocol 301, Protocol 302, and the associated statistical analysis plan:

1. The protocol and statistical analysis plan contain insufficient detail about how Holm's method will be applied to the change in lesion count endpoints. This proposal appears to treat each of the lesion types as separately measured variables; however, among the lesion count variables, total lesions is structurally defined as non-inflammatory + inflammatory. It should be noted that if there is improvement in both inflammatory and non-inflammatory lesion counts, then this would imply improvement in the total lesion counts. In order to control the type I error it is important to clarify the hypotheses that are being tested in a particular approach. An approach for controlling multiplicity that does not take into account the structural relationship among the endpoints will likely be overly conservative. Clarify the hypotheses and how the chosen method will be applied.

2. The two analyses on the ISGA are likely to have substantial overlap. Although listed separately in the Agency's previous comments, to simplify the endpoint structure, the concept of two grade reduction as well as achieving a score of 0 or 1 at the end of the study could be combined into a single ISGA endpoint with success defined as 0 or 1 with two grades reduction. It should also be noted that because the inclusion criteria specify that the baseline ISGA will be 3 or higher, that in this case the combined endpoint will be the same as achieving 0 or 1.

3. You have not adequately addressed the issue of multiplicity control for the set of secondary endpoints, as no method has been proposed. The Agency reiterates the previous comment that for all secondary endpoints that could be considered for labeling claims, you should include appropriate multiplicity adjustments.

4. The protocol remains vague about how to identify when ANCOVA assumptions may be violated, stating only that if violations are 'noted,' that rank ANCOVA will be used instead. The protocol should include objective criteria for determining whether a rank analysis will be used in place of the standard ANCOVA analysis.

5. Although you have added sensitivity analyses for missing data, additional sensitivity analyses that use alternate assumptions and frameworks (such as multiple imputation) are also recommended (at least two sensitivity analyses per endpoint) to adequately assess the impact of missing data. While the proposed methods for continuous data (LOCF and ordinary least square multiple regression) use different assumptions, there is likely to be little difference in the results from LOCF vs. missing as failure for the binary endpoints.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include: (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, contact Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

SUSAN J WALKER
12/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105564

ADVICE

Stiefel Laboratories, Inc.
Attention: Brandy Muchanic
Manager, Regulatory Affairs
20 T.W. Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Muchanic:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazarotene foam, 0.1%.

We also refer to your amendment dated July 2, 2010 containing a nonclinical response to information request.

We have the following comment:

> It appears that a 90-day repeat-dose dermal toxicity study in rats treated with tazarotene foam and other available nonclinical information on tazarotene will be appropriate to support an NDA for tazarotene foam, 0.1%. The adequacy of the 90-day repeat-dose dermal toxicity study in rats will be a review issue.

If you have any questions, contact Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105564	ORIG-1	STIEFEL LABORATORIES INC	Tazarotene foam 0.1%

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/s/

SUSAN J WALKER
08/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105564 **ADVICE/INFORMATION REQUEST**

Stiefel, a GSK Company
Attention: Devon Allen, M.S., R.A.C.
Senior Director, Regulatory Affairs
20 TW Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. Allen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazarotene foam, 0.1%.

We have the following comments and requests for information:

Nonclinical

1. A three-month dermal toxicity study in minipigs using the clinical formulation should be conducted to support the proposed 12-week phase 3 clinical studies as well as an NDA. This nonclinical study should be conducted instead of the proposed (b) (4).

2. Provide the level of (b) (4) (a possible carcinogen) contained in your propellant.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, contact Cristina Attinello, Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105564	ORIG-1	STIEFEL LABORATORIES INC	Tazarotene foam 0.1%

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/s/

SUSAN J WALKER
05/25/2010