

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-991

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER
21-991

NAME OF APPLICANT / NDA HOLDER
Merck & Co., Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZOLINZA™ (vorinostat)

ACTIVE INGREDIENT(S)
Suberoylanilide Hydroxamic Acid

STRENGTH(S)
100 mg

DOSAGE FORM
Gelatin Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by the FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number RE 38, 506 E	b. Issue Date of Patent April 20, 2004	c. Expiration Date of Patent November 29, 2011
d. Name of Patent Owner Sloan-Kettering Institute for Cancer Research; The Trustees of Columbia University in the City of New York See Attachment 1	Address (of Patent Owner) Office of Industrial Affairs, 1275 York Avenue	
	City/State New York, New York	
	ZIP Code 10021	FAX Number (if available)
	Telephone Number 212-638-6111	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address for agent or representative named in 1.e.i	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		

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For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent): Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or methods(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product. Yes

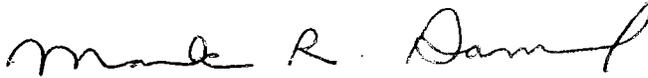
BEST POSSIBLE COPY

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

March 10, 2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Mark R. Daniel

Address

Merck & Co., Inc., P.O. Box 2000, RY60-30

City/State

Rahway, NJ

ZIP Code

07065-0907

Telephone Number

(732) 594-6609

FAX Number (if available)

(732) 594-4720

E-Mail Address (if available)

mark_daniel@merck.com

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Attachments to Form FDA 3542a
ZOLINZA™ (vorinostat)
NDA No. 21-991
US Patent No. RE 38, 506 E

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ATTACHMENT 1

Item 1(d)

Name of Second Patent Owner:

The Trustees of Columbia University in the City of New York

Address of Second Patent Owner:

Michael Cleare, Executive Director, Office of Science and Technology Ventures
80 Claremont Avenue
4th floor, Mailcode 9606
New York, NY 10027-5712

Office of General Counsel
412 Low Memorial Library
535 W 116th st.
Mailcode 4308
New York, NY 10027

Telephone number:
212-854-6777

ATTACHMENT 2

Items 2.2, 2.3 and 2.4

The claims of Patent No. RE 38, 506 E are not limited to any particular polymorphic form of the drug substance. The patent claims the form of the drug substance described in the NDA for which approval is being sought in addition to all other polymorphic forms to the extent that they exist. Because the patent is submitted for listing on that basis, no testing of other polymorphic forms of the drug substance is required.

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1. GENERAL

a. United States Patent Number US 6,087,367	b. Issue Date of Patent July 11, 2000	c. Expiration Date of Patent October 4, 2011
--	--	---

d. Name of Patent Owner Sloan-Kettering Institute for Cancer Research; The Trustees of Columbia University in the City of New York See Attachment 1	Address (of Patent Owner) Office of Industrial Affairs, 1275 York Avenue	
	City/State New York, New York	
	ZIP Code 10021	FAX Number (if available)
	Telephone Number 212 639 6100	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously, for listing, is the expiration date a new expiration date? Yes No

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March 10, 2006

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NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

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Attachments to Form FDA 3542a
ZOLINZA™ (vorinostat)
NDA No. 21-991
US Patent No. 6,087,367

ATTACHMENT 1

Item 1(d)

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Michael Cleare, Executive Director, Office of Science and Technology Ventures
80 Claremont Avenue
4th floor, Mailcode 9606
New York, NY 10027-5712

Office of General Counsel
412 Low Memorial Library
535 W 116th st.
Mailcode 4308
New York, NY 10027

Telephone number:
212-854-6777

EXCLUSIVITY SUMMARY

NDA # 21-991

SUPPL #

HFD # 150

Trade Name Zolinza (proposed)

Generic Name vorinostat

Applicant Name Merck

Approval Date, If Known

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:

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d) Did the applicant request exclusivity?

YES NO

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

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).

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NDA#

NDA#

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

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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:

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 YES NO

Investigation #2 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 YES NO

Investigation #2 YES NO

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Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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: Paul Zimmerman
Title: Project Manager
Date: 8-29-06

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Division Director

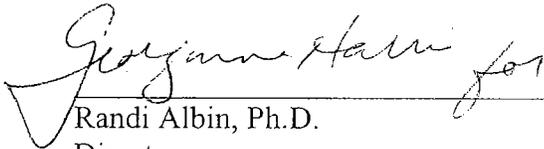
Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

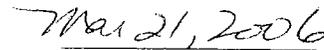
/s/

Robert Justice
10/6/2006 01:46:35 PM

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.



Randi Albin, Ph.D.
Director
Regulatory Affairs


Date

**APPEARS THIS WAY
ON ORIGINAL**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-991	Efficacy Supplement Type SE-	Supplement Number
Drug: Zolanza (vorinostat)		Applicant: Merck
RPM: Paul Zimmerman		HFD-150 Phone # 3017961489
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		I
• Other (e.g., orphan, OTC)		V
User Fee Goal Dates		10-7-06
❖ Special programs (indicate all that apply)		
		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid UF ID number
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<ul style="list-style-type: none"> • This application is on the AIP 	() Yes (X) No
<ul style="list-style-type: none"> • Exception for review (Center Director's memo) 	
<ul style="list-style-type: none"> • OC clearance for approval 	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
<ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
<ul style="list-style-type: none"> • 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)
<ul style="list-style-type: none"> • [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). 	
<ul style="list-style-type: none"> • [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 box below (Exclusivity)). • [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. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(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)).</p> <p>If "Yes," skip to question (4) below. If "No," continue with question (2).</p> <p>(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)?</p> <p>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 box below (Exclusivity).</p> <p>If "No," continue with question (3).</p> <p>(3) Has the patent owner, its representative, or its exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	() N/A (no paragraph IV certification) () Verified () Yes () No () Yes () No () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity)

If "No," continue with question (5)

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • 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.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" 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. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager: ADR #) (indicate date of each review)	

Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	
<ul style="list-style-type: none"> Status of advertising (approvals only) 	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	(X) Yes () Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	() None (X) Press Release/Burst () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	
<ul style="list-style-type: none"> Reviews 	DDMAC, SEALD, DMETS, DSRCS reviews included
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	9-18-06 e-mail
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	9-9-03
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	11-30-05
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date, approvals only) 	8-15-06
<ul style="list-style-type: none"> Other 	
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	N/A
<ul style="list-style-type: none"> 48-hour alert 	
❖ Federal Register Notices, DESI documents, NDA SARR reports (if applicable)	

Summary Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	9-18-06 JJohnson Team Ldr Rev.
Label Information	
❖ Clinical review(s) (indicate date for each review)	9-9-06 joint
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	8-16-06
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	n/a for Orphan
❖ Demographic Worksheet (NME approvals only)	n/a anymore
❖ Statistical review(s) (indicate date for each review)	9-9-06 joint
❖ Biopharmaceutical review(s) (indicate date for each review)	9-18-06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	8-29-06
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	9-18-06
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	n/a
❖ CAC/ECAC report	n/a

Appendix A to NDA/Efficacy Supplement Action Package Checklist

n application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

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NDA # 21-991 Supplement # Efficacy Supplement Type SE-

Trade Name: Zolinza
Established Name: vorinostat
Strengths: 100 mg

Applicant: Merck & Co., Inc.
Agent for Applicant:

Date of Application: 4-5-06
Date of Receipt: 4-7-06
Date clock started after UN:
Date of Filing Meeting: 5-25-06
Filing Date: 6-6-06
Action Goal Date (optional):

User Fee Goal Date: 10-7-06

Indication(s) requested: **for the treatment of patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease subsequent to other therapies.**

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.) Orphan, fast track

Form 3397 (User Fee Cover Sheet) submitted. YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication

Version: 12/15/2004

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for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted in accordance with 343.4? YES NO

- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant is not required to request exclusivity; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby 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." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 58,915
- End-of-Phase 2 Meeting(s)? Date(s) 9-9-03, 10-15-03, 12-2-03, 12-19-03 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 11-30-05 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/DSRCS? N/A YES NO
submitted N/A
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies all OTC labeling and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: 5-25-06

BACKGROUND: This new NDA provides for Zolinz

ATTENDEES:

Robert Justice, M.D., Acting Division Director
Ann Farrell, M.D., Acting Deputy Division Director
John Johnson, M.D., Medical Team Leader
Bhupinder Mann, M.D., Medical Officer
Rajeshwari Sridhara, Ph.D., Statistical Team Leader
Kun He, Ph.D., Statistical Reviewer
Brian Booth, Ph.D., Biopharmaceutics Team Leader
Sophia Abraham, Ph.D., Biopharmaceutics Reviewer
Leigh Verbois, Ph.D., Pharmacology Reviewer
David Morse, Ph.D., Pharmacology Team Leader
Josephine Jee, Ph.D., Chemistry Reviewer
Sarah Pope, Ph.D., PAL, ONDQA
Ravi Harapanhalli, Ph.D., Branch Chief, ONDQA
Lloyd Johnson, Ph.D., DSI
Paul Zimmerman, R.Ph., Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Bhupinder Mann
Secondary Medical:	John Johnson
Statistical:	Kun He
Pharmacology:	Leigh Verbois
Statistical Pharmacology:	NA
Chemistry:	Josephine Jee
Environmental Assessment (if needed)	
Biopharmaceutical:	Sophia Abraham
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	Lloyd Johnson
Regulatory Project Management:	Paul Zimmerman
Other Consults:	Tradename and carton 4-20-06
	DDMAC 4-20-06
	QOL 5-2-06
	DSI 5-1-06
	Consultant for photos MPittlekow 5-11-06

Per reviewers, are all parts in English or English translation?
If no, explain:

YES NO

CLINICAL

FILE

REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY

N/A

FILE

REFUSE TO FILE

STATISTICS

N/A

FILE

REFUSE TO FILE

BIOPHARMACEUTICS

FILE

REFUSE TO FILE

- Biopharm. inspection needed? YES NO

PHARMACOLOGY

N/A

FILE

REFUSE TO FILE

- GLP inspection needed? YES NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is not ready for filing. Explain why.
- The application, as submitted, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who has received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center

Director) or denying (for signature by ODE Director) an exception for review.

3. Convey document filing issues/no filing issues to applicant by Day 74.

Paul Zimmerman
Regulatory Project Manager, HFD-150

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II (ORP). Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO
6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution")
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.54(b)(1) (Paragraph I certification) (Patent information has not been submitted to FDA. Patent number(s): _____)
 - 21 CFR 314.54(b)(2) (Paragraph II certification) (Patent number(s): _____)

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval for a new indication and not for the indications approved for the listed drug if the BA/BE study is submitted for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv))?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES NO

• EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

IND# _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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Randi Albin, Ph.D.
Director
Regulatory Affairs

October 4, 2006

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Fax 732 594 1030
randi_albin@merck.com

Robert L. Justice, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, Maryland 20705-1266



Dear Dr. Justice:

NDA 21-991: ZOLINZA™ (vorinostat) Capsules

**Response to FDA Request for Information
(Phase IV Commitments)**

Reference is made to the New Drug Application cited above for ZOLINZA™ (vorinostat) capsules submitted on April 5, 2006 by Merck Research Laboratories (MRL), a division of Merck & Co., Inc. Further reference is made to the e-mail communication on September 18, 2006 from FDA in which the Agency requested MRL to provide Phase IV commitments for vorinostat and to the subsequent e-mail communication on September 20, 2006 from FDA that provided clarification to the September 18, 2006 e-mail. Further reference is made to the e-mail communication on September 26, 2006 in which MRL provided a response to the proposed Phase IV commitments and to the e-mail communications on September 28 and 29, 2006 and October 3, 2006 between FDA and MRL in which the proposed Phase IV commitments were further discussed.

MRL agrees to the Phase 4 commitments as outlined in the October 3, 2006 e-mail from FDA.

With this submission, MRL agrees to the Phase IV commitments that are provided in [Sec. 1.6.3].

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification*. As an enclosure to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one (1) Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one (1) CD and is not more than 100 MB. Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec

Robert L. Justice, M.D., Acting Director
NDA 21-991: Zolinza™ (vorinostat) Capsules
Page 2

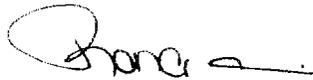
AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Drug Oncology Products who should be provided access to this electronic submission on their desktops may be obtained from Paul Zimmerman, Regulatory Health Project Manager, Division of Drug Oncology Products.

We consider the filing of this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Randi Albin, Ph.D. (732-594-4240) or, in my absence, to Georgianna Harris, Ph.D. (732-594-7641).

Sincerely,



Randi Albin, Ph.D.
Director
Regulatory Affairs

Enclosure: CD

Desk Copy: Paul Zimmerman, Regulatory Health Project Manager (*cover letter*)
Division of Drug Oncology Products

Q:\Weikel\SAHANDA 21-991\Responses\Phase4CommitmentsOct06.doc

Phase IV Commitments for NDA 21-991
October 4, 2006

Commitment 1:

Merck commits to provide updates of the exposure and safety data (adverse experiences leading to dose interruption, dose modification, or dose discontinuation) collected for CTCL patients who initially received vorinostat on Protocol 001 and continued to receive vorinostat on Protocol 007. A report will be provided annually starting in October 2007 and will continue until the final CTCL patient discontinues from Protocol 007 or for a maximum of 3 years.

First Report Submission: October 2007

Final Report Submission: October 2009

Commitment 2:

Merck agrees to conduct a pharmacokinetic study in cancer patients with hepatic impairment. Merck will submit the protocol to the Agency prior to conduct of the study for agreement with the study design. Merck will conduct this pharmacokinetic study in the advanced cancer patient population with mild to moderate hepatic insufficiency, according to the Child-Pugh classification or the NCI criteria. Pharmacokinetic sample collection will occur after single-dose administration. The minimum target sample size will be approximately 4. If the study cannot be fully enrolled, the study will be closed after completion of the moderate impairment cohort.

Protocol submission date: April 1, 2007

Study Start (study enrollment open): October 1, 2007

Final Report Submission: October 2012

Commitment 3:

Merck agrees to study the effect of vorinostat on the ECG QT interval in the advanced cancer patient population. Intensive ECG monitoring, as well as pharmacokinetic sampling, will occur at baseline and after single-dose administration. The target sample size will be approximately 18.

Protocol submission date: January 1, 2007

Study Start (study enrollment open): April 1, 2007

Final Report Submission: April 2009

Commitment 4:

Merck commits to assess safety and laboratory monitoring data from ongoing Merck studies in patients treated concomitantly with vorinostat and warfarin. A report will be submitted annually starting October 2007 and will continue until data has been analyzed for 40 patients or for a maximum of three years.

First report submission date: October 2007

Final Report Submission: October 2009

BEST POSSIBLE COPY

Commitment 5:

Merck commits to submit all adverse experiences reported as vorinostat-drug interactions in the post-marketing environment as expedited (15-day) reports. Each adverse experience from Merck clinical trials which meets the criteria of serious according to the regulatory definition and is considered to be a result of a vorinostat-drug interaction will be submitted as an expedited (15-day) report. A summary of these adverse experiences will be submitted annually starting in October 2007 and will continue for three years.

First report submission date: October 2007

Final Report Submission: October 2009

Commitment 6:

Merck commits to conduct two in vitro efflux studies; one to determine whether vorinostat is a substrate of P-glycoprotein and one to determine whether vorinostat is an inhibitor of P-glycoprotein.

Studies Start: December 2006

Final Reports Submission: March 2007

**APPEARS THIS WAY
ON ORIGINAL**

Pease, Dorothy W

From: Harris, Georgianna [georgianna_harris@merck.com]
Sent: Friday, September 29, 2006 1:56 PM
To: Pease, Dorothy W
Subject: NDA 21,991 Phase IV commitments - revised Sept29

Attachments: Phase IV Commitment With Revised From FDA.doc



Phase IV
Commitment With R

Dotti,

Merck accepts the FDA changes made to the Phase IV Commitments with a minor edit to Commitment 3. Merck also proposes to change the commitment dates for #2 and #3 for the reasons described below.

Commitment 2: Merck proposes to conduct this study as such proposes to revise the protocol submission date to because of the time required on this study design. Merck proposes to revise the study start date to because of the limited availability of advanced cancer patients with hepatic impairment. Accordingly, the final report submission date has been adjusted.

Commitment 3: Due to the limited number of patients who may be willing to participate this study, Merck proposes to revise the study start date to. Accordingly, the final report submission date has been adjusted.

Once we get FDA agreement on the revised dates we will streamline the wording of these commitments so that they can be submitted officially to the NDA.

Please let me know if you have any questions.

Georgianna Harris
732-594-7641

<<Phase IV Commitment With Revised From FDA.doc>>

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available at <http://www.merck.com/contact/contacts.html>) that may be confidential, proprietary copyrighted and/or legally privileged. It is intended solely for the use of the individual or entity named on this message. If you are not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

"EMF <fda.hhs.gov>" made the following annotations.

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=====

A

3 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Pease, Dorothy W

From: Justice, Robert
Sent: Thursday, September 28, 2006 10:33 AM
To: Pease, Dorothy W
Subject: RE: NDA 21-991 Phase IV commitments

OK with me.

-----Original Message-----

From: Pease, Dorothy W
Sent: Thursday, September 28, 2006 9:54 AM
To: Johnson, John R; Booth, Brian P; Mann, Bhupinder; Abraham, Sophia
Cc: Zimmerman, Paul F; Rahman, Nam Atiqur; Garnett, Christine; Justice, Robert; Farrell, Ann T
Subject: RE: NDA 21-991 Phase IV commitments

Here is the updated version of the PMCs (not yet in letter format) showing tracking of FDA changes to
— proposal. OK to convey to —

Dotti

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To: Booth, Brian P; Pease, Dorothy W; Mann, Bhupinder; Abraham, Sophia
Cc: Zimmerman, Paul F; Rahman, Nam Atiqur; Garnett, Christine
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From: Booth, Brian P
Sent: Wednesday, September 27, 2006 7:37 AM
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I think these are mostly good

For PMC 2; hepatic impairment, there are two things:

--They plan on using child Pugh to stratify. Often, in oncology these studies are done using the NCI hepatic
impairment criteria, based largely on bilirubin. Should we tell them that they may use either the Child Pugh or

Pease, Dorothy W

From: Pease, Dorothy W
Sent: Thursday, September 28, 2006 10:32 AM
To: 'Harris, Georgianna'
Cc: Zimmerman, Paul F
Subject: RE: NDA 21-991 Phase IV commitments

Attachments: PMCs updated 9-28-06.doc



PMCs
19-28-06.doc

Sorry, I was too fast. Here's the attachment.

Dotti

-----Original Message-----

From: Pease, Dorothy W
Sent: Thursday, September 28, 2006 10:32 AM
To: 'Harris, Georgianna'
Cc: Zimmerman, Paul F
Subject: RE: NDA 21-991 Phase IV commitments

Here is our revision of your response re: PMCs.

Thanks

Dotti

-----Original Message-----

From: Harris, Georgianna [mailto:georgianna_harris@merck.com]
Sent: Tuesday, September 26, 2006 10:21 PM
To: Pease, Dorothy W
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732-594-7641

<<Phase IV Commitment.doc>>

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Ok with me.

John

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The QT prolongation protocol should be submitted to FDA by April 1, 2007 (not _____) and the study initiated by October 1 2007 (not June 2009).

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I think these are mostly good

For PMC 2; hepatic impairment, there are two things

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From: Booth, Brian P
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Cc: Zimmerman, Paul F; Rahman, Nam Atiqur; Garnett, Christine; Justice, Robert; Farrell, Ann T
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looks okay to me...

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They propose to close the study after three years finished or not. I recommend that we tell them they have to finish the moderate impairment cohort as a minimum.

B

3

_____ Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Pease, Dorothy W

From: Johnson, John R
Sent: Wednesday, September 27, 2006 10:36 AM
To: Rahman, Nam Atiqur; Booth, Brian P; Pease, Dorothy W; Mann, Bhupinder; Abraham, Sophia
Cc: Zimmerman, Paul F; Garnett, Christine
Subject: RE: NDA 21-991 Phase IV commitments

No IRB approval is required prior to protocol submission to FDA.CDER
John

-----Original Message-----

From: Rahman, Nam Atiqur
Sent: Wednesday, September 27, 2006 10:35 AM
To: Johnson, John R; Booth, Brian P; Pease, Dorothy W; Mann, Bhupinder; Abraham, Sophia
Cc: Zimmerman, Paul F; Garnett, Christine
Subject: RE: NDA 21-991 Phase IV commitments

I agree with John's comments on timelines.
I am sure Merck can submit the protocols for hepatic impairment and QT studies with _____ after approval of the drug.

Paul, is it required for a protocol be approved by IRB before it is submitted to the Agency?
My understanding is "no". Please confirm.

Thanks,
tik

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Sent: Wednesday, September 27, 2006 9:32 AM
To: Booth, Brian P; Pease, Dorothy W; Mann, Bhupinder; Abraham, Sophia
Cc: Zimmerman, Paul F; Rahman, Nam Atiqur; Garnett, Christine
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Sent: Wednesday, September 27, 2006 7:57 AM
To: Pease, Dorothy W; Mann, Bhupinder; Johnson, John R; Abraham, Sophia
Cc: Zimmerman, Paul F; Rahman, Nam Atiqur; Garnett, Christine
Subject: RE: NDA 21-991 Phase IV commitments

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They propose _____ (I recommend and we tell them they have to) _____
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2. They propose _____ I recommend that we tell them they have to finish the moderate impairment cohort as a minimum

For PMC 3, QT study.

Mostly good. They are proposing a minimum of _____. I think we should tell them a minimum of 18. Christine Garnett's work suggests that less than 18 will be too few to see anything. Pharmacokinetic samples should also be obtained at/near the ECG measurements

Thanks

brian

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To: Mann, Bhupinder; Johnson, John R; Abraham, Sophia; Booth, Brian P
Cc: Zimmerman, Paul F
Subject: FW: NDA 21-991 Phase IV commitments

PMCs

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PMCs

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Dotti

Attached is the MRL proposal for the Phase IV commitments. Commitments 2 and 3 are longer than may be necessary but we want to make sure we are adequately addressing the FDA request. Once we receive FDA feedback we can streamline the commitments. I would be happy to discuss by phone on Wednesday if you think it would be helpful.

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Attachments: Phase IV Commitment.doc



Phase IV
Commitment.doc (5)

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Georgianna Harris
732-594-7641

<<Phase IV Commitment.doc>>

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Attachments: Phase IV Commitment.doc



Phase IV
Commitment.doc (3'
PMCs

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Georgianna Harris
732-594-7641

<<Phase IV Commitment.doc>>

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C

3 Page(s) Withheld

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 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

10 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

E

9 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, MAIL STOP 4447)**

DATE RECEIVED: April 20, 2006	DESIRED COMPLETION DATE: July 17, 2006	OSE REVIEW #: 06-0119
DATE OF DOCUMENT: March 16, 2006	PDUFA DATE: October 7, 2006	

TO: Robert Justice, M.D.
Director, Division of Drug Oncology Products, HFD-150

THROUGH: Linda Y. Kim-Jung, PharmD., Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Diane C. Smith, PharmD., Project Manager
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Zolinza (Vorinostat) capsules	NDA SPONSOR: Merck Research Laboratories
NDA#: 21-991	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Zolinza. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Zolinza, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have any questions for DDMAC, please contact Michelle Safarik or Suzanne Berkman at 301-796-1200. If you have any other questions or need clarification, please contact the medication errors project manager, Diane Smith, at 301-796-0538

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II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Zolinza to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The SAEGIS⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Zolinza. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Zolinza, acceptable from a promotional perspective
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Zolinza. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.

³ AMF Decision Support System (DSS), the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06 and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Comparison System (POCS).

⁵ www location <http://www.uspto.gov/mdb/init.cfm>

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

Table 1: Potential Look-Alike/Sound-A-Like Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Strength(s)	Other**
Zolinza	Vorinostat 100 mg capsule	400 mg capsule once a day, 100 mg capsule once daily
Relenza	Zanamivir 5 mg Blister packs	2 inhalations (one 5-mg blister per inhalation for a total dose of 10mg twice daily (approximately 12 hours apart) for 5 days. Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses.
		SA
		A
<p>*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike) ***NOTE: This review contains proprietary and confidential information that should not be released to the public.***</p>		

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B. PRESCRIPTION ANALYSIS STUDIES

Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Zolinza with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each set of three studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written for each name, which consisted of a combination of marketed and unapproved drug products and a prescription for Zolinza (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and answers. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p><i>Zolinza 100mg</i> <i>#120</i> <i>4 caps daily</i></p>	<p>Zolinza 100 mg #120 4 capsules daily</p>
<p>Inpatient RX:</p> <p><i>Zolinza 100mg 4 caps daily</i></p>	

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Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A (page 8) for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Zolinza, the primary concerns identified relating to look-alike and sound-alike confusion with Zolinza were Relenza and

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Zolinza.

1. Relenza was found to have sound-alike potential with Zolinza. Relenza is used in treating uncomplicated acute illness due to influenza A and B in adults and pediatric patients 7 years and older who have been symptomatic for no more than 2 days. Relenza is for administration to the respiratory track by oral inhalation only, using the Diskhaler device provided. The recommended dose for treatment of influenza of Relenza is 2 inhalations (one 5 mg blister per inhalation for a total dose of 10 mg) twice daily for 5 days. Relenza is supplied in a circular double foil pack (a Rotadisk) containing 4 blisters of the drug along with the Diskhaler inhalation device.

Both names contain three syllables which contributes to the sound-alike similarity between the two names. Phonetic similarities also stem from the second and third syllables of each name ("lenza" vs "linza"). However, the pronunciation of the first syllable "Re" in Relenza is distinct from the "Zo" sound in Zolinza. This distinct sound will aid in phonetically distinguishing this name pair.

Additionally, these products have distinguishing product characteristics such as dosage form (tablet vs. inhaler), strength (100 mg vs. 5 mg), dose (4 capsules vs. 2 inhalations), and frequency of administration (once daily vs. twice daily). Overall, DMETS believes that the differences in the beginning syllables and the aforementioned differences in product characteristics may lessen any confusion stemming from sound-alike similarities involving this name pair.

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/s/

Diane Smith
9/22/2006 04:19:32 PM
CSO

Linda Kim-Jung
9/22/2006 04:22:23 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/22/2006 04:26:49 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/22/2006 04:46:14 PM
DRUG SAFETY OFFICE REVIEWER

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, September 20, 2006 12:42 PM
To: 'Harris, Georgianna'
Cc: 'Albin, Randi L'
Subject: NDA 21-991 for vorinostat

Additional comments may be provided as our review continues

General container label Comments

1. Currently, the company information and the lot number is  and thus this information appears to be more prominent than the established name and the strength of the product. Revise so that the drug product information, such as the established name and the strength is the primary focus of the label.
2. Ensure that the established name is at least one-half the size of the proprietary drug name in accordance with 21 CFR 201.10(g)(2).
3. Decrease the prominence of the net quantity by de-bolding.
4. It appears the drug is packaged in a "unit of use" container; ensure that the container has a child-resistant closure in accordance with "The Poison Prevention Packaging Act".

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ON ORIGINAL**

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/s/

Paul Zimmerman
9/20/2006 01:11:13 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Monday, September 18, 2006 3:34 PM
To: 'Harris, Georgianna'
Cc: 'Albin, Randi L'
Subject: 21-991 for vorinostat - Phase 4 commitments

Regarding NDA 21-991 for vorinostat, FDA requests that you provide the following Phase 4 commitments. Additional comments may be provided as our review continues. Please respond as soon as possible and provide the commitments in the following format.

Commitment:

Protocol submission date: by Month Year

Study Start: by Month Year

Final Report Submission: by Month Year

1. The applicant should make a Phase 4 commitment to follow all patients who remain on treatment in the pivotal (Protocol 001) and the continuation trials (Protocol 007) and submit annual and final study reports.
2. As vorinostat is predominantly eliminated through metabolism, the applicant should make a Phase 4 commitment to conduct a pharmacokinetic study in cancer patients with hepatic impairment to provide proper dosing recommendations. We refer you to the FDA published Guidance for Industry, Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (<http://www.fda.gov/cder/guidance/3625fnl.pdf>).
3. The applicant should make a Phase 4 commitment to provide adequate data on the effect of Vorinostat on ECG QT interval prolongation in cancer patients.
4. The applicant should make a Phase 4 commitment to collect and submit data on Vorinostat and coumadin interaction as these data become available.
5. The applicant should make a Phase 4 commitment to collect and submit data on Vorinostat-other drug interactions as these data become available.
6. The applicant should make a Phase 4 commitment to conduct *in vitro* efflux studies to determine whether vorinostat is a substrate and/or inhibitor of P-glycoprotein.

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/s/

Paul Zimmerman
9/18/2006 03:49:54 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Monday, September 18, 2006 1:54 PM
To: 'Harris, Georgianna'
Cc: 'Albin, Randi L'
Subject: NDA 21-991 for vorinostat

We have the following comments from our Clinical Pharmacology review.

1. You have collected blood samples in Studies 005, 006, and 008 to evaluate the levels of the pharmacodynamic marker, histone acetylation, in peripheral blood mononuclear cells. Please submit these data to the Agency.
2. As vorinostat is glucuronidated by several UGTs including UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT2B7, and UGT2B17, we recommend that you collect blood samples that could be used in the future to determine if UGT polymorphisms are correlated with individual variation of PK parameters or adverse events. It would be prudent to collect the samples during the clinical studies as vorinostat was glucuronidated by multiple UGTs that are known to have polymorphisms that can lead to large inter-individual variability in drug concentrations.

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/s/

Paul Zimmerman
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CSO

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§ 552(b)(4) Draft Labeling

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: September 5, 2006

TO: Robert Justice, M.D., Director
Division of Drug Oncology Products

VIA: Paul Zimmerman, Project Manager
Division of Drug Oncology Products

FROM: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of ZOLINZA (vorinostat) Capsules PPI, N 21-991

Background and Summary

ZOLINZA (vorinostat) Capsules is a new molecular entity, first-in-class, anti-neoplastic agent for the proposed indication:

ZOLINZA holds priority review status as well as Orphan Drug status.

DSRCS was consulted to review the sponsor proposed Patient Package Insert (PPI) which was included as part of the electronic submission to the NDA, dated April 5, 2006. The sponsor subsequently submitted a revised PI on August 4, 2006 in the PLR format. A revised PPI was not provided in that submission.

See the attached patient labeling (PPI) for our recommended revisions to the draft PPI submitted for ZOLINZA, NDA 21-991. We conducted this review based on the PPI submitted on the April 5, 2006 and the PI submitted in PLR format on August 4, 2006. The purpose of patient information is to enhance appropriate use and provide important risk information about medications. We have simplified wording where possible, made it consistent with the PI and removed unnecessary information. We have also put this PPI in the patient-friendly format (specified in 21 CFR 208) that we are recommending for all FDA approved patient labeling, although this format is not required for voluntary PPIs. These recommended changes are

XXXXXXX

consistent with current research to improve risk communication to a lower literacy audience.

Comments and Recommendations

1. The draft PPI submitted by the sponsor has a Flesch Kincaid grade level of 69.7, and a Flesch Reading Ease score of 6.2. These reading scores as submitted by the sponsor are acceptable; we have made only minor changes where indicated. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level).
2. A PPI for ZOLINZA is voluntary. The sponsor proposes to supply ZOLINZA in “unit of use bottles of 120.” The sponsor should clarify how they intend to distribute the PPI to patients and whether it will be enclosed with the drug product in the packaging.
3. All serious side effects listed in the Warnings and Precautions section of the PI should be listed in the PPI. The pertinent signs and symptoms of these serious side effects as well as any actions that the patient should take should be listed in the PPI. We have revised the PPI to reflect this.
4. In the “Patient Counseling” section of the PI (section 17.1), the sponsor should clarify what is meant by “excessive” vomiting and diarrhea as well as under “Tell your doctor if you develop” in the proposed PPI. This will not be intuitive to patients.

Comments to the review division are **bolded, underlined and italicized**. We are providing a marked-up and clean copy of the revised document in Word to the review division.

Please call us if you have any questions.

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§ 552(b)(4) Draft Labeling

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/s/

Sharon Mills
9/5/2006 01:24:53 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
9/6/2006 01:20:06 PM
DRUG SAFETY OFFICE REVIEWER

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§ 552(b)(4) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 28, 2006

TO: Paul Zimmerman, Regulatory Project Manager, OND/OODP/DDOP
Bhupinder Mann, M.D., Medical Officer, OND/OODP/DDOP
John R. Johnson, M.D., Medical Officer & Team Leader, OND/OODP/DDOP

THROUGH: Leslie Ball, M.D., Branch Chief, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

FROM: J. Lloyd Johnson, Pharm.D., Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: NDA 21-991

APPLICANT: Merck & Co., Inc.,

DRUG: Zolinza™ (vorinostat) Capsules

CHEMICAL CLASSIFICATION: 1S (New Molecular Entity; Priority Review)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Advanced, refractory CTCL

CONSULTATION REQUEST DATE: May 5, 2006

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: September 5, 2006

ACTION GOAL DATE: October 7, 2006

I. BACKGROUND

Merck submitted an NDA for Zolinza™ (Vorinostat, MK-0683, suberoylanilide hydroxamic acid, SAHA) an anti-neoplastic agent for the treatment of patients with advanced cutaneous T-cell lymphoma (CTCL). Vorinostat (suberoylanilide hydroxamic acid (SAHA) is an active, potent inhibitor of histone deacetylase (HDAC), an enzyme involved in removing acetyl groups from histones and proteins.

Histone deacetylase inhibitors are a novel class of agents that can induce tumor cell growth arrest, differentiation or apoptosis *in vitro*, and inhibit tumor cell growth.

CTCL is an uncommon, incurable hematological malignancy with predominantly cutaneous manifestations. These include patches, plaques, tumors, and generalized erythroderma; fissuring of the skin or ulceration of tumors. Systemic manifestations include adenopathy and circulating leukemic cells. The disease is usually diagnosed in middle to adulthood; approximately 1200 to 3000 new cases are diagnosed annually in the U.S. Mortality is reported to be at 120 patients per year. The disease is chronic, with survival related to stage. Patients with early disease (limited skin involvement) have a median survival of 12 years. Those with more advanced disease (Stages II and IIB) have a median survival of 5 years; those with nodal disease or visceral involvement have a median survival of only 2.5 years. Patients with early stage disease are likely to die of other causes, but those with advance, extensive CTCL generally die of problems related to malignancy. Stage IIB and higher subjects all have tumor, lymph node, or visceral involvement or a combination of these findings.

The sponsor submitted safety and efficacy data from a Phase II and a pivotal Phase IIB (Protocol P001, CL-01-0303) study in subjects with advance, refractory CTCL. The sponsor claims that in both studies, vorinostat demonstrates notable clinical efficacy in refractory CTCL population as measured by responses in cutaneous disease and pruritis.

The focus of the inspection assignments was the pivotal Phase IIB (Protocol P001, CL-01-0303) study. The purpose of this inspection is to validate data submitted in support of the NDA submitted for Zolinza™ (vorinostat).

II. RESULTS (by site):

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECTN DATE	EIR-REC'VD	FIELD CLASS.
Timothy M. Kuzel , M.D. (Site 0009)	Chicago, IL	USA	Study: Protocol P001 (CL-01-0303)	July 14 – 21, 2006	Pending	NAI
Theresa R. Pacheco M.D. (Site 0011)	Aurora, CO	USA	Study: Protocol P001 (CL-01-0303)	July 13 – 20, 2006	August 21, 2006	NAI
Merck & Co., Inc.,	Blue Bell, PA	USA	Study: Protocol P001 (CL-01-0303)	July 27 – Aug 10, 2006	Pending	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviations(s) from regulations. Data acceptable

VAIr= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection/Report not completed

Study Protocol:

Protocol P001 (CL-01-0303): A Phase IIb Multicenter Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Advance Cutaneous T-Cell Lymphoma.

The focus of the inspections was Study Protocol P001 (CL-01-0303) listed above.

Study Protocol P001 (CL-01-0303):

Protocol P001 (CL-01-0303) is a multicenter, open label, single arm, Phase IIb, non-randomized study in subjects with advanced CTCL. Eligibility was restricted to subjects with histological diagnosis of CTCL and advanced disease (stage 1B or higher) with progressive, persistent, or recurrent disease on or following two systemic therapies, one of which must contain Targretin unless the patient is intolerant of or not a candidate for Targretin therapy; ECOG performance status of 0-2; and adequate hematologic, and hepatic and renal function.

A total of 74 subjects were enrolled in the participating study centers (17 US and 1 Canada). A total of 58 subjects discontinued treatment due to progressive disease, clinical adverse experience or laboratory adverse experience. Subjects were administered 400 mg capsules of vorinostat daily on an outpatient basis. Subjects visited the clinic every 2 weeks for the first 8 weeks, and then every 4 weeks thereafter. Subjects continued treatment until disease progression or experienced intolerable toxicities.

The primary efficacy endpoint is response rate of overall skin disease by physician's assessment using a Severity Weighted Assessment Tool (SWAT) in patients with Stage IIB and higher disease (See Section 5.1 of the Clinical Protocol). Secondary efficacy endpoint included response duration, relief of pruritus - a tumor-related symptom in patients with CTCL, the effect of treatment on clinically abnormal lymph node, and the duration of stable disease. Photographs were taken to record changes in skin disease during treatment. Reliefs of pruritus were assessed by subjects using a 0 -10 point scale. The effect of vorinostat on clinically abnormal lymph nodes was evaluated by CT scans performed at baseline and during treatment.

Safety assessments included physical findings, ECG, laboratory measurements, adverse events and serious adverse events.

The study began on January 15, 2005 and concluded on January 15, 2005.

The inspections audited a two domestic clinical investigators that participated in Study Protocol P001 (CL-01-0303) and a sponsor/monitor inspection. The clinical investigator inspections were conducted under the Bioresearch Monitoring Program (CP 7348.811), the sponsor/monitor inspection was conducted under (CP 7348.810. The clinical investigator and sponsor/monitor audits were issued by DSI in consultation with the clinical reviewers.

Basis for site selection: The Division of Oncologic Drug Products (DODP) selected two study sites based on evaluation of the data submitted in the NDA supplements. The two sites were inspected to validate data submitted in support of the NDA. DSI issued the sponsor-monitor inspection for data validation of the sponsor's data.

- (1) Timothy M.Kuzel, M.D. (Site #0009) (Protocol P001 CL-01-0303) (6 Subjects)
Norwestern University Medical School, Suite 850
676 North Saint Clair
Chicago, IL 60611

Inspection dates: July 14 – 21, 2006

Methodology: Inspection assignments were issued to the field office.

- a. What was inspected?
The study records of 6 subjects enrolled in the study were audited.
- b. Limitations of inspection: None
- c. General observations/commentary:

CHI-DO is currently preparing the EIR. Investigator Lisa Hayka reported by e-mail that the inspection result was NAI (No Action Indicated). The primary efficacy endpoints including the severity weighted assessment tool (SWAT) values for all subjects in the data listings were compared to source data for all the 6 subjects. Data listing for secondary efficacy endpoints including pruritis scores were also reviewed for the 6 subjects. No discrepancies were found with the primary and secondary endpoints records. Data listings of screening, treatment CTs scans, and adverse events were also reviewed and several minor discrepancies were found in the source records. However, most of the discrepancies were corrected during the inspection and Dr. Kuzel promised corrections for all other observations for future studies. No drug accountability discrepancies were observed.

No FDA Form 483 was issued.

The observations noted above are based on communication from the field investigator. Further review and evaluation of the observations will be made when the EIR and exhibits are submitted. An inspection summary addendum will be generated if conditions change upon receipt and review of the EIR.

Recommendation: Data from this site are acceptable. Preliminary review does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

- (2) Theresa R. Pacheco, M.D. (Site #0011) (Protocol P001 CL-01-0303) (5 Subjects)
University of Colorado
Health Sciences Center
Room CP-3245
1665 North Ursula Street
Aurora, CO 80010

Inspection dates: July 13 – 20, 2006

Methodology: Inspection assignments were issued to the field office.

a. What was inspected?

Records of 5 subjects enrolled in Study.

b. Limitations of inspection: none.

c. General observations/commentary:

A comprehensive audit comparing the data listings with completed case report forms was performed for adverse events, and primary efficacy endpoints (dates of observations, pruritis scores, and SWAT scores). A spot check of the data entries showed two minor differences between the source documents and the CRFs but Dr. Pacheco provided a verbal explanation for the differences. There were no deaths or serious adverse events. One verbal observation was that a clinical lab (Rosetta Inpharmatics) used for testing frozen skin samples for RNA gene expression was not listed on the FD 1572. The sponsor apparently informed the site that the lab was owned by Merck, and therefore, did not need to be listed as a separate testing facility.

No FDA Form 483 was issued.

Recommendation: Data from this site are acceptable. There were no serious deviations/findings that would impact the validity or reliability of the submitted data.

(3) Sponsor/Monitor Inspection:

Merck & Co., Inc.,

Worldwide Official Regulatory files: Blue Bell, PA Facility

Merck & Co., Inc.

Unisys Building

785 Jolly Road

Blue Bell, PA 19422

Inspection dates: July 14 – 21, 2006

Methodology: Inspection assignments were issued to the field office.

d. What was inspected?

Sponsor standard operating procedures (SOPs), and the study records for Protocol P001(CL-01-0303).

e. Limitations of inspection: None.

f. General observations/commentary:

PHIL-DO's Field Investigator Mike Rashti reported by e-mail that the EIR is currently being prepared and will be forwarded DSI when completed. The inspection covered review of the sponsor's various SOPs including monitoring SOPs, study records of 6 subjects from Dr Kuzel's (Site #009) study site and the 5 subjects from Dr. Pacheco's (Site #0011) study site. Subjects' CRFs were compared with the sponsor's data listings for primary and secondary

efficacy endpoints. IRB approvals, FDA 1572s, monitoring reports, ADR reporting, correspondence records with the study sites and drug accountability records were also reviewed. There were no deficiencies or significant observations found.

No FDA Form 483 was issued.

The observations noted above are based on communication from the field investigator. Further review and evaluation of the observations will be made when the EIR and exhibits are submitted. An inspection summary addendum will be generated if conditions change upon receipt and review of the EIR.

Recommendation: Data from this site are acceptable. Preliminary review does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Observations noted above are based on Form FDA 483s, preliminary results, and e-mail communications from the Field Investigators. An inspection summary addendum will be generated if conclusions changes significantly upon receipt and review of each final EIR.

In general, based on the inspection of the two clinical study sites combined with the sponsor/monitor audit for this NDA, it appears that sufficient documentation to assure that study subjects audited at the three sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

Follow-up action: none.

J. Lloyd Johnson, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:

Leslie Ball, M.D.
Branch Chief, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

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/s/

J. Lloyd Johnson
8/28/2006 04:07:34 PM
PHARMACOLOGIST

Leslie Ball
8/29/2006 02:02:20 PM
MEDICAL OFFICER

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Date: August 22, 2006

From: Jeanne M. Delasko, RN, MS
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

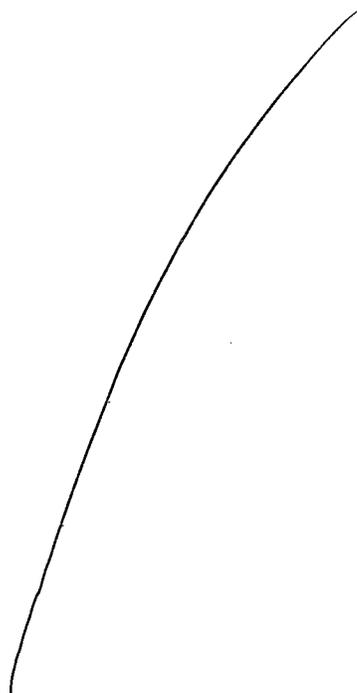
Lilliam A. Rosario, Ph.D.
Senior Pharmacologist, SEALD

Through: Laurie B. Burke, RPh, MPH
Director, SEALD

To: Paul Zimmerman
Regulatory Health Project Manager, DDOP

Subject: Proposed Labeling Format Review
NDA 21-991 (Vorinostat)

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant. Please contact Jeanne Delasko (796-0146) or Lilliam Rosario (796-1446) with questions or concerns.



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/s/

Jeanne Delasko
8/23/2006 10:20:36 AM
CSO

Laurie Burke
8/23/2006 07:05:21 PM
INTERDISCIPLINARY



MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 10, 2006

TO: Richard Pazdur, MD, Director
Division of Oncology Drug Products

VIA: Lee Zimmerman, Project Manager
Division of Oncology Drug Products

FROM: Office of Surveillance and Epidemiology (OSE) Risk Management Team

DRUG: Zolinza (vorinostat capsules)

NDA #: 21-991

APPLICANT: Merck and Company

SUBJECT: Review of Proposed Risk Management Plan (RMP) submitted
April 5, 2006 and dated March 15, 2006

PID #: D060488

INTRODUCTION/BACKGROUND

The Office of Surveillance and Epidemiology (OSE) has reviewed the proposed Risk Management Plan (RMP) for Zolinza and concludes that it does not appear to differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance.

Vorinostat is an orally active inhibitor of histone deacetylase (HDAC) activity. Histone deacetylase inhibitors are a new therapeutic class of medications that are being studied for cancer treatment. In cell culture studies vorinostat induces accumulation of acetylated histones and tubulin and induces cell cycle arrest and apoptosis in a variety of transformed cell lines. It also has biological and anti-neoplastic activity in murine and human xenograft models. In several *in vivo* nonclinical models (human breast, colon, and prostate xenografts; carcinogen-induced breast and lung tumors; and a transgenic murine leukemia model) vorinostat inhibits tumor growth.

The proposed indication of Zolinza is indicated

The most common clinical adverse experiences include fatigue, nausea, anorexia, weight loss, and diarrhea. Common laboratory abnormalities are thrombocytopenia, anemia, increased creatinine and increased glucose. The most common serious adverse experiences across populations and dose levels were venous thromboembolic episodes (VTEs), dehydration, thrombocytopenia, and anemia. Although formal drug interaction studies were not conducted with Zolinza, prolongation of prothrombin time and International Normalized Ratio (INR) were observed in some patients receiving vorinostat concomitantly with coumarin-derivative anticoagulants. There was also one patient administered valproic acid concurrently with vorinostat who experienced early Grade 4 thrombocytopenia with associated gastrointestinal bleeding and anemia.

The Medical Officer believes that the risk of DVT and PE as well as the hematological adverse events are common among cancer patients and consistent with other cancer therapies and that these risks do not warrant risk management measures beyond standard labeling and routine pharmacovigilance.

REVIEW OF SPONSOR'S RMP

The Sponsor does not believe that a Risk Minimization Action Plan is warranted for this product because Zolinza has no anticipated drug interactions at the intended dosage and is not likely to be used illicitly for mood altering effects. They are proposing the following Pharmacovigilance/Surveillance and Post-marketing Activities:

- Labeling – professional labeling and the patient package insert will be utilized to convey to prescribers, other healthcare professionals, and patients about the risks associated with Zolinza. A separate Patient Package Insert (PPI) consult was performed by the OSE Division of Surveillance, Research and Communication Support (DSRCS)¹.
Pharmacovigilance Practices – The Sponsor proposes routine post-marketing surveillance for vorinostat. They do plan to conduct “enhanced surveillance”, which consists of soliciting detailed adverse event in the postmarketing arena and clinical trials via a questionnaire to providers who report a thromboembolic event.

CONCLUSION

The OSE has reviewed the submitted RMP and has consulted with the DDOP and determined that the serious safety issues with vorinostat are consistent with those of other cancer therapies and agree that the Sponsor's proposal for routine risk management measures including labeling and routine pharmacovigilance are sufficient at this time. If the sponsor or

¹ Sharon Mills, *need title.*, DSRCS Review of Patient Labeling for Januvia, *PENDING*.

Division of Oncology Products identifies a safety concern and determines that an RMP is warranted, refer to the guidance documents.

Development of Use of Risk Minimization Action Plans:

<http://www.fda.gov/cder/guidance/6358fnl.htm> and

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:

<http://www.fda.gov/cder/guidance/6359fnl.htm>

Should the review division wish OSE to review a proposed RMP, RiskMAP, Phase IV protocols, or epidemiological post-marketing studies in the future for this product, please provide a consult request.

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/s/

Nancy Clark
8/16/2006 02:54:49 PM
CSO

Vorinostat Pre-approval Safety Meeting Summary
August 15, 2006

Attendees: DODP: Robert Justice, John Johnson, Bhupinder Mann, Sophia Abraham, Josephine Jee, Paul Zimmerman, Sheau-Rong Lon
DDRE: Mark Avigan, Susan Lu, Jennie Chang, Sam Chan

Overview: Vorinostat is an oral histone deacetylase (HDAC) inhibitor used as monotherapy for the treatment of cutaneous T-cell lymphoma. Of 74 patients entered in the clinical trial study, 58 patients were discontinued due to progression of disease. 9 patients discontinued therapy due to AE. The reported AEs included DVT, pulmonary embolism, chest pain, spinal cord injury, angioneurotic edema, ischemic stroke, asthenia and death.

15% patients had elevations in ALT and alkaline phosphatase. No patients had grade 3 or 4 elevations and were fairly transient.

The following safety issues were discussed:

- Increased serum creatinine (Patients with creatinine \geq 2.1 mg/dl or creatinine clearance of \leq 59 ml/min were excluded from the pivotal trial)
Per Dr. Mann, patients in studies with solid tumor and hematologic malignancies are likely previously exposed to chemotherapy, including cis-platinum, and more prone to developing renal toxicity.
- Muscle Spasm (17.4% in treatment population, but severe in 2.3%, are these of concern?)
It was determined that increased muscle spasms were not a major safety concern. Two patients had severe muscle spasms. Patients did not experience seizures. Cases of mild hypomagnesemia and hypocalcemia were reported infrequently and are not the likely causes of the reported muscle spasms.
- Hyperglycemia
It was determined that hyperglycemia was not a major safety concern. Patients on insulin had pre-existing diabetes. None developed new-onset diabetes requiring treatment.
- Cardiovascular events, including arrhythmias
It was determined that phase 4 commitment for a study to evaluate the effect on QT interval is required. Three patients had QT prolongation, in one case it was longer than 500 msec.
- Elevated LFTs (Increased ALT in 15%, no patient with grade 3 or 4)
It was determined that phase 4 commitment for a study to evaluate the effect of hepatic impairment is required.
- All patients received the same dose of the drug - it is not possible to relate adverse events to the dose in the pivotal study.

- Dr. Mann stated that he did not identify any particular adverse events of concern for postmarketing monitoring by DDRE safety evaluator.

Action items:

- 1) Dr. Mann will provide more detail information on drug eruption.
- 2) Phase 4 study to evaluate the effect on QT interval is required.
- 3) Phase 4 study to evaluate the effect of hepatic impairment is required.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, July 18, 2006 2:43 PM
To: 'Albin, Randi L'
Subject: NDA 21-991 for Vorinostat

Randi,

We have the following requests from our Clinical Pharmacology reviewer.

Please provide data (Table and/or Figure) to support the following statements:

- Vorinostat was not a potent reversible inhibitor ($IC_{50} > 75 \mu M$) of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 activities in human liver microsomes.
- Vorinostat was not a time-dependent inhibitor of human liver CYP1A2, CYP2C9, CYP2C19 or CYP3A4 activities.

Thanks,

Paul

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/s/

Paul Zimmerman
7/18/2006 02:51:10 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, July 18, 2006 9:29 AM
To: 'Albin, Randi L'
Subject: NDA 21-991 for vorinostat

Randi,

We have the following request from our Clinical Pharmacology reviewer.

Please submit the studies that support the following statement (under the clinical pharmacology section of the NDA):

Thanks,
Paul

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/s/

Paul Zimmerman
7/18/2006 09:38:16 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, July 13, 2006 2:59 PM
To: 'Albin, Randi L'
Subject: NDA 21-991 for Vorinostat

Randi,

We have the following requests from our Clinical team.

1) Currently, for the Time to Progression calculation, progression is defined as $\geq 25\%$ increase in skin assessment scores compared to baseline (or $\geq 50\%$ increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes, documented by biopsy when possible) while the patient is actively taking the study drug. This must be confirmed at a second examination on a subsequent visit 1-4 weeks later.

For each patient in Study 001 please re-calculate Time to Progression defining progression as $\geq 25\%$ increase in skin assessment scores compared to nadir measurements (or $\geq 50\%$ increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes, documented by biopsy when possible). Confirmation at a second visit is not required and the patient need not be actively taking study drug.

Currently, for the Duration of Overall Response calculation, the duration of overall response is measured from the time when criteria are first met for CCR or PR (whichever first recorded) until the first date when an increase in skin assessment by SWAT score is greater than 50% of the difference between baseline score and nadir score. Patient must be actively taking the study drug and the loss of response must be confirmed at a second visit 1-4 weeks later.

For each responding patient in Study 001 please re-calculate the Duration of Overall Response measuring the duration of overall response from the time when criteria are first met for CCR or PR (whichever first recorded) until the first date when an increase in skin assessment by SWAT score is $\geq 50\%$ from the nadir score. Confirmation at a second visit is not required and the patient need not be taking study drug.

2) For the updated data from study 001 submitted on 6/30/06, please submit the photographs supporting the updated response and progression status of each patient that was updated.

Thanks, Paul

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/s/

Paul Zimmerman
7/13/2006 03:17:54 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Monday, July 10, 2006 11:14 AM
To: 'Albin, Randi L'
Subject: NDA 21-991 for vorinastat-Clinical Pharm request

Randi,
We have the following request from our ClinPharm team.
Paul

Please submit the data from Study 008 in a single .xpt file with the following columns:

ID	Patient Identifier
Dose	Dose of drug received at dosing event preceding measurement
Daily	Dose Daily dose of drug received by patient
Day	Day relative to start of dosing; Numeric value E.g. Day =1 : First day of dosing
Time	Time of measurement relative to time of dose; Numeric value for hours E.g. 30 minutes post-dose value: 0.5; Range of values will be 0-24
QT	QT interval in milliseconds
QTc	QT corrected for heart rate in milliseconds; specify correction used (i.e. Call column QTcF if Fridericia; QTcB if Bazetts)
RR	RR interval in milliseconds
Conc.MK0683.Ser	Concentration of MK-0683 in Serum; in ng/mL
Conc.Vstatgluc.Ser	Conc of Vstat-gluc in serum; in ng/mL
Conc.AOA.Ser	Conc of AOA in Serum; in ng/mL
Complete on	Binary flag variable: does subject have complete data? i.e. If subject has measures on Day=1,5 and 28: Complete=1. If not, Complete=0

Please submit a balanced dataset. E.g. If there is no particular measure of concentration available for a given patient at any particular time, but a QT measure is available, provide the QT measure but indicate that the concentration is not available with a flag variable. Likewise, if there is no measure of QT available in a given patient at any particular time, but a concentration measure is available, provide the concentration measure but indicate that the QT measurement is not available with a flag variable.

Please submit whatever scripts you use to derive this dataset from raw datasets. If raw datasets are used that have not been already been submitted, please submit these raw datasets, as well.

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/s/

Paul Zimmerman
7/10/2006 11:23:58 AM
CSO

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGY DRUG PRODUCTS**



DIVISION OF DRUG ONCOLOGY PRODUCTS

**5901-B Ammendale Road
Beltsville, Maryland 20705**

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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Randi Albin, Ph.D.
Director, Regulatory Affairs
Merck & Co., Inc.
(732) 594-1030

FROM: Carl Huntley, R. Ph., MBA *for Paul Zimmerman*
Regulatory Project Manager

DATE: July 6, 2006

Total number of pages, including cover sheet: 2--

COMMENTS: Regarding NDA 21-991 and SAHA for cutaneous t-cell lymphoma (CTCL), please see comments below.

Currently, for the Time to Progression calculation, progression is defined as $\geq 25\%$ increase in skin assessment scores compared to baseline (or $\geq 50\%$ increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes, documented by biopsy when possible) while the patient is actively taking the study drug. This must be confirmed at a second examination on a subsequent visit 1-4 weeks later.

For each patient in Study 001 please re-calculate Time to Progression defining progression as $\geq 25\%$ increase in skin assessment scores compared to nadir measurements (or $\geq 50\%$ increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes, documented by biopsy when possible). Confirmation at a second visit is not required and the patient need not be actively taking study drug.

Currently, for the Duration of Overall Response calculation, the duration of overall response is measured from the time when criteria are first met for CCR or PR (whichever first recorded) until the first date when an increase in skin assessment by SWAT score is greater than 50% of the difference between baseline score and nadir score. Patient must be actively taking the study drug and the loss of response must be confirmed at a second visit 1-4 weeks later.

For each responding patient in Study 001 please re-calculate the Duration of Overall Response measuring the duration of overall response from the time when criteria are first met for CCR or PR (whichever first recorded) until the first date when an increase in skin assessment by SWAT score is greater than 50% from the nadir score. Confirmation at a second visit is not required and the patient need not be taking study drug.

Regards,

-carl

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/s/

Carl Huntley
7/6/2006 10:55:05 AM
CSO

Zimmerman, Paul F

From: Abraham, Sophia
Sent: Thursday, June 29, 2006 2:44 PM
To: Zimmerman, Paul F
Subject: RE: NDA 21-991 for Vorinostat

Paul, this is ok

From: Zimmerman, Paul F
Sent: Wednesday, June 28, 2006 7:53 AM
To: Zimmerman, Paul F; Abraham, Sophia
Subject: RE: NDA 21-991 for Vorinostat

Sophia,

Please let me know if this is sufficient to address your request or if anything further is needed.

Paul

From: Zimmerman, Paul F
Sent: Wednesday, June 28, 2006 7:44 AM
To: Abraham, Sophia
Subject: FW: NDA 21-991 for Vorinostat

Sophia,

This is the applicant's response regarding your following request:
Request the sponsor to validate the assay method used in Study 006 and submit this assay validation ASAP
Paul

From: Albin, Randi L [mailto:randi_albin@merck.com]
Sent: Tuesday, June 27, 2006 4:29 PM
To: Zimmerman, Paul F
Subject: RE: NDA 21-991 for Vorinostat

Paul,

In response to the request from the Biopharm reviewer, in Protocol 006 an unvalidated assay was used for sample analysis. At the End of Phase II meeting with FDA on September 9, 2003 the Agency indicated that the pharmacokinetic data from this study were not sufficient for registration because a validated assay was not used for sample analysis. Therefore, another study was conducted, Protocol 008, to provide the definitive pharmacokinetic information. In the course of developing a validated assay to support Protocol 008, experiments suggested that vorinostat is not stable in plasma. Therefore, although the original assay used for sample analysis in Protocol 006 was based upon plasma as the matrix, the validated analytical method uses serum as the matrix. The assay development report for the validated assay was submitted as part of the Clinical Study Report for Protocol 008, which is included in the eCTD. Because the pharmacokinetic data from Protocol 006 were deemed to be insufficient, information about the unvalidated assay was not provided in the eCTD.

Is the reviewer asking us to retrospectively validate the assay method used in Protocol 006? If so, this

may not be possible. Moreover, we do not believe such an approach would be meaningful based on our observations that vorinostat is not stable in plasma which was the matrix used for analysis in Protocol 006.

Please let me know if this is sufficient to address the reviewer's request or if further discussion would be helpful.

Sincerely,
Randi

Randi Albin, Ph.D.
Director
Regulatory Affairs
Merck & Co., Inc.
RY 32-605
P.O. Box 200
Rahway, NJ 07065
Ph: 732-594-4240
Fax: 732-594-1030
E-mail: randi_albin@merck.com

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-----Original Message-----

From: Zimmerman, Paul F [<mailto:paul.zimmerman@fda.hhs.gov>]
Sent: Thursday, June 22, 2006 10:03 AM
To: Albin, Randi L
Subject: NDA 21-991 for Vorinostat

Randi,

We have the following request from our Biopharm reviewer.

Please validate the assay method used in Study 006 and submit this assay validation ASAP.

Paul

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Paul Zimmerman
6/29/2006 03:43:29 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, June 27, 2006 10:16 AM
To: 'Albin, Randi L'
Subject: NDA 21-991 for vorinostat-QTc

Randi,
We have the following request from our Biopharm reviewer.

Please submit all data sets and modeling programs used to support your assessment of QTc interval.

Paul

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/s/

Paul Zimmerman
6/27/2006 10:23:45 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, June 06, 2006 7:38 AM
To: 'Albin, Randi L'
Subject: NDA 21-991 for Zolanza

Randi,

We have the following comment from our Biopharm reviewer.

Please submit Study P006.

Paul

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/s/

Paul Zimmerman
6/6/2006 08:17:18 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, May 30, 2006 8:36 AM
To: 'Albin, Randi L'
Subject: NDA 21-991 for vorinostat

Randi,

We have the following comment from our Biopharm reviewer.

Regarding the datasets for PK Study 008, PK parameter data file, please provide ASAP the raw data file for PK parameters and plasma concentration/time data for Study 008.

Paul

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/s/

Paul Zimmerman
5/30/2006 08:46:22 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, May 02, 2006 9:04 AM
To: 'Albin, Randi L'
Subject: NDA 21-991 for Zolanza

Please submit the photographs from study CL-01-0303/ 001 on a CD ROM. The photographs should be in ascending numerical order by patient number. Submit first the 18 responders in the 61 patients with greater than or equal to Stage IIB disease, then the remainder of the responders and last the non-responding patients.

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/s/

Paul Zimmerman
5/2/2006 10:46:02 AM
CSO

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

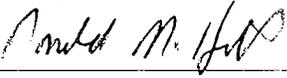
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Tables C-1 and C-2	
	Vorinostat Capsules – Cutaneous T-Cell	
	Lymphoma (CTCL)	<input checked="" type="checkbox"/>

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Donald M. Hill Director, Office of Biotechnology Services	
FIRM/ORGANIZATION Merck & Co., Inc.	
SIGNATURE 	DATE 3/22/06

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

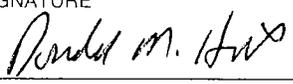
TO BE COMPLETED BY APPLICANT

The following information concerning See Table D-1, who participated as a clinical investigator in the submitted study Vorinostat Capsules – Cutaneous T-Cell Lymphoma (CTCL) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests

NAME	DATE
Donald M. Hill	3/22/06
FIRM/ORGANIZATION	
Merck & Co., Inc.	
SIGNATURE	DATE
	3/22/06

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Pre NDA

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, November 30, 2005 12:53 PM
To: 'Albin, Randi L'
Subject: PreNDA meeting responses

Hi Randi,

Attached are the FDA answers to your questions. You have the option of canceling our meeting of 12-5-05 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Sincerely,



preNDA PRE-NDA
Items and ISG BULLETS.d

Ann

Ann Staten, RD
CDR, United States Public Health Service
Food and Drug Administration
Division of Drug Oncology Products
ph: 301.796.1468
fax: 301.796.9867

AGENDA ITEMS AND ISSUES FOR DISCUSSION

A. Introduction

Vorinostat [suberoylanilide hydroxamic acid (SAHA), L-001079038, MK-0683], a novel inhibitor of histone deacetylases, is being evaluated for

On December 3, 2003 vorinostat was designated "Fast Track" by FDA due to evidence presented to the Agency supporting its potential to: 1) treat an uncommon, incurable hematologic malignancy with potentially life-threatening sequelae, and 2) treat a serious aspect of the condition. Thus, while additional indications of vorinostat may be sought, the initial filing of a New Drug Application (NDA) will be supportive of the indication described in Tab 3, namely for the

MRL proposes to file the planned NDA for vorinostat as an electronically archivable Common Technical Document (eCTD), and provide, by rolling submission, certain sections of the planned NDA. Each of these sections will be comprised of the modules of the eCTD that would constitute a reviewable unit. The sections of the NDA submitted before the final target date will be submitted electronically. The proposed timing for the submission of each section of the planned NDA is listed in the table, below. The target date for submission to the Agency for the full NDA is April 12, 2006.

Reviewable Units [eCTD Module(s)]	Expected Submission Date
Nonclinical Toxicology Reviewable Unit <ul style="list-style-type: none">Module 4 (Nonclinical Study Reports) including Nonclinical Overview (Section 2.4) and Nonclinical Written and Tabulated Summaries (Section 2.6)	December 6, 2005
Chemistry, Manufacturing and Controls Reviewable Unit <ul style="list-style-type: none">Module 3 (Quality) including Quality Overall Summary (Section 2.3)	February 22, 2006
Clinical Reviewable Unit and Administrative Information <ul style="list-style-type: none">Module 1 (Administrative Information)Module 5 (Clinical Study Reports) including Clinical Overview (Section 2.5) and Clinical Summary (Section 2.7)	April 12, 2006

1. In accordance with provisions of the Fast Track regulations, does the Agency concur with the proposed timeline to roll out Module 4 (Nonclinical Study Reports, including the Nonclinical Overview and Nonclinical Written Tabulated Summaries) and Module 3 (Quality, including quality Overall Summary) components of the planned NDA for vorinostat as described

above?

FDA Response: Yes.

Chemistry: The proposed timeline and submission date of 22-FEB-2006 are acceptable. Please ensure that all drug substance and drug product manufacturing sites are ready for inspection at the time of the Quality unit submission. Also confirm that all referenced Drug Master Files are updated and ready for review at the time of the Quality unit submission.

Clinical Pharmacology: Please provide a list of completed and ongoing clinical pharmacology and biopharmaceutical studies.

On March 16, 2004, vorinostat was granted orphan drug designation for the treatment of T-cell non-Hodgkin's lymphoma.

2. In accordance with 21 CFR 314.55(d), it is MRL's understanding that submission of pediatric data is not required for the planned NDA for vorinostat in the proposed indication, and that a waiver is not needed. Does the Agency concur?

FDA Response: Pediatric data will not be required and a waiver is granted.

3. Based on the potential of vorinostat to offer significant improvement compared to marketed products and to treat an uncommon, incurable hematologic malignancy with potentially life-threatening sequelae, does the Agency concur that the planned NDA may be eligible for priority review?

FDA Response: Yes (Final determination to be made after complete NDA is received and decision to file is made)

B. Quality

Drug substance and drug product information will be organized as outlined in the Table of Contents presented under Tab 4.

4. Does the proposed Table of Contents for Module 3 fulfill the requirements of the Agency reviewer(s)?

FDA Response: See comments above in response to question #1. The proposed Table of Contents is acceptable. Additionally, the Agency recommends that the new Drug Master File be submitted in advance of the NDA chemistry section. This will ensure the appropriate processing time for assignment of DMF number and immediate reviewer access, upon submission

of the NDA.

Additional CMC comments:

1. Please confirm the date of USAN adoption for the drug's established name. If the date of adoption is very recent, the inclusion of the appropriate correspondence in the NDA is recommended.
2. Any stability updates should be submitted no later than two months prior to the submission's PDUFA date.

C. Nonclinical Study Reports

The complete list of studies and the proposed Table of Contents for Module 4 is presented under Tab 5.

5. Does the proposed Table of Contents for Module 4 fulfill the requirements of the Agency review(s)?

FDA Response: The completed nonclinical data for Module 4 appears "on the surface" to be adequate for Agency review.

D. Clinical Documentation

Prototypes of the clinical study reports (CSRs) for Protocol 001 and Protocol 005 are presented under Tabs 8 and 9, respectively.

6. Does the Agency agree that the presentation and documentation of efficacy and safety as displayed in the prototype CSRs will be adequate to support the review of the planned NDA?

FDA Response: Yes

On December 1, 2003 the FDA provided responses to questions following review of the Special Protocol Assessment (SPA) for Protocol 001. Clarification to these responses was provided in the meeting minutes of December 19, 2003. The FDA responses and meeting minutes are provided under Tab 13.

7. Does the Agency concur that the CSR for Protocol 001 complies with the comments raised in response to the SPA?

FDA Response: We will not be able to answer this until we have the complete study report.

In the CSR for Protocol 001 supportive digital photographs for all patients will be provided in the Appendix. A series of photographs will be provided for each individual patient. These photographs will be organized by body area and further stratified by visit

number. In addition, the body diagram work sheet for each patient will also be included in the Appendix to the CSR. These body diagram work sheets will be electronically linked to that patient's photographs and stratified by visit number.

8. Does the Agency agree with the proposal to include the body diagram work sheets for each patient in the Appendix to the CSR for Protocol 001 with the supportive digital photographs?

FDA Response: Yes. However, digital photographs should be submitted as .pdf files

Drug metabolism data for vorinostat from Protocol 008 will be provided as SAS® transport files (XPT).

9. Does the Agency concur with these plans?

FDA Response: Yes

A protocol synopsis for the proposed Expanded Access Program (EAP) of vorinostat for patients with CTCL is provided under Tab 11. Safety assessment for patients enrolled on the proposed protocol will be limited to serious adverse events and adverse events that result in discontinuation or dose reduction. To gain information on the potential of predictive or reactive biomarkers to identify a responder population, the proposed protocol includes a request for optional skin biopsies at baseline and after 14 days of treatment.

10. Does the Agency concur with the plans to initiate an EAP?

FDA Response: We do not have sufficient information in the briefing package to determine whether an EAP is acceptable. In order to make this determination we will need an updated summary of safety and efficacy in patients with CTCL.

11. Does the Agency concur with the plans to report only serious adverse events and adverse events that result in discontinuation or dose reduction?

FDA Response: Yes, however, all new/unexpected AEs must be included.

12. Does the Agency agree that optional skin biopsies may be requested as part of the EAP?

FDA Response: See response to above. question #10.

E. Summary of Clinical Safety/Safety Table Format

A summary of the proposed approach for the Summary of Clinical Safety (Section 2.7.4) is presented under Tab 7.

The proposed format for the Summary of Clinical Safety and prototype data displays are summarized under Tab 7.

13. Does the Agency concur with the proposed approach to the integration of safety information as summarized under Tab 7?

FDA Response: Yes

14. Does the Agency concur with the approach to the data displays presented under Tab 7?

FDA Response: Yes

15. Does the Agency concur with the proposed subgroups for the data displays in the proposed Summary of Clinical Safety?

FDA Response: Yes

MRL has established October 24, 2005 as the cut-off date for inclusion of adverse events from the nine (9) ongoing clinical studies of vorinostat in the integrated safety database of the planned NDA. The cut-off date for inclusion of case report form data for the pivotal clinical study (Protocol 001) will be established as November 25, 2005. The cut-off date for reporting of serious adverse events (WAES reports) will be established as November 30, 2005. The Safety Update Report (SUR) will be submitted to the NDA 4 months after filing.

16. Does the Agency accept a date of October 24, 2005 as the cut-off for reporting adverse events in the nine (9) ongoing studies of vorinostat to support a submission date of April 12, 2006 of the planned NDA?

FDA Response: Yes

17. Does the Agency accept a date of November 25, 2005 as the cut-off for inclusion of case report form data for the pivotal clinical study (Protocol 001)?

FDA Response: Yes

F. Statistical Documentation/Data Analysis Plan

The Data Analysis Plan (DAP) for Protocol 001 is presented under Tab 10. Please note that this DAP was previously submitted to IND 58,915 [October 4, 2004, (Serial No. 116)]. The DAP conforms to prior agreements reached between MRL and the Agency and established principles of clinical trial analysis.

18. Does the Agency request any additional analyses beyond what is presented in the submitted DAP?

FDA Response: Not at this time.

G. Electronic Submission

MRL intends to file the planned NDA for vorinostat as an electronically archivable Common Technical Document (eCTD) in accordance with the "Guidance for Industry: M2 eCTD: Electronic Technical Document Specification", April 2003 and the FDA draft "Guidance for Industry: Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions", August 2003. A summary of our plans is provided under Tab 12.

19. Does the Agency concur with MRL's approach for electronic submission of the planned NDA?

FDA Response: Yes

MRL intends to provide the proposed content of labeling in Structured Product Labeling (SPL) format in accordance with the Guidance to Industry: *Providing Regulatory Submissions in Electronic Format – Content of Labeling, April 2005* as described under Tab 12.

20. Does the Agency concur with MRL's proposal to provide the proposed label in SPL format?

FDA Response: Yes, SPL is now required.

Additional FDA Comments:

Please make sure that you include the individual investigator site, address and contact information.

Statistical Comment:

Please include in your submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, (c) SAS programs by which the derived variables were produced from the raw variables. For example, the SAS program(s) for deriving response status (such as CR, PR SD, PD) from original individual tumor measurements.

Office of Drug Safety Comments:

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:
 - Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>
 - Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>
 - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>
- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

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OTHER FDA COMMENTS:**A. REGULATORY****1. NDA/sNDA Presentations to CDER's Division of Oncology**

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

3. PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and

conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

4. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gender:	Males	All Females	Females >50
Age:	0-#1 Mo.	>1 Mo.-#2Year	>2-#12
	12-16	17-64	≥65
Race:	White	Black	Asian
	Other		

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

/s/

Ann Staten
11/30/2005 02:21:39 PM
CSO

Staten, Ann M

From: Lorraine Sachs [lsachs@atonpharma.com]
Sent: Friday, December 19, 2003 3:38 PM
To: Staten, Ann M
Subject: RE: FDA reply to your 12-12-03 submission (responses to SPA letter)

Dear Ann,

Thank you so much for the prompt response. It has been very helpful to us, and we will incorporate the appropriate changes to our Phase IIb protocol for CTCL and submit the revised protocol to the IND before we initiate the trial.

Since this response addresses our questions, we also request that the Type A meeting scheduled for January 5, 2004 be cancelled.

Lorraine

-----Original Message-----

From: Staten, Ann M [mailto:STATENA@cder.fda.gov]
Sent: Friday, December 19, 2003 12:56 PM
To: Lorraine Sachs
Subject: FDA reply to your 12-12-03 submission (responses to SPA letter)

Dear Lorraine,

Here are our responses to your 12-12-03 request for clarification/meeting request.

Please let me know if a teleconference is still needed for 1-5-04.

Sincerely,

Ann

**APPEARS THIS WAY
ON ORIGINAL**

12/23/2003

Staten, Ann M

From: Staten, Ann M
Sent: Friday, December 19, 2003 12:56 PM
To: 'Lorraine Sachs'
Subject: FDA reply to your 12-12-03 submission (responses to SPA letter)

Dear Lorraine,

Here are our responses to your 12-12-03 request for clarification/meeting request.

Please let me know if a teleconference is still needed for 1-5-04.

Sincerely,

Ann

**APPEARS THIS WAY
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12/19/2003

8. Issues for Discussion

For ease of review, Aton's questions are stated in normal font with FDA responses in bold and Aton's reply to the responses in italic.

1. Is the study population adequately defined in the study protocol to support the proposed indication?

FDA Response: The patient population actually entered into the study and the results of the study will determine the indication. The proposed population for your phase 2 study will include only 50 patients. This may not be sufficient to establish efficacy if the response in more advanced stages of disease is less convincing.

We suggest that you provide a precise definition of eligibility: e.g. \geq stage IB (\geq T2 = tumors involving \geq 10% TBSA) and that you study more advanced tumor stage (T3 and T4) patients separately, since these patients have a worse prognosis. You may wish to propose a separate statistical analysis plan and larger sample size for patients with more advanced stage disease since these patients may be less likely to respond to therapy and the response rate of interest may be different.

For the systemic therapies outlined in the inclusion criteria, you should specify a minimum amount of time on therapy to ensure that patients have been given an adequate therapeutic trial. Please clarify whether there is a maximum number of therapies that will be allowed.

The safety database should include additional safety data from your other studies

Aton response: Aton agrees with the Division that the patient population actually entered into the study and the results of the study will determine the indication. Aton also agrees to include additional safety data from other studies of oral SAHA in the NDA submission.

The Inclusion Criteria in section 3.2 specifies that "Patients must have advanced disease documented at study entry as stage IB or higher including Sezary syndrome with progressive, persistent, or recurrent disease on or following two systemic therapies, one of which must contain Targretin (bexarotene) unless the patient is intolerant of or not a candidate for Targretin (bexarotene) therapy." The TNMB classification and clinical staging are provided in section 1.6 (tables 1.6a and 1.6b) of the protocol. At the next protocol amendment, Aton will include TNMB and clinical staging in the protocol appendices for ease of reading.

In the phase II study of CTCL and PTCL unresponsive to conventional therapy (CL-01-0202), 13 patients with CTCL were treated on the once daily dosing

schedule and five patients achieved a partial response based on Physician Global Assessment. The following table lists the T and N classification of disease and number of prior systemic therapies in patients who have achieved a partial response:

T and N Classification and Best Response

<i>Patient ID</i>	<i>T</i>	<i>N</i>	<i>Number of Prior Systemic Therapies</i>	<i>Best Response</i>
001	T4	N2	6	PR
007	T4	N3	6	PR
008	T3	N1	4	PR
012	T4	N1	3	PR
014	T4	N1	5	PR

Although all 5 partial responses occurred in heavily pre-treated patients with T3 or T4 disease, Aton agrees with the Division that the response rate in patients with T3 or T4 disease may be different from the response rate in those with T2 disease in the upcoming multicenter phase IIb study. Aton proposes that a pre-specified subgroup analysis be performed in those with T3 or T4 disease, in which the response rate in overall skin disease will be calculated along with its 95% confidence interval. Does the Division concur with this approach?

In view of the promising anti-tumor activity observed in heavily pre-treated patients with T3 or T4 disease, Aton anticipates the enrollment of a significant number of patients with advanced disease in the upcoming multicenter phase IIb study. Aton does not feel it is necessary to specify the number of patients with T3 or T4 disease because ultimately the indication of SAHA will be determined by the results of patients actually entered into the study. Does the Division concur?

FDA Response: Yes

Aton wishes to clarify that there is no limit on the maximum number of therapies allowed in the inclusion criteria.

Aton has discussed with CTCL investigators the Division's request to specify a minimum amount of time on therapy in the inclusion criteria to ensure that patients have been given an adequate therapeutic trial. CTCL investigators do not believe this can be implemented because the minimum amount of time considered adequate for a therapeutic trial varies with the type of anti-cancer agents used, the severity of the disease being treated, the patient's willingness to remain on treatment, and the treating physician's clinical judgment. Based on CTCL investigators' feedback, Aton does not believe it is possible to pre-specify a minimum amount of time on therapy in the inclusion criteria. Does the Division concur?

FDA Response: Yes, however the CRF and datasets should capture the length of time and specific type of therapy.

2. Is the response rate of overall skin disease based on the Physician Assessment of Overall Skin Disease acceptable as the primary efficacy endpoint?

FDA Response: The primary endpoint, overall skin response, is acceptable. However, the determination of response as a composite endpoint could be problematic if there is a discrepancy between the tumor volume assessment of response and the Severity- Weighted Assessment Tool (SWAT) response assessment. We propose the following response criteria:

Response	Skin	Tumor	Node	SS Cells ³
CR ¹	NED	*	*	NED
PR ²	≥50% reduction in skin score for 4 weeks	≥50% reduction In tumor volume For 4 weeks	≥50% reduction In SPD for 4 Weeks	≤95% reduction In circulating SS cells
PD	≥25% increase In skin score	≥50% increase in tumor volume	≥50% increase In SPD of Abnormal node	≥50% increase in Circulating SS cells

¹Designation of complete response (CR) requires that all four parameters be achieved as applicable to the extent of disease at baseline. *See Cheson, *et. al.* Response criteria for NHL (JCO 17: 1244-1453, 1999) for tumor and node criteria for Complete Response.

²A partial response (PR) for skin or tumor stage is not achieved with patients meeting criteria for progressive disease in any of the other 3 parameters, or when there is evidence of involvement in the other parameters when not present initially.

³As assessed quantitatively by flow cytometry.

Response duration will be a critical factor in establishing clinical benefit.

Aton response: Aton agrees with the Division that there may be a discrepancy between the tumor volume assessment of response and the Severity-Weighted Assessment Tool (SWAT) response assessment. In order to avoid such confusion, Aton proposes to eliminate the use of tumor volume for determining response in overall skin disease. All patients will be assessed by SWAT, including those with primarily T3 disease and ≤ 2% BSA involvement. The response in overall skin disease will be determined by the criteria listed in the following table:

Assessment of Overall Skin Disease

<i>Completely clear</i>	<i>No evidence of disease; 100% improvement</i>	<i>CCR</i>
<i>Marked improvement</i>	<i>Greater than or equal to 50% decrease in skin scores compared to baseline which is maintained for 4 weeks</i>	<i>PR</i>
<i>Slight improvement</i>	<i>Less than 50% decrease in skin scores compared to baseline</i>	<i>SD</i>
<i>Worse</i>	<i>≥ 25% increase in skin scores compared to nadir or ≥50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to nadir</i>	<i>PD</i>

Aton proposes to capture the reduction in overall tumor volume in all patients with T3 disease as a secondary endpoint. Three to 5 index tumors representative of the overall tumor status will be measured at baseline and followed during study. The proportion of T3 patients who have had a ≥50% decrease in index tumor volume will be calculated with its corresponding 95% confidence interval. Does the Division concur with this approach?

FDA Response: Yes, the proposal to assess all patients using SWAT scores, and using tumor volume as a secondary endpoint is acceptable. Do you have any estimate of the percentage of patients you expect to enroll with T3 disease and <2% BSA involvement?

- The primary efficacy measurement will be the Physician Assessment of Overall Skin Disease performed at baseline and every four weeks during the study. The physician will use a Severity- Weighted Assessment Tool (SWAT) for assessment of skin disease. For patients who have primarily tumor stage disease (T3) and ≤2% total body surface involvement by disease, overall tumor volume will be used to assess skin disease. Is this method of response assessment acceptable?

FDA Response: Determination of response as a composite endpoint could be problematic (see our response to Question # 2 above). We suggest that you provide updated response criteria in order to resolve potential response assessment discrepancies or explain how your present proposal will avoid these potential problems.

Aton response: Please see Aton response to the Division's comments to question #2.

FDA Response: Refers to #2.

4. The extent of patient's skin disease will be recorded using photographs at baseline and every four weeks. Full body photographs, front and back, will be obtained. Special instructions to standardize camera settings and lighting requirements across trial sites will be provided to the trial sites. The photographs are meant to be supportive documentation of changes in skin disease and cannot be used to derive skin scores or overall tumor volumes. The skin scores and/or overall tumor volumes must be based on physician's assessment of the patient in clinic and recorded on the Physician Assessment of Overall Skin Disease page of the case report forms. The primary method of documentation is the case report form page of the Physician Assessment of Overall Skin Disease. Is this method of documentation of primary efficacy endpoint acceptable?

FDA Response: The case report forms (CRF's) and digital photographic techniques described are probably adequate but they may be difficult to audit. We suggest you consider including Polaroid-type photographs at baseline and follow-up in the patient's medical record in order to provide additional documentation of responses.

The case report forms provided for review in your protocol did not include a place to record and document the extent of skin involvement by drawing on a body diagram. Your sample body surface area assessment form included in the EOP2 meeting minutes included outlines of the body on which could be recorded areas of involvement. The reference cited in your protocol, Stevens SR *et. al.*, Arch Dermatol. 138:42-8, 2002, also described using body diagrams, called SWAT forms, to record and document the area and severity of involvement. We suggest you consider including body diagrams in the CRF's to help document responses and to assist with the review.

Please provide information regarding how the physicians will be trained in the assessment procedure and what methods may be used to evaluate intra-observer objectivity and the reproducibility of assessments.

Aton response: Aton will include a body diagram in the CRF for recording and documenting skin involvement. However, the body diagram is meant to be a worksheet for the investigators and cannot be used to derive skin scores or overall tumor volumes.

Aton appreciates the Division's feedback on using digital photography for the full body photographs. According to the photography experts at _____ the qualities of Polaroid-type photographs are quite different from digital photographs, which make it very difficult to make comparison between images generated by Polaroid photography and those by digital photography. _____ can provide printouts of electronic imaging within a week of receiving the compact flash card, the media used to record images, and these photographs will be mailed back to the study sites for audit purposes. Does the Division concur with this approach?

Only Investigators who have had experience in assessing skin tumors will participate in the upcoming multicenter Phase IIb trial. The assessment of BSA

involvement and the severity of disease, i.e., patch, plaque, tumor, and erythema, are standard clinical practice in the care of CTCL patients. To the extent possible, the protocol specifies that the same investigators will perform serial assessments of skin disease of each patient. Investigators will be trained on the protocol-specified skin assessments, the documentation of skin scores, and photographic techniques at an Investigator's Meeting in early 2004. For those who are unable to attend the Investigator's Meeting, training will be provided at study initiation visit before patient enrollment begins. Documentation of training will be kept in the study file.

FDA Response: The proposal to use digital photographs is acceptable. Please provide a sample of the photographic printout in addition to your revised final protocol. Please also provide the revised CRF incorporating a body diagram and any algorithm or instructions which will be used by the investigators to assist in the determination of skin scores.

It might be helpful also to include some sample cases with resulting skin scores and tumor volumes so the reviewers can be familiar with the scoring system.

5. Are there any additional data that the Division would require or recommend to be captured on the case report forms?

FDA Response: We suggest that additional space be provided on the CRF to capture any additional comments or observations by the clinicians regarding the patient's response to therapy and to assist in resolving discrepancies between the tumor volume assessment of response and the SWAT responses.

We suggest you consider including body diagrams in the CRF's to help document responses and to assist with the review (see our response to question #4 above).

Aton Response: Because Aton proposes to eliminate response determination based on tumor volume in T3 patients with $\leq 2\%$ BSA, there does not appear to be a need for additional space on the CRFs to help resolving the discrepancies between tumor volume assessment for response and the SWAT responses.

Aton agrees to include body diagrams in the CRFs, which is meant to be a worksheet for the investigators and cannot be used to derive skin scores or tumor volumes.

FDA Response: Comments of investigators regarding the patient's clinical status documented on the CRF's is sometimes helpful during the review process but is not required.

FDA Clinical comment:

Your secondary endpoint of pruritis response as defined by a 3-point decrease on a 10-point scale may be difficult to interpret outside of the context of a blinded

randomized trial. We suggest you analyze for the incidence of complete resolution of pruritis that was initially greater than or equal to 3 on a 10-point scale at study entry.

Section 4 of the protocol describing study treatment, does not include specific prohibition of radiation, PUV A, photopheresis or interferon, all of which have activity in CTCL. We suggest that these treatments be prohibited, and that patients who require these therapies be withdrawn from the study.

Section 5.3 states that patients will be seen in the clinic every 2 weeks for the first 8 weeks on study and then monthly until study completion. Patients with lymph nodes assessable by CT scan will have the first assessment at week 9 and monthly thereafter (study flow chart). Therefore there could potentially be a discrepancy between the initial assessments of visceral and cutaneous disease. We suggest you consider scheduling an initial CT scan at week 5.

Please ensure that the physical exam and laboratory results are well documented in the medical record as well as on the CRF's to maintain optimal patient care.

Aton Response: The basis for considering a 3-point drop in pruritus intensity as clinically significant is based on the standard deviation of pruritus intensity at baseline among patients who had pruritus at study entry in the phase II study at MD Anderson (CL-01-0202). Ten patients had pruritus at baseline. The median pruritus intensity is 10 with standard deviation (SD) of 2.4. In general, 0.5 SD change is considered clinically meaningful. A 3-point change in pruritus intensity represents one SD change, which indicates a large effect and should be interpretable in the context of an open label single arm study.

Aton agrees with the Division that radiation, PUVA, photopheresis or interferon should be prohibited during the study and patients who require these therapies be withdrawn from the study. This is reflected in the exclusion criteria in section 3.3. To emphasize this further in the protocol, Aton will add in section 4 that radiation, PUVA, photopheresis or interferon are not allowed during study and patients who require these therapies should be considered to have progressive disease and be withdrawn from the study.

After further discussion with CTCL investigators, it becomes obvious that the majority of lymphadenopathy in CTCL is peripherally located and palpable. It is exceedingly rare to have mediastinal or intra-abdominal adenopathy. The standard clinical practice in CTCL is to assess lymph nodes regularly by physical exam. CT scans are not routinely obtained in patients without palpable adenopathy. For those with stable palpable adenopathy, CT scan is generally performed every 6-12 months. Based on CTCL investigators' feedback, Aton proposes to revise the protocol to state that follow-up CT scan will only be performed in patients who have had $\geq 50\%$ shrinkage in adenopathy by physical exam to confirm the physical exam findings. Subsequent CT scans will be performed as clinically indicated to confirm complete resolution of adenopathy. Of note, all patients will have baseline CT scans for accurate staging. Clinically palpable lymph nodes will be measured and recorded on the CRFs. Does the Division concur with this approach?

Aton agrees that adequate documentation of physical exam and laboratory results in the medical chart is essential for optimal patient care. The laboratory results from a central lab will be sent to the investigator for optimal care of the patient.

FDA Response/Further comments:

Complete or near complete resolution of pruritis are more easily interpretable in the context of a single arm trial than a relative change in pruritis scores.

If disease is easily evaluable by physical examination then follow-up by serial physical examination is appropriate. If disease is primarily evaluable by CT scan, then follow-up should be by CT scan.

We encourage you to document responses by CT in cases where this is practical.

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/s/

Ann Staten
12/23/03 10:30:23 AM

Ramzi Dagher
12/23/03 10:49:46 AM

MEETING MINUTES

MEETING DATE: December 19, 2003

IND/NDA: 58,915 **Meeting Request Submission Date:** December 12, 2003 (N088)

FDA Response Date: December 15, 2003

Briefing Document Submission Date: December 12, 2003 (N088)

Other Submissions: December 3, 2003 (N086) GC

DRUG: SAHA

SPONSOR/APPLICANT: Aton Pharma

TYPE of MEETING/TELECON:

Follow-up to EOP2 - Clarification of Special Protocol Assessment response letter

FDA PARTICIPANTS:

Ramzi Dagher, MD, Medical Team Leader

Peter Bross, MD, Medical Reviewer

Ann Staten, RD, Project Manager

BACKGROUND: On 12-3-03, Aton requested clarification to the Agency's Special Protocol Assessment letter dated 12-1-03. On 12-12-03, Aton submitted a complete meeting request.

On 12-19-03, the FDA e-mailed responses to Aton's request for clarification (attached). The sponsor requested on 12-19-03 that the meeting be cancelled since further clarification was not needed (attached).

MEETING/TELECON OBJECTIVES:

To clarify the 12-1-03 Special Protocol Assessment response letter.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

See attachment

ACTION ITEMS:

No action items identified.

Ann Staten, RD, Project Manager

Concurrence Chair: _____
Ramzi Dagher, M.D.,
Medical Team Leader

Attachment: FDA e-mail and Aton's reply (both dated 12-19-03)

**APPEARS THIS WAY
ON ORIGINAL**

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ON ORIGINAL**

Staten, Ann M

From: Lorraine Sachs [lsachs@atonpharma.com]
Sent: Friday, December 05, 2003 6:14 AM
To: statena@cder.fda.gov
Subject: Type A meeting and EOP2 nonclin Type B meeting

Ann,

Regarding the Type A meeting we requested to discuss the SPA responses, I can tell you right now that we will want to discuss the responses to questions 1 to 5. We do not need to discuss the comments made regarding clinical pharmacology. We will submit a preread package next week.

I have asked my team about availabilities the week of Dec 29 and it doesn't look like we can do it that week. Is there any chance for the first week in January?

Regarding the EOP2 nonclin meeting scheduled for Dec 10, we are in receipt of the responses and have decided that we do not need to have the teleconference, therefore we are requesting that you cancel it. We will submit a letter next week with some comments to the responses.

Thank you.

Regards,

Lorraine

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

/s/

Ann Staten
12/16/03 01:08:51 PM

David Morse
12/17/03 12:55:20 PM

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Lorraine W. Sachs

From: Ann Staten, Project Manager

Fax: 914-347-2031

Fax: 301-827-4590

Phone: 914-784-1108

Phone: 301-594-0490

Pages: 4

Date: 12-4-03

Re: IND 58,915 SAHA

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Dear Ms. Sachs,

Please refer to your EOP2 meeting request dated October 14, 2003 and the briefing package dated November 7, 2003.

Attached are the FDA answers to your questions. You have the option of canceling our meeting of December 10, 2003 if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible if you are canceling the meeting.

Sincerely,

Ann Staten

IND 58,915 Non-clinical EOP2 meeting

1. We believe the proposed pharmacology and pharmacokinetic/toxicokinetic studies will be adequate for supporting a New Drug Application (NDA) for CTCL — Does the Division concur?

FDA Response:

The general pharmacology and mechanism of action data, as outlined in your meeting packet of November 7, 2003, appear adequate to support the filing of an NDA for CTCL — In addition, the pharmacokinetic/toxicokinetic data for toxicologically relevant doses studied in the rat and dog appear adequate to support an NDA filing. However, we note the absence of meaningful excretion and tissue distribution data for the species utilized in the toxicologic evaluation of SAHA, and strongly encourage the development of this information. Further, we note an apparent increase in the metabolism of SAHA to the "succinate" with repeat dosing, and encourage further kinetic/metabolic assessment in your long-term toxicity studies.

2. We believe the proposed nonclinical toxicology program will be adequate for supporting a NDA for CTCL — Does the Division concur?

FDA Response:

The Division generally concurs with the adequacy of the proposed 6-month rat and dog repeat dose toxicity studies to support your proposed clinical indications. However, we note your intent to initiate the 6-month toxicology studies based on dose selection from your previous 1-month repeat dose studies. Moreover, results of the 6-month studies (to be initiated in December 2003 and February 2004) are not likely to be available until the end of 2004 or early 2005. Thus, during 2004, it is likely that the duration of dosing in clinical trials will far exceed the duration of significant toxicologic support. Therefore, we encourage you to consider the inclusion of satellite treatment groups in your 6-month toxicology studies, with these groups being used for interim sacrifice at 3 months treatment duration. Lastly we encourage you to initiate the non-clinical toxicity studies sufficiently in advance of your extended duration clinical trials, such that the toxicologic support precedes progression of significant patient exposure.

3. A number of dosing schedules are being considered for the clinical trials intended to support the marketing application, including once a day (q.d.) or twice a day (b.i.d.) either continuously or with a rest period of up to one week. The maximum-tolerated dose or recommended phase 2 doses in humans is 400 mg q.d. or 200 mg b.i.d given continuously without a rest period. The dose-limiting toxicities in humans by q.d. or b.i.d. dosing without a rest period are similar and consist of anorexia, dehydration, fatigue, and diarrhea (non-hematologic). We are currently testing a variety of intermittent dosing schedules in humans and have found that a rest period of 2 days after 5 consecutive days of dosing (i.e., 5 consecutive days of dosing per week) does not change the attainable total daily dose (400 mg) or the adverse event profile

IND 58,915 Non-clinical EOP2 meeting

compared to continuous administration. Based on the above findings, we propose to conduct the 6-month rat study using daily oral gavage and the 6-month dog study using capsules of the to-be-marketed formulation administered 5 days per week for 26 weeks. We believe this plan will support the safety of all of the mentioned schedules. Does the Division concur?

FDA Response:

The proposed dosing plan for the rat and dog 6-month repeat dose studies appears acceptable.

4. FDA has provided guidance on the acceptable duration of chronic toxicity testing in nonrodents (*Fed. Reg.* 64:34259-34260, 1999). FDA stated that 6-month studies may be acceptable for drugs intended for indications of life-threatening diseases for which substantial long-term human clinical data are available, such as cancer chemotherapy in advanced disease or in adjuvant use. We believe that a substantial number of patients will have been treated chronically with SAHA at the time of the NDA submission. Moreover, we believe that 6 months of treatment will be adequate to identify the toxicological hazards associated with chronic SAHA administration in dogs. Does the Division concur that a 6-month dog study will be acceptable for fulfilling the need for a chronic nonrodent study to support NDAs for CTCL or

FDA Response:

Yes. The proposed 6-month non-rodent toxicity assessment of SAHA appears adequate to support the proposed indications. However, future changes in product indication, or demonstration of efficacy resulting in significant prolongation of life expectancy (with continued chronic use) could necessitate further toxicologic evaluation.

5. Based on the toxicities observed to date in rats, dogs, and humans we believe that the standard toxicology study assessments will be adequate to identify and monitor SAHA toxicity in the chronic animal studies. Does the Division concur that additional, non-standard toxicity assessments do not need to be included in the chronic studies in order to fully investigate the safety of this class of compounds or SAHA in particular?

FDA Response:

Your plan to include only standard toxicology study assessments in your 6-month repeat dose studies of SAHA appears adequate to support product testing in cancer patients. However, we recommend the assessment of chromosomal aberrations in your chronic toxicity studies.

IND 58,915 Non-clinical EOP2 meeting

Additional Pharmacology/Toxicology Comment:

We request that you submit an outline (e.g., gant chart) describing the expected initiation and completion dates for your non-clinical studies in relation to timing of clinical studies in CTCL and DLBCL.

Clinical Pharmacology and Biopharmaceutics Comments:

1. **In Vitro Inhibition and Induction studies:** Based on your summary of the in vitro studies, it appears that a number of drug interaction studies may be necessary. Please submit complete study reports for the in vitro inhibition and induction studies. We also expect that many of these findings will need to be investigated in vivo. Please submit your plans for in vivo studies.
2. **Metabolism - glucuronidation:** We recommend that you determine the specific UDP-glucuronyl transferase pathway involved in the formation of the SAHA glucuronide.
3. **Organ Impairment studies:** We remind you of our recommendation that you conduct studies to evaluate the effect of — hepatic impairment on the pharmacokinetics (PK) of SAHA and its metabolites (Please refer to the Sept 9, 2003 meeting minutes, additional comments).

**APPEARS THIS WAY
ON ORIGINAL**

MEETING MINUTES

MEETING DATE: December 2, 2003

IND/NDA: 58,915 **Meeting Request Submission Date:** October 14, 2003 (N079)

FDA Response Date: October 23, 2003

Briefing Document Submission Date: November 7, 2003 (N084)

DRUG: SAHA

SPONSOR/APPLICANT: Aton Pharma

TYPE of MEETING/TELECON:

End of Phase 2 – non-clinical (pharmacology/toxicology)

FDA PARTICIPANTS:

Grant Williams, MD, Deputy Director, DODP

David Morse, Ph.D., Pharmacology/Toxicology Team Leader

Doo Young Lee-Ham, Ph.D., Pharmacology/Toxicology Reviewer

Ramzi Dagher, MD, Medical Team Leader

Gene Williams, Ph.D., Acting Clinical Pharmacology Team Leader

Roshni Ramchandani, PhD, Clinical Pharmacology Reviewer

Ann Staten, RD, Project Manager

BACKGROUND: Previous EOP2 clinical/statistical meeting held on 9-9-03. Previous CMC EOP2 meeting minutes 10-15-03.

Following the internal pre-industry meeting on 12-2-03, FDA's responses were sent to the sponsor in a facsimile dated 12-4-03 (attached). The sponsor requested on 12-5-03 that the meeting be cancelled since clarification was not needed (attached).

MEETING/TELECON OBJECTIVES:

To obtain guidance on the non-clinical development plan for SAHA.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

See attachment

ACTION ITEMS:

No action items identified.

Ann Staten, RD, Project Manager

Concurrence Chair: _____
David Morse, Ph.D.,
Pharmacology/Toxicology Team Leader

Attachment: FDA facsimile dated 12-4-03
Aton e-mail dated 12-5-03

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6 Page(s) Withheld

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



IND 58,915

Aton Pharma
777 Old Saw Mill River Road
Tarrytown, New York 10591

Attention: Lorraine W. Sachs, RAC
Director, Regulatory Affairs

Dear Ms. Sachs:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Suberoylanilide Hydroxamic Acid (SAHA).

We also refer to your September 26, 2003, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Suberoylanilide Hydroxamic Acid (SAHA) for cutaneous T-cell lymphoma (CTCL) as a fast track product.

We are granting fast track designation for the following reasons:

1. Cutaneous T-cell lymphoma (CTCL) is an uncommon incurable hematological malignancy that is characterized by cutaneous infiltration of the skin with malignant T-cells. CTCL is incurable by current therapies and can cause substantial impact on day-to-day functioning with disfiguring skin manifestations and intractable pruritis. Patients may also develop life threatening visceral involvement.
2. Treatment with SAHA has demonstrated the potential to treat a serious aspect of the condition by inducing partial responses in 5/13 patients with CTCL who were unresponsive to conventional therapy and decreasing symptoms of pruritis in 5/10 patients in a small phase 2 trial.

If you pursue a clinical development program that does not support use of Suberoylanilide Hydroxamic Acid (SAHA) for cutaneous t-cell lymphoma (CTCL), we will not review the application under the fast track development program.

If you have any questions, call Ann Staten, Project Manager, at (301) 594-0490.

Sincerely,


Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Richard Pazdur
11/26/03 03:03:02 PM

BACKGROUND: For CTCL, Aton is proposing a single arm study of patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease on or following a Targretin (bexarotene)-containing regimen; or are intolerant of or are not a candidate for Targretin therapy.

After the September 2, 2003 pre-meeting, FDA faxed our responses to the questions to sponsor on September 3, 2003. Sponsor chose to have the face-to-face meeting for clarification of several questions/responses, which are indicated by italics.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Given the rareness of CTCL and the lack of alternative efficacious therapy for patients with CTCL who have progressive, persistent, or recurrent disease on or following a Targretin (bexarotene)-containing regimen, or are intolerant of or are not a candidate for Targretin (bexarotene) therapy, Aton believes the proposed non-randomized phase IIb study will support *Does the Division concur?*

FDA - A well-conducted single arm study might support

Targretin capsules are indicated 'for the treatment of cutaneous manifestations of T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.' Eligibility criteria for your study should include only patients who are refractory to or intolerant of Targretin and at least one prior systemic therapy. The reasons for Targretin intolerance will need to be clearly documented on the CRF. Inclusion of a significant number of patients who have not been treated with Targretin may not support registration in a refractory indication if the responses are mostly observed in the untreated population.

The sponsor noted they and will have the 3 populations clearly defined and prospectively specified at entry. FDA concurred.

Sponsor inquired whether combination therapies could count singly and we agreed, i.e. a combination of two systemic therapies used concomitantly would count as two systemic therapies.

2. Aton believes response as measured by the overall skin assessment is an acceptable primary endpoint for demonstrating efficacy in patients with CTCL who have progressive, persistent, or recurrent disease on or following a Targretin (bexarotene)-containing regimen, or are intolerant of or are not a candidate for Targretin (bexarotene) therapy. *Does the Division concur?*

FDA – Yes, we believe so but will examine further in the SPA. Your protocol outline proposes to use two methods of response assessment, depending on the stage of disease. A Severity-Weighted Assessment Tool (SWAT) (Stevens et al. 2002) will be used for MF, and a separate skin score (Edelson et al. 1987) will be used for erythrodermic patients. A primary endpoint defined by two different tools in the different subpopulations could make the results of such a trial difficult to interpret.

The sponsor is now proposing SWAT as the only tool (see attached overheads). FDA agreed to look at this proposal in the SPA.

3. If SAHA demonstrates an adequate safety profile, Aton believes that response rate based on overall skin assessment is a clinical benefit measure that can be used to support
Does the Division concur?

FDA - Consistent demonstration of impressive cutaneous responses in hematologic malignancies could be considered to be evidence of clinical benefit. Whether the proposed trial can support will be a review issue and depends upon the results of the trial. The proposed skin scoring system method was not described in the reference (Edelson et al. 1987) with sufficient clarity to determine its acceptability. Please submit a complete description of the proposed skin scoring system including proposed method of documentation (photos, etc) as well as sample CRF's as a Special Protocol Assessment prior to initiating any studies for registration in CTCL.

See #2. FDA also noted the importance of having uniformity of photographic procedures. Photos are meant to be supportive documentation.

4. Aton has selected response duration and symptomatic relief of pruritus as secondary efficacy endpoints to support the primary efficacy endpoint. Does the Division concur?

FDA - Adequate demonstration of response duration would be essential to support the primary efficacy endpoint. Although subjective patient reported outcomes such as pruritus are generally difficult to interpret in the absence of a blinded, randomized trial, we encourage collection of pruritus data.

5. Aton has evaluated the available safety, pharmacokinetics, and efficacy data and has chosen 400 mg QD as the proposed dosing schedule for the CTCL phase IIb clinical trial. Does the Division concur?

FDA - Your meeting package (p23) states that "the MTD or recommended phase 2 dose has been established at 400 mg QD, 200 mg BID, or 300 mg BID 3 days/week." Your phase 1 study CL-01-01-01 was ongoing at the time the summary data (Table 2) was presented. We do not have sufficient information to make a recommendation based on the data provided. If you wish to provide updated and more detailed information we can discuss this issue further.

6. Aton believes that the proposed phase IIb study plus efficacy data from the phase II single center study in CTCL (Study No. CL-01-02-02) will be adequate to demonstrate substantial evidence of clinical effectiveness. Does the Division concur?

FDA - This is a review issue. Please provide information indicating why it would not be possible to complete a randomized study comparing SAHA and Targretin for confirmation of clinical benefit in patients with CTCL.

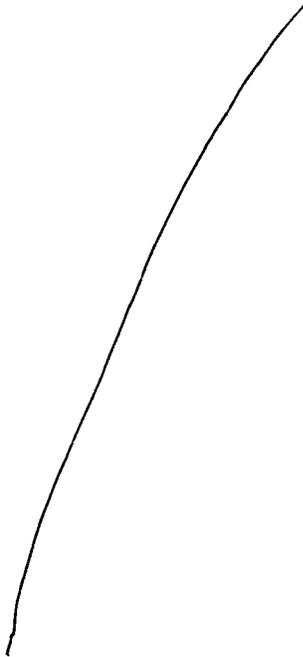
Sponsor presented their arguments against a randomized study, including the point that there are few if any Targretin-naive patients, the onset of effect of Targretin is much later than that of SAHA, and dose titration is very difficult with Targretin.

7. At the time of the NDA filing there will be safety data on approximately 250 subjects who have received SAHA capsules. Is this safety database adequate to support the registration of SAHA for the proposed indication in CTCL?

FDA - This is also a review issue and may depend on the nature of the safety data and efficacy results, i.e., risk/benefit assessment in the proposed CTCL patient population.

8. Aton believes that preliminary efficacy and safety data of SAHA in CTCL patients demonstrate that SAHA has the potential to treat this serious and life-threatening disease, that the proposed development plan in CTCL patients who have progressive, persistent, or recurrent disease on or following a Targretin (bexarotene)-containing regimen, or are intolerant of or are not a candidate for Targretin (bexarotene) therapy addresses an unmet medical need, and that the proposed development plan of SAHA in CTCL will support an application for Fast Track designation. Does the Division concur?

FDA - Your preliminary results appear promising. Please submit your most recent available updated clinical data for consideration of Fast Track designation for the treatment of persistent or recurrent CTCL following a Targretin containing regimen and at least one additional systemic therapy.



Clinical Pharmacology

13. In the clinical protocols for the proposed phase IIb trials, Aton will specify that SAHA may be taken with or without food. This is based on pharmacokinetic data from 22 patients enrolled in a phase I clinical trial conducted at — (Study No. CL-01-01-01). Using a research analytical method to determine SAHA concentrations in plasma, food did not appear to alter the rate or extent of absorption. Does the Division concur that these data are sufficient to allow SAHA to be taken with or without food during the proposed phase IIb clinical trials?

FDA – No. The study design and methods have several limitations which make the results inconclusive. The limitations include:

- 1) a relatively small number of subjects given the relatively high variability in pharmacokinetic parameters and inadequate power to detect a difference.
- 2) fasting is for less than 2 hours rather than the suggested 10 hours.
- 3) sequential rather than randomized balanced design, however given the half life of the drug this may not be an issue.
- 4) A nonvalidated assay was used.

Moreover, the upper limits of the 90% confidence interval of the ratio of fed:fasted for C_{max} , $AUC_{(0-1)}$ and $AUC_{(0-8)}$, are all greater than 125 %, suggesting that there might be a food effect, which may become more apparent with a 10 hour fast and a larger sample size. Therefore we recommend that SAHA be given under fasted conditions in the proposed Phase 2B trial and a prospective study be done to examine the food effect according to the guidance (please refer to the FDA guidance document Food-Effect

Bioavailability and Fed Bioequivalence Studies: Study design, data analysis, and labeling at www.fda.gov/cder/guidance.htm

14. In a phase I clinical trial conducted at — (Study No. CL-01-01-01), oral pharmacokinetic data were obtained in 22 patients using a research LC/MS analytical method for plasma concentration of SAHA.

Aton presented their case for not doing their Phase 2B trial fasting and FDA found it acceptable to proceed as proposed with a nonfasting study, although we still recommend a fasting study be conducted at some point.

15. Aton plans to determine the pharmacokinetics in serum of oral SAHA using a validated analytical method in 6 patients from the phase IIb clinical trial in CTCL. Exploratory studies have identified SAHA glucuronide and SAHA succinate as major metabolites in human urine. Aton also plans to determine the pharmacokinetics of these metabolites (which are inactive as inhibitors of histone deacetylase or cell proliferation) in these patients. Does the Division agree that this plan is adequate to support the future NDA filing?

FDA - No. This plan by itself is not adequate. With regard to the pharmacokinetics (PK) component of the proposed Phase 2B part of the clinical trial, it is recommended that you plan to evaluate the PK of the parent and the metabolite(s) in plasma/serum and in urine.

Six patients will not be adequate for reliable estimation of PK parameters. We recommend that you assess PK in at least 12 to 18 patients. Please see below for additional comments for other studies to be included for future NDA submission.

Aton proposes to do PK — We said this may be acceptable, depending on the variability of the drug. Aton also inquired whether the urine study could be done in the food effects study. We concurred as long as the result is a characterization of the disposition of the drug and its major metabolites.

ADDITIONAL FDA COMMENTS:

Clinical Pharmacology and Biopharmaceutics

- 1. You should plan to examine the exposure-response relationship for SAHA to correlate the pharmacokinetics (PK) of SAHA with response measures in your Phase 2 studies. You can assess the PK by using a sparse sampling population PK approach or you can use a rich sampling scheme to estimate PK parameters, or alternatively rich sampling in 12-18 patients combined with a sparse sampling in the rest of the patients. Also, a richer sampling in special populations (e.g. renal impairment) might be beneficial.**

2. **You should do mass balance studies to evaluate the disposition characteristics of SAHA and also the different routes of elimination.**
3. **You should plan to do a study to evaluate PK in renally-impaired patients, if appropriate.**
4. **You should also plan to do a study to evaluate PK in hepatically-impaired patients, if appropriate.**
5. **You should also conduct in vitro CYP450 studies to characterize the metabolic profile for SAHA, if not done already.**
6. **You should plan to do the appropriate drug interaction studies based on in vitro CYP450 studies.**
7. **You should also conduct studies to assess the inhibition and induction potential of SAHA.**
8. **You should do protein binding studies for SAHA and any active metabolites.**
9. **If the clinical formulation is different from the to-be-marketed formulation a bioequivalence study is required.**
10. **Please include a detailed report of the analytical method for serum and urine assay for the parent and its metabolites.**

Additional comment regarding methods:

In the phase 1 study (week 1), for the IV dose, in the study description section (section 10.1, page 29) it is mentioned that the infusion was administered for 2 hours. However, the mean concentration vs. time plots for the 200 and 400 mg dose appeared to indicate that there is already a decline after the 1 hour time point. Please clarify this discrepancy.

ACTION ITEMS:

1. Sponsor will submit SPAs for CTCL
2. FDA will verify with pharm/tox teams re: appropriateness of a volunteer study for food effects given the geno-tox status (sponsor will submit these studies ASAP).
3. Aton will schedule a separate meeting with biopharmaceutics.

Dotti Pease
Chief, Project Management Staff

Concurrence Chair: _____
Peter Bross, M.D.
Medical Officer

IND 58,915 SAHA 9-9-03 EOP2 Meeting

Page 8

ATTACHMENTS: Standard EOP2 Bullets (SPAs, Clinical Trials Database, Financial Disclosure, Pediatrics, Demographics, chemistry meeting

Sponsor overheads (3)

Sponsor's overall development plan and protocol outlines for each indication

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STANDARD EOP2 BULLETS

FINAL PROTOCOLS

Please refer to the December 1999 DRAFT "*Guidance for Industry - Special Protocol Assessment*" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF) should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we would like to use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs till 45 days after we receive the consultant's written comments.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fml.htm>

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system by will be made available to the public on the Internet at <http://clinicaltrials.gov>.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

FINANCIAL DISCLOSURE FINAL RULE

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

PEDIATRIC FINAL RULE

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

PEDIATRIC EXCLUSIVITY

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. 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 on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) 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.

DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gender	Males	All Females	Females >50
Age:	0-#1 Mo.	>1 Mo.-#2Year	>2-#12

	12-16		17-64		65+	
Race:	White		Black		Asian	
	Other					

CHEMISTRY

Prior to initiating pivotal clinical studies, we request a complete, updated submission of chemistry, manufacturing and controls (CMC). Please refer to the appropriate CDER guidelines for assistance in preparing this submission. At the time of this submission, we strongly urge you to request a meeting to discuss CMC issues, e.g., impurity profile, stability protocols, approaches to specifications, and attributes, packages, etc.

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§ 552(b)(4) Draft Labeling

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/s/

Peter Bross

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