CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

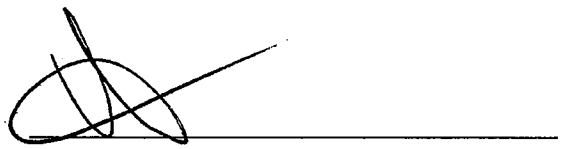
22-542Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.3.5.2 PATENT CERTIFICATION

In the opinion and to the best knowledge of Axcan Pharma US, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs (21 CFR 314.50(i)(1)(ii)).

The reference listed product, COTAZYM® (NDA 20-580), has no patents listed in the Orange Book.



October 26, 2009

Richard Tarte
General Counsel
Axcan Pharma US, Inc.

Date

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
22-542

NAME OF APPLICANT/NDA HOLDER
AXCAN PHARMA US, 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)
TRADENAME (PANCRELIPASE, USP)

ACTIVE INGREDIENT(S)	STRENGTH(S)
TRADENAME (PANCRELIPASE, USP)	10 440 U Lipase, 39 150 U Amylase, 39 150 U Protease 20 880 U Lipase, 78 300 U Amylase, 78 300 U Protease

DOSAGE FORM
Tablet

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 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	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	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)*
	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? ☐ Yes ☐ No

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

PSC Graphics (301) 443-1090 EF

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 pending 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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) 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.)*	

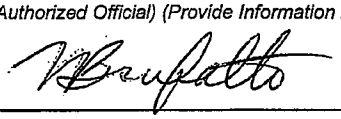
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(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

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
	OCTOBER 29, 2009

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 NICOLE BRUFATTO	
Address 450 NORTH LAKESHORE DRIVE	City/State MUNDELEIN, IL
ZIP Code 60060	Telephone Number 866-722-6734
FAX Number *(if available)* 905 689 1465	E-Mail Address *(if available)* NBRUFATTO@CANREGINC.COM

EXCLUSIVITY SUMMARY

NDA # 022542 SUPPL # HFD # 180

Trade Name Viokace

Generic Name pancrelipase

Applicant Name Aptalis Pharma US, Inc.

Approval Date, If Known March 1, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

The applicant claims exclusivity for viokace but does not specifically indicate the years of exclusivity.

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☐

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

NDA#

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 ☐

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 ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

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

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

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

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

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

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

Investigation #1 !
!
YES ☐ ! NO ☐

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

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Jagjit Grewal, M.P.H.
Title: Senior Regulatory Health Project Manager
Date: February 15, 2012

Name of Office/Division Director signing form: Julie Beitz, M.D.
Title: Director, Office of Drug Evaluation III

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.

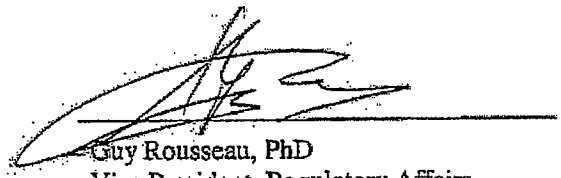
/s/

JAGJIT S GREWAL
02/28/2012

JULIE G BEITZ
02/28/2012

1.3.3 DEBARMENT CERTIFICATION

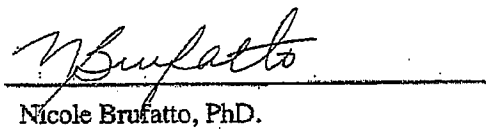
Axcan Pharma US, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 22-542) for VIOKASE® (pancrelipase, USP) Tablets.



26 Oct 2009

Guy Rousseau, PhD
Vice President, Regulatory Affairs
Axcan Pharma US, Inc.

Date



26 Oct 2009

Nicole Brufatto, PhD.
Director, U.S. Regulatory Affairs
CanReg Inc.
(U.S. Agent)

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022542 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Viokace Established/Proper Name: pancrelipase Dosage Form: Tablets		Applicant: Aptalis Pharma US Inc. Agent for Applicant (if applicable):
RPM: Jagjit Grewal, M.P.H.		Division: Gastroenterology and Inborn Errors Products

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

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

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

None.

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

☒ If no listed drug, check box and explain: Literature based

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

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

☒ No changes ☐ Updated Date of check: 3/1/2012

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

❖ Actions	
• Proposed action • User Fee Goal Date is March 1, 2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AP 3/1/2012, CR 11/28/2010
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]

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

☒ Fast Track
☒ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

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

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

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

Comments:

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

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

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

Version: 6/18/10

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	3/1/2012
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): AP 3/1/2012; CR 11/28/2010
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2/14/2012
• Original applicant-proposed labeling	October 30, 2009
• Example of class labeling, if applicable	Creon, Pancreaze, Zenpep, Foreign labeling: Canadian

[3] Fill in blanks with dates of reviews, letters, etc.
Version: 6/18/10

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2/14/2012
• Original applicant-proposed labeling	10/30/2009
• Example of class labeling, if applicable	Creon, Pancreaze, Zenpep
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	1/9/2012
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	12/8/2011, 1/25/2010 12/5/2011, 6/23/2010, 10/18/2010, 1/22/2010
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 11/29/2009 ☒ DMEPA 10/31/2011, 10/18/2010, 2/5/2010 ☒ DRISK 2/6/2012, 7/19/2010 ☒ DDMAC 2/8/2012, 6/29/2010 ☐ CSS ☒ Other reviews PMHS: 8/17/10 OBP RPM: 2/15/2012 SEALD: 2/9/2012
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	12/11/2009
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 2/13/2012
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 2/28/2012
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 2/28/2012
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7/7/2010 If PeRC review not necessary, explain: ____ • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 6/18/10

❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	2/27/2012, 2/24/2012, 2/21/2012, 2/13/2012, 2/10/2012, 2/1/2012, 12/21/2011, 12/20/2011, 12/1/2011, 11/7/2011, 9/15/2011 (2), 10/27/2010, 10/5/2010, 9/16/2010, 9/14/2010, 8/19/2010, 8/12/2010, 8/5/2010, 7/30/2010, 7/7/2010, 7/6/2010, 6/18/2010, 6/4/2010, 5/11/2010, 1/11/2010, 1/6/2010, 11/12/2009
❖ Internal memoranda, telecons, etc.	3/1/12, 2/22/2012, 1/6/2010
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 7/17/2007
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 2/7/2007, 10/4/2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	12/29/2006, 10/31/2006, 8/29/2002
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 2/29/2012, 11/24/2010
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 2/9/2012, 11/24/2010
PMR/PMC Development Templates *(indicate total number)*	☐ None 13 PMCs 2/29/2012
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Signature concurrence with primary review; see also CDTL review
• Clinical review(s) *(indicate date for each review)*	12/12/2011, 11/10/2010, 12/23/2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None n/a
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	11/10/2010, Clinical review pg. 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)* PMHS, Drug Utilization	☐ None PMHS: 2/16/2010 Drug Utilization: 2/1/2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

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

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	10/29/2009 amended: 8/20/2010, 9/17/2010 None ☐ None 7/19/2010 OSE/DRISK (see labeling review)
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Review: 6/30/2010; Letters: 6/1/2010, 8/19/2010
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 11/03/2010; 12/2/2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/17/2010, 12/18/2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 6/30/2010
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 2/10/2012, 6/29/2010, 12/9/2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 2/28/2012, 2/9/2012, 11/23/2010
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 2/1/2012, 10/12/2010 (ONDQA), 9/28/2010 (ONDQA), 9/24/2010, 12/24/2009
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 2/3/2012, 11/10/2010, 6/21/2010, 12/7/2009
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/24/2010, page 2
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 2/2/2012 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested (review pg 23) ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.
Version: 6/18/10

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

/s/

JAGJIT S GREWAL
03/01/2012

MEMORANDUM OF MEETING MINUTES

Meeting Date:	February 27, 2012
Meeting Time:	2:00 PM-2:20 PM EST
Meeting Type:	Teleconference
Applications:	NDA 022542 Viokace (pancrelipase) Tablets
Sponsor/Applicant:	Aptalis Pharma US, Inc.
Meeting Chair:	Julie Beitz, M.D.
Meeting Recorder:	Jagjit Grewal, M.P.H.

FDA ATTENDEES:

Office of Drug Evaluation III

Julie Betiz, M.D.	Director

Division of Gastroenterology and Inborn Errors Products

Anil Rajpal, M.D.	Medical Team Leader
Jagjit Grewal, M.P.H.	Senior Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Aptalis Pharma US, Inc

Ruth Thieroff-Ekerdt, M.D.	Chief Medical Officer
David Ellis, PhD.	Vice President Global Regulatory Affairs
Guy Rousseau, Ph.D.	Executive Director, Regulatory Affairs
Ivan Shaw	Director, Clinical Development

BACKGROUND:

Reference is made to NDA 022542 Viokace (pancrelipase) Tablets dated October 29, 2009. Reference is also made to the class 2, NDA re-submissions dated September 1, 2011.

On February 10, 2012, FDA issued to Aptalis Pharma a proposal for postmarketing commitments (PMCs) and postmarketing requirements (PMR) for the referenced NDA. Aptalis submitted email correspondence on February 14, 2012, containing their rationale for why the proposed PMR to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Viokace was not needed (see Attachment #1). Aptalis also sent email correspondence on February 23, 2012, containing additional justification for not requiring the PMR and expanding upon the rationale provided earlier (see Attachment #2). On February 27, 2012, FDA requested a brief teleconference with the sponsor to discuss the final determination on the need to establish this PMR for Viokace.

TELECONFERENCE DISCUSSION:

FDA asked Aptalis if Viokace, when available, was used more on an intermittent basis to treat acute exacerbations rather than chronic use in cystic fibrosis patients. Aptalis indicated that dietary and lifestyle changes are more important aspects to address regarding treatment of

chronic pancreatitis (CP) patients. Viokace would be used in these patients for sudden onset of steatorrhea. Aptalis referred FDA to guidelines provided by the Cleveland Clinic and the references noted in their February 23, 2012 correspondence.

FDA asked if Viokace would be used more for acute exacerbations of pain and if patients would cease taking the product when the pain subsides. The sponsor noted that Viokace would not be indicated for use to treat pain, but rather steatorrhea. To treat steatorrhea, the product would be used short term.

FDA noted that Viokace may be used in some CP patients for relief of pain and asked if the sponsor would be interested in conducting a formal study in the future to evaluate this potential treatment. Aptalis replied that they currently have no plans to conduct a trial evaluating the use of Viokace to treat pain in CP patients. Aptalis noted that in their review of various studies (meta-analyses), Viokace did not demonstrate adequate control of pain.

Aptalis confirmed that they plan to include Ultresa in the ongoing collaborative viral transmission PMR study being conducted by (b) (4). Aptalis stated that the point prevalence study will capture the time before and after the first PERT products were approved. The protocol would not capture PERT use by brand as it is difficult to re-construct the specific PERT a patient may be taking during any one period. The PMR study would collect a history of PERT exposure, but not specifically by brand. The point prevalence study will be conducted in CF patients.

Aptalis noted that Viokace was used in CF patients before the advent of enteric coated products in the 1980s. Viokace may also be used in CF patients for gastrostomy tube procedures. It may be possible to capture some use of Viokace within the ongoing point prevalence viral PMR study, but it is difficult to reliably determine what specific PERT a patient may have been on at a given time.

Aptalis further indicated that with respects to the point prevalence study in CF patients, to demonstrate seropositivity a patient would need at least 6 consecutive months of chronic PERT therapy with a suitable dose of enzyme. CP patients will not meet the long term exposure required. CF patients take large quantities of enzyme over a long period of time. Additionally, since Viokace has been off of the market for a period of time, it is not known if patients that switched to an enteric coated product may have received viral exposure from that enteric coated PERT. There are also environmental factors to consider that may increase the potential viral exposure.

Aptalis stated that not many studies in CP patients are conducted in the US. There are a limited number of sites available to participate in CP studies and most are based in the eastern US. This provides a challenge in establishing an appropriate representation of potential viral exposure across the population.

Aptalis believes that the amount of information and evidence generated from the porcine viral transmission PMR in CF patients (b) (4) would far outweigh the information that may be obtained from a separate study of Viokace in CP patients.

FDA acknowledged the feasibility issues in conducting a viral PMR study for Viokace as outlined by the sponsor. Therefore, the viral transmission PMR will not be established for Viokace. FDA indicated that if a safety signal is observed from the ongoing viral PMR study in CF patients, an additional safety study may be needed in the future with all approved PERTs, including Viokace. Aptalis acknowledge this point.

ATTACHMENTS:

1. Attachment #1 – Aptalis rationale for why a viral transmission PMR is not needed for Viokace (dated February 14, 2012)
2. Attachment #2 – Aptalis additional information to support justification that the viral PMR should not be required (dated February 23, 2012)

Please review the following proposed postmarketing requirement (PMR) and postmarketing commitments (PMCs) for NDA 022542 Viokace (pancrelipase) tablets. With your response, provide milestone dates as requested or your concurrence with the dates proposed by FDA.

POSTMARKETING REQUIREMENT UNDER 505(o) of the FDCA

1. An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients with chronic pancreatitis or history of pancreatectomy taking VIOKACE (pancrelipase) Tablets compared with patients with an appropriate control group.

Provide the following milestone dates: Final Protocol Submission, Study Completion Date, and Final Report Submission.

Aptalis Response 2/14/12:

Aptalis, sponsor for ZENPEP, ULTRESA and VIOKACE, is currently working (b) (4) to develop and conduct a harmonized protocol to fulfill post marketing requirements (PMRs) for ZENPEP. This harmonized protocol is a retrospective study that examines patients taking Pancreatic Enzyme Replacement Therapy (PERT) and is intended to estimate the prevalence of antibody seropositivity to selected porcine viruses in cystic fibrosis patients.

Since the indication for which Viokace will be approved is different to that for which the other PERTS are indicated this will necessitate a separate study for Viokace involving patients who have received the product for pancreatic insufficiency due to chronic pacreatitis or pancreatectomy. While this is potentially feasible, Aptalis would like FDA to consider the following points and whether such a study would meaningfully add to the sum of knowledge that will likely be gained from the planned harmonized study described above:

1. The existing proposed point prevalence study protocol does not envisage discriminating between different PERTs, since it is a retrospective study, and switching between PERTS (i.e. Zenpep, Creon, Pancrease, and ULTRESA) cannot be excluded or reliably documented.
2. ULTRESA will be added to this study since it is indicated for pancreatic insufficiency due to cystic fibrosis.
3. There does not appear to be any evidence to suggest that patients with chronic pancreatitis or pancreatectomy (the indications for which Viokace will be approved) have any difference in their susceptibility to potential infection by the viruses of interest.
4. The number of patients expected to receive Viokace in its approved indication is expected to be considerably less than the number of patients receiving PERT therapy for cystic fibrosis, and the duration of therapy is likely to be over a shorter period of time; i.e. exposure to PERT is much higher in cystic fibrosis patients with a higher likelihood of viral transmission, if any.

The number of patients expected to receive Viokace in its approved indication is expected to be considerably less than the number of patients receiving PERT therapy for cystic fibrosis, and the duration of therapy is likely to be over a shorter period of time; i.e. exposure to PERT is much higher in cystic fibrosis patients with a higher likelihood of viral transmission, if any.

The point prevalence protocol under consideration for the detection of potential transmission of porcine virii in the cystic fibrosis (CF) population proposes:

(b) (4)

There are approximately 35,000 CF patients in the United States, and effectively 100% of these patients are registered and known to the network of approximately 200 CF centres.

Study centres: Following a review of pancrelipase studies in chronic pancreatitis registered on ClinicalTrials.gov, it is estimated that under thirty American clinical study centres active in chronic pancreatitis (CP) research have access to a population potentially using PERT. The majority of these centres are located in the eastern United States and there is presently no uniform distribution of or coordinated network of study centres to permit full representation of the American CP population across all regions.

Population size: The prevalence of CP is difficult to ascertain, with estimates ranging from 0.45% to 5.0% of the global population and approximately 120,000 patient visits per annum (Stevens and Conwell, retrieved 2012). There is no nation-wide registry of patients, in part due to multiple etiologies resulting in CP. Based on IMS data for 2009, it is estimated that approximately (b) (4) CP patients in the United States had received at least one 30-day prescription for a PERT (VIOKACE or other product). The same data suggests that an average of three such prescriptions (an exposure averaging 90 days) are issued per patient, though it is not known if these prescriptions run uninterrupted, whether they are staggered, or if patients are fully compliant with prescribed treatment. Therefore we estimate that only a small number of CP patients will have received PERT for a six month or greater period for management of steatorrhea.

It is estimated that up to 5000 patients per annum may be prescribed VIOKACE for short-duration treatment within five calendar years following approval and re-introduction of the product.

Exposure to PERT: Consistent long-term use of PERT for the management of steatorrhea in CP patients does not appear to be the norm, as lifestyle management including avoidance of alcohol, reduction of daily fat intake and inclusion of medium chain triglycerides in diet are important components of patient management. PERT has often been relegated to the management of the sudden appearance of steatorrhea suggestive of a temporally-associated physical block of pancreatic ducts at the time of occurrence. Long-term use of PERT for steatorrhea is therefore likely only to occur in a small minority of the CP population.

References

Freedman SD. Patient information: Chronic pancreatitis (Beyond the Basics). http://www.uptodate.com/contents/patient-information-chronic-pancreatitis-beyond-the-basics (retrieved 22-Feb-2012)

Stevens T, Conwell DL. Chronic pancreatitis. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/gastroenterology/chronic-pancreatitis/ (retrieved 22-Feb-2012)

VIOKACE IMS Data; Aptalis Pharma US, Inc. Data on file.

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

/s/

JAGJIT S GREWAL
03/01/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Monday, February 27, 2012 5:39 PM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: NDA 022542 Viokace (pancrelipase) - FDA PMC Proposal 2-27-12

Importance: High

Attachments: Viokace FDA Proposed Additional PMC 2-27-12.doc

Hello Dr. Rousseau,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

Attached is FDA's proposal for an additional drug substance related postmarketing commitments (see annotated text). Please review the attached information and provide your response by Tuesday, February 28, 2012.

Please acknowledge receipt of this correspondence. I can be reached at the below phone number or through email with any questions.

Viokace FDA
roposed Additiona..

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

FDA is proposing an additional drug substance related postmarketing commitment (PMC) as shown below for NDA 022542 Viokace (pancrelipase) tablets. Please review this information and respond with your concurrence and/or proposed revisions by February 28, 2012

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

Drug Substance:

1. Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the drug substance manufacturing facility.

   Final Report Submission by September 1, 2012

2. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

   Final Report Submission by March 1, 2013

3. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

   Final Report Submission by March 1, 2013

4. Perform additional monitoring of viral load entering the drug substance manufacturing process. The control program should include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.

   Final Report Submission by May 15, 2013

5. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria should be submitted to the Agency.

   Final Report Submission by April 15, 2013

6. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

   Final Report Submission by June 1, 2012

7. Revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program should include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

   Final Report Submission by March 15, 2013

8. Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.

   Final Report Submission by June 1, 2012

9. Revise release specifications after 30 lots of 1206 and 1252 drug substance have been manufactured.

   Final Report Submission by May 15, 2013

Drug Product:

10. Revise release and stability specifications after 30 lots of drug product have been manufactured.

    Final Report Submission by July 2014

11. Include accelerated and/or stressed stability conditions in the annual stability protocol.

    Final Protocol Submission by June 2012

12. Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

    Final Protocol Submission by June 2012

13. Perform *in vitro* studies to determine the feasibility of administering Viokace (pancrelipase) Tablets in an appropriate solution through a gastrostomy tube.

    Final Report Submission by March 2013

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/s/

JAGJIT S GREWAL
02/27/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, February 24, 2012 9:44 AM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: NDA 022542 Viokace (pancrelipase) - FDA PMC Revisions 2-24-12

Importance: High

Attachments: FDA Proposed Viokace PMC Revisions 2-24-12 final.doc

Hello Dr. Rousseau,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets. We also refer to your email correspondences dated February 14, 2012 and February 22, 2012, containing your response to FDA's proposals for postmarketing commitments (PMCs).

We have reviewed your responses and have additional edits to the Viokace PMCs. Please review the attached information and provide your response by Monday, February 27, 2012.

Please acknowledge receipt of this correspondence. I can be reached via email or at the below phone number with any questions

FDA Proposed
Viokace PMC Revis..

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

FDA is proposing the following revisions to the postmarketing commitments (PMCs) for NDA 022542 Viokace (pancrelipase) tablets. Please review the changes and respond with your concurrence and/or proposed revisions by February 27, 2012.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

Drug Substance:

1. Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the drug substance manufacturing facility.

   Final Report Submission by September 1, 2012

2. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

   Final Report Submission by March 1, 2013

3. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance (b) (4)

   Final Report Submission by March 1, 2013

4. Perform additional monitoring of viral load entering the drug substance manufacturing process. The control program (b) (4) should include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy (b) (4) hould be proposed.

   Final Report Submission by May 15, 2013

5. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria (b) (4) should be submitted to the Agency.

   Final Report Submission by April 15, 2013

6. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

   Final Report Submission by June 1, 2012

7. Revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program (b) (4) should include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

Final Report Submission by March 15, 2013

8. Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.

   Final Report Submission by June 1, 2012

Drug Product:

9. Revise release and stability specifications after (b) (4) 30 lots of drug product have been manufactured.

   Final Report Submission by (b) (4) July 2014

10. Include accelerated and/or stressed stability conditions in the annual stability protocol.

    Final Protocol Submission by June 2012

11. (b) (4) Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

    Final (b) (4) Protocol Submission by June (b) (4) 2012

12. Perform *in vitro* studies to determine the feasibility of administering Viokace (pancrelipase) Tablets dissolved in an appropriate solution through a gastrostomy tube.

    Final Report Submission by DATE (Month/Year)

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/s/

JAGJIT S GREWAL
02/24/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Tuesday, February 21, 2012 6:14 PM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: NDA 022542 Viokace (pancrelipase) - FDA Proposed PMCs

Importance: High

Attachments: NDA 022542 - FDA Proposed PMCs 2-21-12.doc

Hello Dr. Rousseau,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

Attached is FDA's proposal for additional drug substance related postmarketing commitments. Please review the attached information and provide your response by Thursday, February 23, 2012.

Please acknowledge receipt of this correspondence. I can be reached at the below phone number or through email with any questions.

NDA 022542 - FDA Proposed PMCs...

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

Please review the following proposed postmarketing commitments (PMCs) for NDA 022542 Viokace (pancrelipase) Tablets. Provide your concurrence with the proposed PMCs and milestone dates by Thursday, February 23, 2012.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

1. Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the facility.

   Final Report Submission by September 1, 2012

2. Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

   Final Report Submission by March 1, 2013

3. Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for drug substance (b) (4).

   Final Report Submission by March 1, 2013

4. Perform additional monitoring of viral load entering the manufacturing process. The control program (b) (4) include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy (b) (4).

   Final Report Submission by May 15, 2013

5. Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria (b) (4) be submitted to the Agency.

   Final Report Submission by April 15, 2013

6. Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

   Final Report Submission by June 1, 2012

7. Revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program (b) (4) include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

   Final Report Submission by March 15, 2013

8. Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.

   Final report submitted by June 1, 2012

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/s/

JAGJIT S GREWAL
02/21/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Monday, February 13, 2012 4:13 PM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: NDA 022542 Viokace (pancrelipase) - FDA proposed Med Guide revisions

Importance: High

Attachments: FDA Proposed Viokace Med Guide 2-13-12.doc

Hello Dr. Rousseau,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) tablets.

Attached are FDA's revisions to your proposed Medication Guide. We ask that you review the attached information and respond with your acceptance and/or proposed changes by Wednesday, February 15, 2012.

Please acknowledge receipt of this correspondence. I can be reached at the below phone number or through email with any questions.

FDA Proposed
/iokace Med Guide..

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
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/s/

JAGJIT S GREWAL
02/13/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, February 10, 2012 8:04 AM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: NDA 022542 Viokace (pancrelipase) - FDA proposed PI and PMR-PMCs

Importance: High

Attachments: FDA Proposed Viokace PI Revisions 2-10-12.doc; FDA Proposed Viokace PMRs-PMCs 2-10-12.doc

Good Morning Dr. Rousseau,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) tablets.

Attached are FDA's revisions to your proposed package insert label. FDA's proposal for postmarketing requirements and postmarketing commitments is also included. Please review the attached information and provide your response by Tuesday, February 14, 2012.

Additionally, please acknowledge receipt of this correspondence. I can be reached at the below phone number or through email with any questions


FDA Proposed Viokace PI Revisi...


FDA Proposed iokace PMRs-PMCs.

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
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/s/

JAGJIT S GREWAL
02/10/2012

Grewal, Jagjit

From: ees_admin@fda.gov
Sent: Thursday, February 02, 2012 5:04 PM
To: Olagbaju, Bose*; Lacana, Emanuela; Grewal, Jagjit; Salganik, Maria*; Bernstein, Ralph; Ledwidge, Richard; Biswas, Sumita *; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 22542/000 Decision: ACCEPTABLE, Decision Date: 02/02/2012, Re-evaluation Date: 02/16/2013

This is a system generated email message to notify you that the
Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send
an email to EESQUESTIONS (EESQUESTIONS@cder.fda.gov).
To contact the EES technical staff, send an email to
CDER EES Help (EESHELP@fda.hhs.gov). Thank you.

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, February 01, 2012 3:45 PM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: NDA 022542 Viokace (pancrelipase) - FDA proposed PI label revisions

Importance: High

Attachments: NDA 022542 Viokace - FDA PI revisions 2-1-12.doc

Hello Dr. Rousseau,

Reference is made to your New Drug Application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

Attached is an annotated WORD document containing the FDA's revisions to your proposed package insert label. Please review the noted changes and respond with your acceptance and/or proposed changes by Monday, February 6, 2012.

Additionally, please acknowledge receipt of this correspondence. I can be reached at the below phone number or through email with any questions.

Regards,

NDA 022542
/iokace - FDA PI re..

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

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/s/

JAGJIT S GREWAL
02/01/2012

MEMORANDUM OF MEETING MINUTES

Meeting Date:	January 30, 2012
Meeting Time:	12:45 PM-1:30 PM EST
Meeting Type:	Teleconference
Applications:	NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules NDA 022542 Viokace (pancrelipase) Tablets
Sponsor/Applicant:	Aptalis Pharma US, Inc.
Meeting Chair:	Emanuela Lacana, Ph.D.
Meeting Recorder:	Jagjit Grewal, M.P.H.

FDA ATTENDEES:

Office of Drug Evaluation III

Julie Betiz, M.D.	Director
Maria Walsh, R.N.	Associate Director for Regulatory Affairs

Division of Gastroenterology and Inborn Errors Products:

Andrew Mulberg, M.D.	Deputy Director
Anil Rajpal, M.D.	Medical Team Leader
Marjorie Dannis, M.D.	Medical Reviewer
Jagjit Grewal, M.P.H.	Senior Regulatory Health Project Manager

Office of Biotechnology Products/Division of Therapeutic Proteins

Emanuela Lacana, Ph.D.	Associate Chief, Lab of Chemistry
Richard Ledwidge, Ph.D.	Reviewer
Joel Welch, Ph.D.	Regulatory Health Project Manager

Office of Compliance/Office of Manufacturing and Product Quality/Division of Good Manufacturing Practice Assessment

Zhong Li, Ph.D.	Interdisciplinary Scientist, Chemist

Office of Surveillance and Epidemiology/Office of Medication Error Prevention and Risk Management/Division of Medication Error Prevention and Analysis

Manizheh Siahpoushan, Pharm.D.	Safety Evaluator

EXTERNAL CONSTITUENT ATTENDEES:

Aptalis Pharma US, Inc

Ruth Thieroff-Ekerdt, M.D.	Chief Medical Officer
David Ellis, PhD.	Vice President Global Regulatory Affairs
Guy Rousseau, Ph.D.	Executive Director, Regulatory Affairs
Jaâfar Zerhouni	Director, Quality Assurance, Canada & Third-Party
Ivan Shaw	Director, Clinical Development
Luigi Ghidorsi	Strategic Projects Manager
Alessandro Martini	Senior Project Manager
Susan Thornton	Director, Regulatory Affairs

BACKGROUND:
Reference is made to NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules dated September 29, 2007 and NDA 022542 Viokace (pancrelipase) Tablets dated October 29, 2009. Reference is also made to the class 2, NDA re-submissions dated September 1, 2011.

On November 15, 2011, Aptalis Pharma informed FDA that they were in the process of transferring the drug product release and stability testing from [redacted] (b) (4). to [redacted] (b) (4) The transfer was necessary due to the expected site closure of [redacted] (b) (4). Aptalis planned to complete the site transfer by December 21, 2011. To support the transfer of test methods from [redacted] (b) (4) to [redacted] (b) (4), Aptalis provided their methods transfer reports in submissions dated December 9, 2011, January 12, 2012, and January 24, 2012.

On January 20, 2012, FDA requested a teleconference with Aptalis to discuss deficiencies with the submitted methods transfer reports and the overall status of the NDA reviews. The teleconference was scheduled for January 30, 2012. FDA provided Aptalis with comments for discussion on January 27, 2012 (see Attachment #1). Prior to the teleconference on January 30, 2012, Aptalis provided a response and clarification to FDA's comments (see Attachment #2).

TELECONFERENCE DISCUSSION:
FDA stated that the methods transfer reports for Ultresa were inadequate and robust equivalency testing is needed for these types of critical assays. FDA expected more than the 1 sample and 2 replicates included in the sponsor's methods testing. Furthermore, FDA indicated that the USP 2012 Guideline is the minimal requirement and not FDA policy. FDA also noted that Aptalis should have informed the Agency earlier about the assay transfer period and timeline.

Aptalis replied that the timing for the transfer was unexpected. Aptalis also expressed concern that the equipment transferred to [redacted] (b) (4) would need to be moved back to [redacted] (b) (4) to conduct the additional testing as requested by FDA.

As an alternative, FDA suggested that Aptalis could use the extensive data available on the reference standard at [redacted] (b) (4) to generate a historical range of values that would have been obtained at this site. This range of values would then be used to test for equivalencies, with an appropriate statistical assessment, at the [redacted] (b) (4) site.

Aptalis asked if there is another alternative approach available. FDA replied that the sponsor could perform a revalidation of the methods at [redacted] (b) (4) and conduct a bridging study to the [redacted] (b) (4) site. This approach would take longer to complete.

For Viokace, Aptalis clarified that the primary release testing lab is [redacted] (b) (4) and [redacted] (b) (4) is the alternate testing site. Aptalis asked if FDA's concerns for this application would be addressed if they remove [redacted] (b) (4) as a testing site from the NDA. FDA noted that this approach was acceptable. Aptalis also indicated that [redacted] (b) (4) (pancrelipase drug substance DMF holder) also utilized [redacted] (b) (4) for Karl Fischer testing. Aptalis proposed to provide [redacted] (b) (4) a letter of

authorization allowing (b) (4) to reference the Viokace NDA for Karl Fischer testing. FDA agreed with this approach.

For Ultresa, Aptalis proposed to use their Pessano, Italy site for the drug product testing for all methods except for HPLC and Karl Fischer testing. The Aptalis Passano site is already included within the NDA submission. Aptalis proposed to revalidate the HPLC and Karl Fischer testing at the Passano site as postmarketing commitments.

FDA replied that it is unlikely that the revalidation of these two tests could be addressed as postmarketing commitments. FDA asked how long it would take to submit the data from the revalidation testing. Aptalis indicated that no drug product samples were currently available and manufacturing would begin in February 2012. Therefore, Aptalis expected the revalidation and submission of data to take approximately 3 months.

FDA indicated that the data would need to be received by early April 2012 to have sufficient time for review if the PDUFA date was extended to June 1, 2012. Aptalis stated that they would further discuss internally their timeline for revalidation testing and submission of data. This information will be shared with FDA to determine if a PDUFA date extension for the current review cycle would be appropriate.

Regarding the Viokace NDA, FDA stated that package insert labeling revisions would be provided later in the week. FDA will need to further discuss potential postmarketing commitments, postmarketing requirements, and revisions to the Medication Guide.

Regarding the Ultresa NDA, FDA will discuss the path forward for the application review after Aptalis provides their timeline for revalidation testing and submission of data.

POST-TELECONFERENCE DISCUSSION:
Upon further internal discussion on February 1, 2012, DTP determined that Aptalis may perform the HPLC and Karl Fischer testing at the (b) (4) site. DTP noted that the data indicated a slight bias upon the transfer of the assays to (b) (4), but the amount of variation was acceptable. Dr. Guy Rousseau (Aptalis) was contacted by Jagjit Grewal (DGIEP) on February 1, 2012 to inform Aptalis that the HPLC and Karl Fischer testing may be retained at (b) (4) Aptalis agreed.

ACTION ITEMS:

1. For Ultresa, Aptalis will provide correspondence that critical assay testing will be performed at the Aptalis Passano, Italy site. HPLC and Karl Fischer testing can be performed at (b) (4).
2. For Viokace, Aptalis will submit correspondence withdrawing the (b) (4) site from the application.

3. Aptalis will provide (b) (4) with a letter of authorization to reference the Viokace NDA for Karl Fischer testing.

ATTACHMENTS:

1. Attachment #1 – FDA comments issued to Aptalis on January 27, 2012.
2. Attachment #2 – Aptalis response to FDA provided on January 30, 2012.

Concurrence: RLedwidge/2-3-12; ARajpal/2-8-12

FDA is providing the following comments in preparation for the January 30, 2012 teleconference with Aptalis Pharma regarding NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules and NDA 022542 Viokace (pancrelipase) Tablets:

You have provided limited data to support the transfer of analytical methods for release and stability testing to the (b) (4) testing site. For example, the lipase and protease potency assays were analyzed from a single drug product lot with two replicates. Your method transfer exercise is inadequate because the analysis of the data did not include a statistical assessment of the equivalency between the two laboratories, which is critical in providing assurance that similar results will be obtained at each testing facility. However, in order to perform a meaningful assessment of equivalency you will need to analyze additional test samples. Furthermore, the use of a single lot of drug product does not evaluate the variability inherent between different test samples. While the transferred assays have been validated for linearity, specificity, etc., a robust assay transfer study should also include different test samples to confirm the validation characteristics the assays are purported to possess.

To address these concerns, we recommend that you provide data on multiple lots of drug product to allow for a wider range of product characteristics and an analysis of the results demonstrating equivalency between the two sites using appropriate statistical methodology (equivalency testing) with defined confidence intervals. The exercise should include justifications of acceptance criteria and sample sizes.

Please be prepared to discuss your timeline for submission of this data.

Grewal, Jagjit

From: Guy Rousseau [Grousseau@aptalispharma.com]
Sent: Monday, January 30, 2012 10:56 AM
To: Grewal, Jagjit
Subject: RE: N022222 Ultresa & N022542 Viokace
Attachments: USP 1224 TAP _20120127_151513.pdf; emfinfo.txt

Hi Mr Grewal:

In preparation for the upcoming teleconference we would like to share with you (and the reviewing team) the following:

To support the transfer of the analytical methods from the (b) (4) site to the (b) (4) site, (b) (4) followed the USP guideline (Proposed new chapter (2009) which is now official 5/1/12 see attached): 1224 Transfer of Analytical Procedures (TAP).

- It indicates that the conventional TAP (comparison and generation of inter-laboratory data) may be omitted under certain circumstances:
- One of the examples given is when the personnel in charge of the development, validation or routine analysis of the product at the transferring unit are moved to the receiving unit which is the case at (b) (4)
- In addition, in the (b) (4) situation, the same equipment has been moved and the Quality system and SOPs remain the same

We would also like to bring to your attention that, in the case of Viokace NDA 22-542, the primary release testing lab is Confab while (b) (4) is an alternate testing lab.

Best regards,
Guy

Guy Rousseau Ph.D.
Executive Director Regulatory Affairs Europe and RoW
Directeur Exécutif Affaires réglementaires Europe et Export

Aptalis Pharma
597, Boul. Laurier, Mont-Saint-Hilaire, Qc, Canada, J3H 6C4
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grousseau@aptalispharma.com | www.aptalispharma.com

De : Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Envoyé : January-27-12 1:58 PM
À : Guy Rousseau
Objet : N022222 Ultresa & N022542 Viokace

Hello Dr. Rousseau,

In follow up to the voice message I left for you, we do not expect to provide you with comments for Monday's scheduled teleconference other than those already issued this morning. Teleconference discussion will focus on our comments regarding the methods transfer reports, status of the application review, and path forward.

Additionally, as noted in your correspondences date December 5, 2011, Aptalis planned to withdraw (b) (4) as a manufacturing facility associated with these NDAs once the methods transfer had been completed. The transfer was expected to be completed by December 21, 2011. Please confirm that the methods transfer has completed and submit updates to your NDAs accordingly.

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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Email: Jagjit.Grewal@fda.hhs.gov

Add the following:

▲〈1224〉 TRANSFER OF ANALYTICAL PROCEDURES

INTRODUCTION

Testing to the specification of an ancillary material, intermediate, and/or ingredient and product is critical in establishing the quality of a finished dosage form. The transfer of analytical procedures (TAP), also referred to as method transfer, is the documented process that qualifies a laboratory (the receiving unit) to use an analytical test procedure that originated in another laboratory (the transferring unit), thus ensuring that the receiving unit has the procedural knowledge and ability to perform the transferred analytical procedure as intended.

The purpose of this general information chapter is to summarize the types of transfers that may occur, including the possibility of waiver of any transfer, and to outline the potential components of a transfer protocol. The chapter does not provide statistical methods and does not encompass the transfer of microbiological or biological procedures.

TYPES OF TRANSFERS OF ANALYTICAL PROCEDURES

TAP can be performed and demonstrated by several approaches. The most common is comparative testing performed on homogeneous lots of the target material from standard production batches or samples intentionally prepared for the test (e.g., by spiking relevant accurate amounts of known impurities into samples). Other approaches include covalidation between laboratories, the complete or partial validation of the analytical procedures by the receiving unit, and the transfer waiver, which is an appropriately justified omission of the transfer process. The tests that will be transferred, the extent of the transfer activities, and the implementation strategy should be based on a risk analysis that considers the previous experience and knowledge of the receiving unit, the complexity and specifications of the product, and the procedure.

Comparative Testing

Comparative testing requires the analysis of a predetermined number of samples of the same lot by both the sending and the receiving units. Other approaches may be valid, e.g., if the receiving unit meets a predetermined acceptance criterion for the recovery of an impurity in a spiked product. Such analysis is based on a preapproved transfer protocol that stipulates the details of the procedure, the samples that will be used, and the predetermined acceptance criteria, including acceptable variability. Meeting the predetermined acceptance criteria is necessary to assure that the receiving unit is qualified to run the procedure.

Covalidation Between Two or More Laboratories

The laboratory that performs the validation of an analytical procedure is qualified to run the procedure. The transferring unit can involve the receiving unit in an interlaboratory covalidation, including them as a part of the validation team at the transferring unit and thereby obtaining data for the assessment of reproducibility. This assessment is made using a preapproved transfer or validation protocol that provides the details of the procedure, the samples to be used, and the predetermined acceptance criteria. The general chapter *Validation of Compendial Procedures* ⟨1225⟩ provides useful guidance about which characteristics are appropriate for testing.

Revalidation

Revalidation or partial revalidation is another acceptable approach for transfer of a validated procedure. Those characteristics described in ⟨1225⟩, which are anticipated to be affected by the transfer, should be addressed.

Transfer Waiver

The conventional TAP may be omitted under certain circumstances. In such instances, the receiving unit is considered to be qualified to use the analytical test procedures without comparison and generation of interlaboratory comparative data. The following examples give some scenarios that may justify the waiver of TAP:

- The new product's composition is comparable to that of an existing product and/or the concentration of active ingredient is similar to that of an existing product and is analyzed by procedures with which the receiving unit already has experience.
- The analytical procedure being transferred is described in the *USP–NF*, and is unchanged. Verifiction should apply in this case (see ⟨1226⟩).
- The analytical procedure transferred is the same as or very similar to a procedure already in use.
- The personnel in charge of the development, validation, or routine analysis of the product at the transferring unit are moved to the receiving unit.

If eligible for transfer waiver, the receiving receiving unit should document it with appropriate justifications.

ELEMENTS RECOMMENDED FOR THE TRANSFER OF ANAYTICAL PROCEDURES

Several elements, many of which may be interrelated, are recommended for a successful TAP. When appropriate and as a part of pretransfer activities, the transferring unit should provide training to the receiving unit, or the receiving unit should run the procedures and identify any issues that may need to be resolved before the transfer protocol is signed.

Training should be documented.

The transferring unit, often the development unit, is responsible for providing the analytical procedure, the reference standards, the validation reports, and any necessary documents, as well as for providing the necessary training and assistance to the receiving unit as needed during the transfer. The receiving unit may be a quality control unit, another intracompany facility, or another company such as a contract research organization. The receiving unit provides qualified staff or properly trains the staff before the transfer, ensures that the facilities and instrumentation are properly calibrated and qualified as needed, and verifies that the laboratory systems are in compliance with applicable regulations and in-house general laboratory procedures. Both the transferring and receiving units should compare and discuss data as well as any deviations from the protocol. This discussion addresses any necessary corrections or updates to the final report and the analytical procedure as necessary to reproduce the procedure.

A single lot of the article may be used for the transfer, because the aim of the transfer is not related to the manufacturing process but rather to the evaluation of the analytical procedure's performance at the receiving site.

PREAPPROVED PROTOCOL

A well-designed protocol should be discussed, agreed upon, and documented before the implementation of TAP. The document expresses a consensus between the parties, indicating an intended execution strategy, and should include each party's requirements and responsibilities. It is recommended that the protocol contain the following topics as appropriate: objective, scope, responsibilities of the transferring and receiving units, materials and instruments that will be used, analytical procedure, experimental design, and acceptance criteria for all tests and/or methods included in the transfer. Based on the validation data and procedural knowledge, the transfer protocol should identify the specific analytical performance characteristics (see 〈1225〉 and 〈1226〉) that will be evaluated and the analysis that will be used to evaluate acceptable outcomes of the transfer exercise.

The transfer acceptance criteria, which are based on method performance and historical data from stability and release results, if available, should include the comparability criteria for results from all study sites. These criteria may be derived using statistical principles based on the difference between mean values and established ranges and should be accompanied by an estimation of the variability (e.g., percent relative standard deviation [% RSD] for each site), particularly for the intermediate precision %RSD of the receiving unit and/or a statistical method for the comparison of the means for assay and content uniformity tests. In instances of impurity testing, where precision may be poorer such as in

the case of trace impurities, a simple descriptive approach can be used. Dissolution can be evaluated by a comparison of the dissolution profiles using the similarity factor f_2 or by comparison of data at the specified time points. The laboratories should provide appropriate rationale for any analytical performance characteristic not included. The materials, reference standards, samples, instruments, and instrumental parameters that will be used should be described.

It is recommended that expired, aged, or spiked samples be carefully chosen and evaluated to identify potential problems related to differences in sample preparation equipment and to evaluate the impact of potential aberrant results on marketed products. The documentation section of the transfer protocol may include report forms to ensure consistent recording of results and to improve consistency between laboratories. This section should contain the additional information that will be included with the results, such as example chromatograms and spectra, along with additional information in case of a deviation. The protocol should also explain how any deviation from the acceptance criteria will be managed. Any changes to the transfer protocol following failure of an acceptance criterion must be approved before collection of additional data.

THE ANALYTICAL PROCEDURE

The procedure should be written with sufficient detail and explicit instructions, so that a trained analyst can perform it without difficulty. A pretransfer meeting between the transferring and receiving units is helpful to clarify any issues and answer any questions regarding the transfer process. If complete or partial validation data exist, they should be available to the receiving unit, along with any technical details required to perform the test in question. In some cases it may be useful for the individuals who were involved with the initial development or validation to be on site during the transfer. The number of replicates and injection sequences in the case of liquid or gas chromatography should be clearly expressed, and, in the case of dissolution testing, the number of individual dosage units should be stipulated.

TRANSFER REPORT

When the TAP is successfully completed, the receiving unit should prepare a transfer report that describes the results obtained in relation to the acceptance criteria, along with conclusions that confirm that the receiving unit is now qualified to run the procedure. Any deviations should be thoroughly documented and justified. If the acceptance criteria are met, the TAP is successful and the receiving unit is qualified to run the procedure. Otherwise, the procedure cannot be considered transferred until effective remedial steps

are adopted in order to meet the acceptance criteria. An investigation may provide guidance about the nature and extent of the remedial steps, which may vary from further training and clarification to more complex approaches, depending on the particular procedure. ▲*USP35*

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
General Chapter	Horacio N. Pappa, Ph.D. Principal Scientific Liaison 1-301-816-8319	(GCPA2010) General Chapters - Physical Analysis

USP35–NF30 Page 876

Pharmacopeial Forum: Volume No. 37(1)

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/s/

JAGJIT S GREWAL
02/22/2012

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, December 21, 2011 3:04 PM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: RE: N022222 Ultresa & N022542 Viokace - requests for information
Importance: High

Hello Dr. Rousseau,

Your proposed timeline for the submission of the methods transfer reports is acceptable. In addition, we have the following comments and requests for additional information:

1. In review of the methods transfer reports provided in your below email, it appears that the following assays are not included:
   a. Ultresa: The amylase (b) (4), Uniformity of dosage and microbiology test methods
   b. Viokace: The amylase, (b) (4) and microbiology test methods

   Please submit the reports for these assays and provide your timeline for submission.

2. Your assay transfer reports should include relevant data and statistical analysis to demonstrate the equivalency of the results obtained from the test method conducted at the two different sites.

3. Aptalis is now responsible for DMF 15681, formerly owned by Eurand, which provides information on the manufacturing process and bulk testing of Ultresa. Please clarify if the drug product manufacturing and bulk release will be maintained under the DMF and provide assay transfer reports, if applicable, for the release testing conducted under DMF 15681.

Please confirm receipt of this correspondence. I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration
Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Guy Rousseau [mailto:Grousseau@aptalispharma.com]
Sent: Tuesday, December 20, 2011 6:19 PM
To: Grewal, Jagjit
Subject: RE: N022222 Ultresa & N022542 Viokace

Hi Mr. Grewal:

As discussed earlier today please find below the due dates for the method transfer reports from (b) (4) to (b) (4). The proposal is to file to our NDAs the reports as available i.e. in two sets: one that would be filed on December 29, 2011 and one on January 12, 2012.

Regards,
Guy Rousseau

Ultresa

Method Number	Method title	Due date
(b) (4)		

Viokace

Method Number	Method title	Due Date
(b) (4)		

(b) (4)

Guy Rousseau Ph.D.
Executive Director Regulatory Affairs Europe and RoW
Directeur Exécutif Affaires réglementaires Europe et Export

Aptalis Pharma
597, Boul. Laurier, Mont-Saint-Hilaire, Qc, Canada, J3H 6C4
Tél.: (450) 467-5138 # 2458 | 1 (877) 982-2600 | Fax: (450) 467-9784
grousseau@aptalispharma.com | www.aptalispharma.com

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/s/

JAGJIT S GREWAL
12/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542 **INFORMATION REQUEST**

Aptalis Pharma U.S., Inc.
Attention: Guy Rousseau, Ph.D.
Executive Director, Regulatory Affairs
22 Inverness Center Parkway, Suite 310
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We also refer to your September 1, 2011 submission, containing your proposed draft carton and container labeling.

We are reviewing the referenced material and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Container Labels and Carton Labeling

1. Revise the warning statement [redacted] (b) (4) to read 'Viokace tablets should be swallowed whole. Do not crush or chew tablets.' As currently presented, the warning statement only contains negative language which may be overlooked by patients and have the opposite effect of the intended meaning. Patients may overlook the words 'Do not' and interpret this statement to mean the tablets can be crushed or chewed.

2. Relocate the warning statement 'Viokace tablets should be swallowed whole. Do not crush or chew tablets.' (after revised from [redacted] (b) (4)) to the principal display panels of the container labels and carton labeling. As currently presented, the warning statement lacks prominence and may be overlooked.

3. Include the dosage form (Tablets) immediately following the established name. As currently presented, the dosage form does not appear on the container labels and the carton labeling, where the proprietary name and the established names appear (i.e., on the principal display panel of the container labels and carton labeling, as well as the side panels of the carton labeling). The revised format may appear as follows:

   'Viokace
   (Pancrelipase)
   Tablets'

4. Revise the color of the proprietary name, Viokace, to appear less prominent. As currently presented, the color orange distracts attention from other important information such as the NDC number and the products strengths. We recommend using a less prominent color (i.e. the color used for the established name) to minimize medication errors due to product selection (i.e. dispensing the wrong strength).

5. We recommend using tall man lettering scheme for the middle portion of the NDC numbers corresponding to the two different strengths of the product. Since this product is available in two different strengths with very similar NDC numbers, and pharmacists normally rely on the middle portion of the NDC number as part of their checking system, highlighting the middle portion of the NDC numbers by using tall man letters can help distinguish the two similar NDC numbers, making them less prone to mix-ups by the pharmacy staff.

6. Update your proposed labeling to reflect the new company name, Aptalis Pharma U.S., Inc.

Container Labels

1. Reduce the prominence of 'Rx only' on the container labels. As currently presented, the 'Rx only' is in close proximity and competes in prominence with the NDC number.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
12/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Aptalis Pharma US, Inc.
22 Inverness Center Parkway
Suite 310
Birmingham, AL 35242 USA

Attention: Guy Rousseau, Ph.D.
Executive Director, Regulatory Affairs

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) dated October 29, 2009, received on October 30, 2009, submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for pancrelipase.

We also refer to:

- Your initial proprietary name submission dated October 30, 2009, for the tradename Viokace;
- Your proprietary name amendment dated November 23, 2009;
- Your September 1, 2011, resubmission as part of the Class 2 Complete Response;
- Your submission dated and received September 29, 2011, requesting re-review of your proposed proprietary name Viokace;

We have completed our review of the proposed proprietary name, Viokace, and have concluded that it is acceptable.

The proposed proprietary name, Viokace, will be re-reviewed 90 days prior to approval. If **any** of the proposed product characteristics as stated in your September 29, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Jagjit Grewal at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
12/08/2011

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Thursday, December 01, 2011 10:59 PM
To: 'Guy Rousseau'
Cc: Grewal, Jagjit
Subject: RE: N022222 Ultresa & N022542 Viokace - request for information
Importance: High

Hello Dr. Rousseau,

Reference is made to your NDA 0222222 Ultresa (pancrelipase) capsules and NDA 022542 Viokace (pancrelipase) tablets. We also refer to your submissions dated November 16, 2011, containing updated manufacturing facility information. In addition, your submissions provided notification that Aptalis is in the process of transferring all test methods from (b) (4). to (b) (4).

We have the following requests for additional information:

1. Please confirm if you plan to withdraw (b) (4) as a manufacturing facility associated with your applications once the methods transfer has been completed. If so, specify when you expect to submit the notice of withdrawal to your NDAs.

2. Provide your timeframe for submitting the assay transfer reports.

3. Please indicate what assays and equipment are being transferred from the (b) (4) site to the (b) (4) site.

I can be reached via email or at the below phone number with any questions.

Regards,

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration
Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Guy Rousseau [mailto:Grousseau@aptalispharma.com]
Sent: Friday, November 18, 2011 12:00 PM
To: Grewal, Jagjit
Subject: RE: N022222 Ultresa & N022542 Viokace - request for information

Hi Mr Grewal:

(b) (4) is still performing the stability testing. The transfer of test methods to (b) (4) (a Division of (b) (4)) is scheduled to be completed by December 21, 2011. Please note that the test methods, SOPs, and personnel will remain the same (NB: the same QA Director has been responsible for both sites since 2007) and that most of the equipments will be transferred from (b) (4) to (b) (4). It is mainly a change of building.

Best regards,
Guy

De : Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Envoyé : November-17-11 6:50 PM
À : Guy Rousseau
Cc : Grewal, Jagjit
Objet : FW: N022222 Ultresa & N022542 Viokace - request for information

Dr. Rousseau,

Could you provide more specific timing as to when Aptalis will complete the transfer of test methods from (b) (4) to (b) (4)? Additionally, is (b) (4) still currently performing testing of the drug products?

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration
Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Guy Rousseau [mailto:Grousseau@aptalispharma.com]
Sent: Tuesday, November 15, 2011 2:15 PM
To: Grewal, Jagjit
Subject: RE: N022222 Ultresa & N022542 Viokace - request for information

Hi Mr Grewal:

As requested please find attached letters confirming that no data or information from (b) (4) is being used in support of our NDAs and that Axcan Scandipharm (Canada) is not involved in the products manufacture.

These letters together with revised sections 3.2.P.3.1 for NDA 22-222 and NDA22-542 will be submitted to the NDA later today or early tomorrow morning. You will note that the microbiological testing is performed at (b) (4), a Division of (b) (4). Also we would like to inform you that all testing will be transferred to (b) (4) by the end of the year.

Please do not hesitate to contact me should you require any further information.

Regards,
Guy

De : Grewal, Jagjit [mailto:Jagjit.Grewal@fda.hhs.gov]
Envoyé : November-14-11 3:33 PM
À : Guy Rousseau
Cc : Grewal, Jagjit
Objet : N022222 Ultresa & N022542 Viokace - request for information
Importance : Haute

Hello Dr. Rousseau,

Per our conversation this afternoon, confirm if any data or information from (b) (4) is being used in support of your NDAs.

Additionally, please indicate if Axcan Scandipharm (Canada) is involved in the product manufacture, and if so, provide their specific responsibilities.

Please formally submit your response to the NDAs and include updated establishment information on the FDA 356h forms as necessary. I can be reached via email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846 || Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
12/01/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

ACKNOWLEDGE CORPORATE NAME CHANGE

Aptalis Pharma U.S., Inc.
Attention: Guy Rousseau, Ph.D.
Executive Director, Regulatory Affairs
22 Inverness Center Parkway, Suite 310
Birmingham, AL 35242

Dear Dr. Rousseau:

We acknowledge receipt on October 14, 2011, of your October 14, 2011 correspondence notifying the Food and Drug Administration that the corporate name has been changed from

Axcan Pharma US, Inc.

to

Aptalis Pharma US, Inc.

for the following new drug application:

NDA 022542 for Viokace (pancrelipase) Tablets.

We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have Drug Master Files (DMFs) referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their DMF(s).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JAGJIT S GREWAL
11/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

ACKNOWLEDGE – CLASS 2 RESPONSE

Axcan Pharma U.S., Inc.
Attention: Guy Rousseau, Ph.D.
Executive Director, Regulatory Affairs
22 Inverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

We acknowledge receipt on September 1, 2011, of your September 1, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We consider this a complete, class 2 response to our November 28, 2010, action letter. Therefore, the user fee goal date is March 1, 2012.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Researc

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/s/

JAGJIT S GREWAL
09/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022222
NDA 022542

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Axcan Pharma U.S., Inc.
Attention: Guy Rousseau, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
22 Inverness Center Parkway
Birmingham, AL 35242

Dear Applicant:

Please refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ultresa (pancrelipase) Delayed-Release Capsules and Viokace (pancrelipase) Tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

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

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

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

searching available documentation to determine which NDAs are impacted by the above findings.

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

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

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

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

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GIUSEPPE RANDAZZO
09/15/2011
Signed for Dr. Donna Griebel

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

INFORMATION REQUEST

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
22 Inverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We are reviewing the Drug Master File (DMF) in support of your NDA and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4) DMF (b) (4) has been found to contain deficiencies. A letter has been sent to (b) (4) listing the deficiencies. (b) (4) should address the deficiencies by submitting the information directly to the DMF. Please notify us when (b) (4) has submitted the requested information.

If you have any questions, or would like to request a meeting, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
10/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

INFORMATION REQUEST

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Inverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We are reviewing the proposed dissolution methodology and specifications of your submission and have the following comment. We request a prompt written response in order to continue our evaluation of your NDA.

1. The proposed dissolution specification needs to be revised as shown below.
   Change Specification: From Q= (b) (4) at (b) (4)
   To Q (b) (4) at 45 min

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Office of Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
10/05/2010

From: Ford, Elizabeth
Sent: Thursday, September 16, 2010 9:17 AM
To: Guy Rousseau; 'Prokipcak, Becky'
Cc: Ford, Elizabeth
Subject: NDA 022542/Labeling comments: PI and MG

Attachments: PI FDA comments 9-16-2010.doc; MG FDA comments 9-16-2010.doc

Hello,

Please find attached FDA comments to the package insert (PI) and medication guide (MG) in response to your 8-20-2010 submission.


PI FDA
ents 9-16-2010


MG FDA
ents 9-16-2010.c

Thanks,
Elizabeth

Elizabeth A.S. Ford, RN
Senior Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-0193

21 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH A FORD
09/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

GENERAL ADVICE

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Inverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We also refer to the August 24, 2010 teleconference between Axcan Pharma US, Inc. and the Division of Gastroenterology Products regarding your *in vitro* studies to determine the feasibility of administering the contents of Viokace (pancrelipase) tablets through a gastrostomy tube (G-tube). We have the following comments and recommendations.

(b) (4)

(b) (4)

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

BRIAN K STRONGIN
09/14/2010

From: Ford, Elizabeth
Sent: Wednesday, August 18, 2010 1:30 PM
To: 'Prokipcak, Becky'; 'Rousseau Guy'
Cc: Ford, Elizabeth
Subject: NDA 022542/labeling comments

Attachments: REMS FDA comments 8-18-2010.doc; MG FDA comments 8-18-2010.doc; PI FDA comments 8-18-2010.doc

Hello,

FDA comments for the PI, medication guide, and REMS, is attached for your review. Please comment, and resubmit the attached documents within one week.

Thanks,
Elizabeth



REMS FDA nents 8-18-2010 | MG FDA ents 8-18-2010 | PI FDA ents 8-18-2010.c

Elizabeth A.S. Ford, RN
Senior Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-0193

31 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH A FORD
08/19/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542 **INFORMATION REQUEST**

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Iverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) (b) (4)

We are reviewing the labeling section of your submission and have the following comments.

1) Container Labels (10,440 U.S.P. Units lipase/ 39,150 U.S.P. Units amylase/39,150 U.S.P. Units protease; 20,880 U.S.P. Units lipase/ 78,300 U.S.P. Units amylase/ 78,300 U.S.P. Units protease)

   a) Established Name:

      i) Per 21 CFR 201.6 and the United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27 Monograph-Pancrelipase Tablets, please revise the established name from (b) (4) to (pancrelipase) Tablets

      ii) Per 21 CFR 201.10(g)(2), revise the established name presentation to letters printed at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

      iii) Remove the color boxing around the established name and change the font color to one color that is legible and provides a sufficient color contrast against the white background. As currently presented, the proprietary name is boxed in green whereas the established name is boxed in gray resulting in an intervening white line separating the proprietary name and the established name boxing.

iv) Ensure that the established name is presented in its entirety on the principle display panel and does not wrap around on the side panel.

b) Revise your container labels so that the three active ingredients are boxed as follows:

Each tablet contains:	
Lipase	XXXX USP Units
Amylase	XXXX USP Units
Protease	XXXX USP Units

Boxes will represent the product strength on the principle display panel. The boxes should be prominently displayed, following the proprietary and established names, and should incorporate strength differentiation between the two available Viokace strengths. Differentiation may be accomplished through the use of colors, shading, highlighting or some other means. Two unique boxing colors should be utilized for the strength differentiation of Viokace and should not incorporate another color already utilized on the labels. See currently approved pancrelipase product labels and labeling for reference.

c) Include a statement on the principle display panel informing patients and healthcare practitioners that Viokace is dosed based on lipase units.

d) Move the statement "ACCOMPANYING MEDICATION GUIDE TO BE DISPENSED TO PATIENT" to a different area of the principle display panel so that it is not intervening between the established name and strength presentation, ensuring that it doesn't wrap around the side panel and is presented in its entirety on the principle display panel. Consider moving the "Rx only" statement to a side panel to ensure adequate room. Remove the bold font from "MEDICATION GUIDE."

e) Per 21 CFR 201.2 and 21 CFR 207.35, please provide the NDC configuration as either a 3-2 or 4-1 Product-package code configuration.

f) Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the statements, "Protect from moisture.", "Avoid excessive heat." and "Store at 20-25°C (68-77°F)" to the storage conditions listed.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

BRIAN K STRONGIN
08/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542 **INFORMATION REQUEST**

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Iverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace, (pancrelipase) Tablets.

We are reviewing the Chemistry Manufacturing and Controls sections of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding the process validation report provided in your amendment dated June 29, 2010:

    a. You have stated that the hold time validation study for the (b) (4) bulk stored in (b) (4) is described in the interim process validation report #PVIRI-F1120-2009, ver. 01. However, you have not provided the report. Submit the validation report #PVIRI-F1120-2009, ver. 01 as an amendment to NDA 022542.

    b. Please provide the validation results for the bulk tablet holding time for lots 116235 and 116242 (Viokace 8), and lots 117123 and 117128 (Viokace 16).

2. You have provided trended stability data acquired under accelerated and stressed conditions. However you have only submitted trended lipase activity results. Provide trended results for all assays you have conducted. In addition, revise the charts you provided by identifying each lot with a separate symbol.

3. You performed the moisture test in the final (b) (4) as an in-process control; however you did not establish an acceptance criterion for the test. We also note that although you have measured lipase activity at the final (b) (4) step during process validation, you are not performing this test routinely as an in-process control. Establish an appropriate acceptance criterion for the moisture test and include the lipase activity assay as a routine in-process control at the final (b) (4) step.

4. You have developed a RP-HPLC assay to monitor product quality at release and stability. For this assay, you propose acceptance criteria based on the mean peak area (b) (4). Your proposed acceptance ranges are too wide, and are not justified by your manufacturing history and process capability. Revise your acceptance criteria for the RP-HPLC assay to reflect manufacturing history and process capability, and include the revised acceptance criteria in your release and stability protocols.

5. (b) (4) DMF (b) (4) has been found to contain deficiencies. A letter has been sent to (b) (4) listing the deficiencies. (b) (4) should address the deficiencies and update the DMF by directly submitting information to the DMF. Please notify us when (b) (4) has submitted the requested information.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

BRIAN K STRONGIN
08/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

REVIEW EXTENSION – MAJOR AMENDMENT

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Iverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your October 29, 2009 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace, (pancrelipase) Tablets.

On July 9, 2010, we received your July 8, 2010 major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 30, 2010.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

DONNA J GRIEBEL
07/30/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

CONFIRMATION OF ISSUES DISCUSSED

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Iverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your new drug application (NDA) for Viokace (pancrelipase) Tablets.

As discussed by telephone on June 29, 2010 between Axcan Pharma US, Inc. and the Division of Gastroenterology Products, you have agreed to provide the following information to your NDA.

1. Clarify which testing site is used for release and stability testing. Identify the location of the assay transfers in the NDA, or submit the assay transfer protocols and results as an amendment to the NDA.

2. Clarify the packaging process to describe whether capping occurs before or after induction sealing.

3. Clarify the qualification program of the drug substance received by (b) (4). Identify the testing site responsible for confirming the quality of the drug substance, and provide representative retesting data.

4. Provide a representative Certificate of Analysis for excipients and critical raw materials, and a summary of the vendor qualification program.

5. The established acceptance range provided in the NDA for oleic acid appears to be too wide; revise the acceptance range based on historical test results, and provide an updated acceptance range.

6. A number of discrepancies have been identified between the Certificate of Analysis and the batch analysis provided in the submission. In particular, assays that were present in the Certificate of Analysis were not present in the batch analysis, and vice versa. Review the NDA submission and harmonize/update data as needed for consistency.

7. Justify why tablet weight was not included as a stability specification.

8. Discrepancies in regard to the proposed storage condition have been identified in the NDA. Clarify which storage condition is recommended.

9. Revise the post-approval stability protocol and stability commitment to include early time points (1, 3 and 9 month). Justify why early stability time points were not provided for the drug product lots used to support the NDA, and provide updated stability data to include the results of the RP-HPLC assay.

10. Justify why the enzyme assays were not included in the forced degradation studies.

11. Provide additional justification to support the conclusion that the (b) (4) difference in protease activity measured in stressed versus unstressed samples is due to experimental conditions.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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BRIAN K STRONGIN
07/07/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542 **INFORMATION REQUEST**

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Iverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We also refer to your March 22, 2010 submission, providing the following information in response to the comments from the FDA Filing Communication letter dated January 11, 2010.

- The tested lipase activity employing the USP method (i.e., titration using olive oil as a substrate).
- The studied enzyme chromatographic profile in Viokace (b) (4) Tablet using UV at 280 nm.
- The tested dissolution of Viokace (b) (4) Tablet using UV but at 260nm.

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For dissolution testing, you reported that you detect the total protein released in the medium at pH 4.5. This UV method is not specific and the percentage of total protein dissolved may be irrelevant to the amount of lipase released and/or the lipase activity present in the pH 4.5 medium.

Please provide justification as to why:

1. the USP method to detect the lipase activity in the dissolution medium is not used. Instead you opted to use the UV method to detect total protein released in the pH 4.5 medium.
2. you used (b) (4) instead of UV 280 nm for the detection in the dissolution testing.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

BRIAN K STRONGIN
07/06/2010

From: Ford, Elizabeth
Sent: Thursday, July 01, 2010 8:01 AM
To: 'Rousseau Guy'; 'Prokipcak, Becky'
Cc: Ford, Elizabeth
Subject: NDA 022542/Viokace/Target Date Communications

Attachments: N22542 PI FDA comments 7-1-2010.doc

Dear Dr. Rousseau,

Reference is made to **NDA 022542/Viokace (pancrelipase) Tablets**. The first draft of the package insert (PI), with initial FDA comments, is attached for your review and comment. We request you resubmit an updated PI within the next two weeks. These comments represent the initial round of comments from FDA, and additional comments may follow with subsequent versions of the label.

Please be advised that **Axcan Pharma US, Inc.** will be responsible for the following Post Marketing Requirements:

PMRs:
1. A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with chronic pancreatitis treated with Viokace (pancrelipase) tablets in the U.S. and to assess potential risk factors for the event. Final protocol Submission Date: October 1, 2011. Study/Clinical trial Completion Date: May 1, 2022. Final Report Submission Date: December 1, 2022.

2. A 10 year, observational study to prospectively evaluate the risk of transmission of selected porcine viruses in patients taking Viokace (pancrelipase) tablets. Final Protocol Submission October 1, 2011, Study/Clinical trial Completion Date: April 1, 2022, Final Report Submission Date: January 1, 2023

PMC:
3. Perform in vitro studies to determine the feasibility of administering the contents of Viokace (pancrelipase) tablets through a gastrostomy tube. Final Report Submission date April 30, 2011.

Please acknowledge receipt of this information to your NDA, and your agreement with the above-mentioned PMRs and PMC.

N22542 PI FDA
mments 7-1-201

Thanks,

Elizabeth

Elizabeth A.S. Ford, RN
Senior Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-0193

13 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH A FORD
07/01/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542 **INFORMATION REQUEST**

Axcan Pharma US, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Iverness Center Parkway
Birmingham, AL 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace, (pancrelipase) Tablets.

We are reviewing the Chemistry Manufacturing and Controls sections of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1) You submitted a process validation protocol for the VIOKACE manufacturing process. Please clarify whether the protocol has been implemented; if the protocol has been implemented, provide the process validation report and results.

2) You included stability data acquired under the proposed storage conditions for VIOKACE. Provide available results and trended data for stability studies conducted under accelerated and stressed conditions. Include the 95% confidence intervals in the trend analysis plots.

3) Clarify whether the to-be-marketed product (TbMP) is the same formulation as the previously marketed product (PMP).
   a) If the TbMP and PMP are the same formulation: identify how long the PMP was marketed, and identify the approximate date at which postmarketing data for the PMP first became available.
   b) If the TbMP and PMP are not the same formulation: provide a brief description of the changes in the formulation.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

BRIAN K STRONGIN
06/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542 **INFORMATION REQUEST**

Axcan Pharma Us, Inc.
Attention: Guy Rousseau, Ph.D.
VP Regulatory Affairs and Quality Assurance
22 Iverness Center Parkway
Birmingham, Al 35242

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We are reviewing the Clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. On pages 35 to 36 of the VIO16EPI07-01 Study Report, you state that drugs or products known to have an effect on fat absorption or to interfere with the fecal fat test were prohibited during the study. One of the prohibited medications on the list that you have provided is Calcium carbonate. Please provide an explanation of why Calcium carbonate is prohibited.

2. In Table 11.4-1 (page 91) of the VIO16EPI07-01 Study Report, you have provided the treatment phase coefficient of fat absorption (CFA) for each treatment group (Viokase 16 and Placebo), and the p-value for the difference between the two groups; however, you have not provided the point estimate and 95% Confidence Interval for the difference between the two groups. Please provide the point estimate and 95% Confidence Interval for the difference between treatment groups of the treatment phase CFA.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

BRIAN K STRONGIN
06/04/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542 **INFORMATION REQUEST**

Axcan Pharma Us, Inc.
c/o CanReg, Inc.
Attention: Nicole Brufatto, Ph.D., RAC
Director, Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Dr. Brufatto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokace (pancrelipase) Tablets.

We are reviewing the Clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For each of the patients with a history of pancreatectomy in Study VIO16EPI07-01, please submit short narratives indexed by subject identification number. These should include a brief clinical history for each of the patients including a description of the type of surgery (i.e., total or partial pancreatectomy).

2. For Study VIO16EPI07-01, please provide summary tables showing washout phase CFA, treatment phase CFA, and change in CFA (from washout phase to treatment phase) separated by treatment arm in subgroups defined by the following: (a) underlying disease (i.e., exocrine pancreatic insufficiency {EPI} due to pancreatectomy vs. EPI due to chronic pancreatitis); and (b) type of surgery (i.e., history of partial pancreatectomy vs. history of total pancreatectomy). Please provide subject identification numbers for the patients in each of these subgroup categories by treatment arm. Please also submit an electronic dataset that includes each of the fields in these summary tables by subject identification number.

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

BRIAN K STRONGIN
05/11/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022542

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Axcan Pharma US, Inc.
c/o CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

ATTENTION: Nicole Brufatto, Ph.D., RAC
Director, Regulatory Affairs, CanReg Inc.

Dear Dr. Brufatto:

Please refer to your New Drug Application (NDA) dated October 29, 2009, received October 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pancrelipase Tablets, 10,440 and 20,880.

We also refer to your October 30, 2009, correspondence, received October 30, 2009, requesting review of your proposed proprietary name, Viokace and to the amendment dated November 19, 2009, received November 20, 2009. We have completed our review of the proposed proprietary name, Viokace and have concluded that it is acceptable.

The proposed proprietary name, Viokace, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 30 and November 19, 2009, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application contact Elizabeth Ford, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

DENISE P TOYER on behalf of CAROL A HOLQUIST
01/25/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

FILING COMMUNICATION

Axcan Pharma Us, Inc.
c/o CanReg, Inc.
Attention: Nicole Brufatto, Ph.D., RAC
Director, Regulatory Affairs
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Dr. Brufatto:

Please refer to your new drug application (NDA) dated October 29, 2009, received October 30, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Tradename, (pancrelipase) Tablets.

We also refer to your submissions dated November 2, 2009, November 19, 2009, November 23, 2009, November 27, 2009, and December 11, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 30, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 7, 2010.

During our filing review of your application, we identified the following potential review issues:

1. You have proposed two strengths, Viokase 8 and Viokase 16, but only used Viokase 16 in the clinical and bioactivity (intubation) studies. Submit a Biowaiver Request for Viokase 8, along with a justification for the request (e.g., (b) (4) similar dissolution profiles with f2 values between 50 and 100).

2. You have proposed dissolution testing using a (b) (4) buffer (pH 4.5) medium for both strengths, Viokase 8 and Viokase 16, to obtain profiles at 10, 20, 40, 60, 90, and 120 minutes (Method AXC-030). However, the dissolution profiles (individual and mean data; n=12/lot) cannot be located in the NDA. In addition, provide a final report with the development data (e.g., using different media/pHs, apparatuses, and speeds in rpm) and validation data to support your final selection of the proposed dissolution methodology, i.e., (b) (4) buffer, pH 4.5.

If you have already submitted this information, identify its location within the NDA [Module, Volume, Section, and Page Number(s)].

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also have the following comments and requests for information:

1. The following issues/deficiencies have been identified in your proposed labeling. Address the identified issues/deficiencies and re-submit labeling by March 16, 2010. This updated version of labeling will be used for further labeling discussions.
    I. Highlights of Prescribing Information

        a) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. See 21 CFR 201.57(d)(8).

        b) The highlights limitation statement must read as follows: "These highlights do not include all the information needed to use Tradename safely and effectively. See full prescribing information for Tradename." See 21 CFR 201.57(a)(1).

        c) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. This information is missing in the SPL version of the label. See 21 CFR 201.57(a)(2).

        d) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. See 21 CFR 201.57 (a)(11).

        e) Remove the optional heading (b) (4)

        f) Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

        g) There should be white space between each major heading in Highlights.

h) The patient counseling information statement should read "**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**."

II. Full Prescribing Information: Contents – Table of Contents

a) The Agency recommends use of a two-column format for the Table of Contents, and if possible, that it be limited in length to one-half page. This is adequately formatted in SPL, but not in WORD.

b) If the Highlights and Table of Contents do not fit on one page, insert the Table of Contents on page 2 of the labeling.

c) Since SPL R4 validation does not permit the inclusion of the Medication Guide (MG) as a subsection under the Patient Counseling Information section, do not include the MG as a subsection heading in the Table of Contents.

III. Full Prescribing Information (FPI)

a) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not See *Pediatric Use* (8.4). The cross reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. This is not done consistently throughout the document.

b) Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.

c) In the ADVERSE REACTIONS section, subsection 6.1 is entitled Clinical Studies Experience. This subsection should be entitled Clinical Trials Experience.

d) In the ADVERSE REACTIONS section, Clinical Trials Experience subsection, include the following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials: "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

e) The Patient Counseling Information must reference any FDA-approved patient labeling. The phrase "See Medication Guide" is appropriately placed at the beginning of the subsection; however, since SPL R4 validation does not permit the inclusion of the MG as a subsection, the MG should not be a subsection under the Patient Counseling Information section. Include at the end without numbering as a subsection.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

BRIAN K STRONGIN
01/11/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

MEETING DENIED

Axcan Pharma US, Inc.
c/o CanReg Inc.
Attention: Nicole Brufatto
Director, Regulatory Affairs
450 Lakeshore Drive
Mundelein, IL 60060

Dear Dr. Brufatto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename (pancrelipase) Tablets.

We also refer to your November 19, 2009, correspondence requesting a meeting to discuss the general progress and review status of NDA 022542. We are denying the meeting because it is too early in the review period to provide for a productive meeting.

If the Division believes a meeting is necessary, we will contact you for a teleconference.

If you have any questions, call me at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, R.N.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	GI-1	AXCAN PHARMA US INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH A FORD
01/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022542

NDA ACKNOWLEDGMENT

Axcan Pharma US, Inc.
c/o CanReg Inc.
Attention: Nicole Brufatto, Ph.D., RAC
Director, CanReg Inc.
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Dr. Brufatto:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Viokase (pancrelipase, USP) Tablets

Date of Application: October 29, 2009

Date of Receipt: October 30, 2009

Our Reference Number: NDA 022542

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 29, 2009 in accordance with 21 CFR 314.101(a).

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

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

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

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

If you have any questions, call me at (301) 796-0193.

Sincerely,

{See appended electronic signature page}

Elizabeth A.S. Ford, RN
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22542	ORIG-1	AXCAN PHARMA INC	VIOKASE (PANCRELIPASE)UNCOATED TABLETS

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/s/

ELIZABETH A FORD
11/12/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,716

Axcan Scandipharm, Inc.
Attention: Diane Turkin, Ph.D.,
Director, US Business Unit
53 Treaty Drive
Wayne, PA 19087

Dear Dr. Turkin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Viokase® (pancrelipase, USP) tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2007. The purpose of the meeting was to discuss the responses provided to your meeting request dated May 1, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE:	July 17, 2007
TIME:	10:00 AM – 11:00 AM
APPLICATION:	IND 60,716
DRUG NAME:	Viokase®
TYPE OF MEETING:	Type B preNDA
CALL IN NUMBER:	(b) (4)
MEETING CHAIR:	Anne Pariser, M.D.
MEETING RECORDER:	Maureen Dewey, M.P.H.

FDA ATTENDEES:

Division of Gastroenterology Products

Daniel A. Shames, M.D., Director
Anne Pariser, M.D., Medical Team Leader
Virginia Elgin, M.D., Medical Reviewer
Ethan Hausman, M.D., Medical Reviewer
Maureen Dewey, M.P.H., Regulatory Project Manager

Division of Clinical Pharmacology 3

Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader
Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products (OBP), Division of Therapeutic Proteins

Gibbes Johnson, Ph.D., Chief, Lab of Chemistry
Wei Guo, Ph.D., Chemistry Reviewer

Division of Microbiology

Stephen Langille, Ph.D., Microbiology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Axcan Scandipharm Inc.

Guy Rousseau, Ph.D., Vice President, Regulatory Affairs
Nathalie L'écuyer, Director, Quality Operations
Carl Gauthier, Ph.D., Sr. Project Manager, Development
Pompilia Ispas Szabo, Project Manager, Development
Stuart Wright, M.Sc., Executive Director, CMC & Quality Systems, CanReg Inc
Anne Tomalin, B.A., B.Sc., Regulatory Consultant, President CanReg Inc.
Diane Turkin, Ph.D., Regulatory Consultant, CanReg Inc.

Phone in:
Jean-René Basque, Ph.D., Clinical Research Scientist, Axcan
Marc Rivière MD, Vice President, Clinical Development, Axcan
Jean Spenard, M.D., Director of Pancreatic Enzymes, Axcan

BACKGROUND:

Axcan, Inc. submitted a Meeting Request on May 1, 2007, received May 2, 2007.

The meeting background package was sent on June 14, 2007. Pre-meeting responses were sent from the Division to Axcan's regulatory representative by facsimile on July 16, 2007 to provide focus for the meeting discussion.

MEETING OBJECTIVES:
The purpose of today's meeting is to clarify and discuss FDA's July 16, 2009, responses, as needed.

Discussion Points: Following introductions, Axcan's questions from the June 14, 2007 background package were addressed. The format of these minutes provides for Axcan's questions in regular typeface, followed by FDA's responses in **bolded** print, followed by the July 17, 2007 meeting discussion in ***italicized and bolded*** print.

Question 1: Axcan Scandipharm Inc. plans to submit the NDA in a timeframe that makes it unlikely to obtain approval for VIOKASE Tablets by April 2008. Can the Agency please advise on how VIOKASE will be handled during the period between April 2008 and the approval date for the NDA.

Response:
We recognize that the April, 2008 deadline may, in some cases, be difficult to meet; however, we are actively working with all Applicants to resolve the technical and clinical issues with the pancreatic enzyme products (PEPs), to ensure that there will not be a shortage in the US market.

Question 2: Axcan Scandipharm Inc. has received a Fast Track Designation for VIOKASE. Because Fast Track designation is intended to expedite interaction with the FDA, we would like some clarification on specific points:

a) Can the NDA for VIOKASE be submitted as a 'rolling NDA', with early submission of the CMC section?
b) Please advise how this designation streamlines the time required for requesting a meeting with FDA personnel.

Response:
Yes, the NDA for VIOKASE can be submitted as a rolling submission. You may submit the CMC section alone if it is complete and contains all of the necessary information required for an NDA submission. Please note, however, per the FDA's 2004 Guidance for Industry Fast Track Drug Development Programs –Designation, Development, and Application Review, that although a Fast Track Designation allows you to submit some documentation early, the PDUFA goal date clock for the NDA submission will begin only after all pieces of the submission have been submitted to the Agency for review.

The Division continues to make every effort to assist PEP manufacturers in their PEP clinical development programs, including the scheduling of meetings in as timely a manner as possible.

Question 3: Are the proposed drug substance specifications acceptable to the Agency?

Response:
No. Drug substance specifications are proposed by the drug substance manufacturer, the DMF holder, and will be reviewed accordingly in support of your NDA. Regarding your in-house testing of drug substance, we have the following comments:

1. **The enzymatic methods for lipase, amylase, and protease activities in drug substance test must meet the following requirements:**
    i. **Utilize specific activity measurements to determine lipase, amylase and protease potencies;**
    ii. **The measurements must be performed under optimal conditions, and use a substrate that has been characterized with regard to identity and purity;**
    iii. **The generation of product must be linear with respect to time; and**
    iv. **The other components in the drug substance must not interfere with the assay. A demonstration that the assays meet these requirements must be provided in the NDA submission.**

Additional Discussion:
The Division clarified that the "product" in statement iii. "The generation of product must be linear with respect to time" refers to the product of the enzymatic reaction in the assay. The Division further explained that requirement iv. can be performed as part of the method validation. The Division recommended conducting a spiking study to demonstrate the lack of interference.

2. **Acceptance criteria of lipase, amylase, and protease activities in drug substance should be specified with justified lower and upper limits.**

3. **You should consult USP <1111> for recommended drug substance microbial limits. A total aerobic microbial count of 10^3 CFU/g, and a total combined yeast and mold count of 10^2 CFU/g are recommended.**

Question 4: Are the proposed drug product specifications for VIOKASE® 8 and 16 tablets acceptable to the agency?

Response:
No. We have the following comments:

1. **The proposed specifications for the drug product (based on the USP monograph) are inadequate. Specifications for the drug product should include validated tests for drug product identity, biological activity of different classes of enzymes, degradants and impurities, water content, and other relevant attributes and justified acceptance criteria. Please refer to the ICH Guidance documents Q2B, Q3B and Q6B on method validation and setting drug product specifications.**

2. **The enzymatic methods for lipase, amylase, and protease activities in drug product release testing and stability studies must meet the following requirements:**
    i. **Utilize specific activity measurements to determine lipase, amylase, and protease potencies;**

ii. **The measurements must be performed under optimal conditions, and use a substrate that has been characterized with regard to identity and purity;**
iii. **The generation of product must be linear with respect to time; and**
iv. **The other components in the drug product must not interfere with the assay. A demonstration that the assays meet these requirements must be provided in the NDA submission.**

3. **Due to the critical role of colipase in lipase activity, adequate control of colipase activity must be ensured in drug product. We recommend that lipase potency be measured in both the absence and presence of excess exogenous colipase. Acceptance criteria for activity under each condition should be established and justified.**

Additional Discussion:
In addition to the USP assay, the sponsor proposes to study the effect of colipase on the lipase enzyme activity. If this seems to have an effect, the sponsor proposes to test each batch for colipase activity. If it does not have an effect, then the sponsor will test periodically for colipase. The Division agrees to consider this proposal assuming that the sponsor can validate that consistent and optimal amounts of colipase are present in lots of drug substance and product.

4. **In addition to the proposed microbial limits, USP <1111> recommends a total combined yeast and mold count of 10^2 CFU/g.**

Question 5: Will the Agency please confirm that this approach will be acceptable?

Response:
No, see answers to questions 3 and 4.

Question 6. Axcan Scandipharm Inc. would like to confirm the following:

a) A bioactivity study (Appendix 2) will be conducted in patients with chronic pancreatitis, evaluating duodenal delivery of lipase, protease, and amylase in a fasted and fed state, with and without VIOKASE; the abbreviated statistical analysis plan (Appendix 3) is also included. Will positive results from the trial satisfy the biopharmaceutics requirement of the VIOKASE NDA?

Response:
A determination of the bioactivity study's adequacy to support NDA approval will be made upon evaluation of the study results at the time of NDA review.

Since we have only recently received the complete study protocol for the bioactivity study (with the proposed initiation date), we have not yet been able to perform a detailed review of this protocol. However, after review of the protocol outline provided in the meeting briefing package, it appears that, in general, the overall study design for the bioactivity study is acceptable.

We have the following preliminary comments and recommended revisions to the study protocol at this time (additional comments, if necessary, will be provided once review of the protocol is complete):

1. **The study should be adequately powered to detect a treatment difference between the Ensure Plus alone and Ensure Plus with Viokase treatments, and should take into account the expected variability in the tests used to measure enzymatic activity levels. Please prespecify what differences between the two treatments will be considered to be clinically meaningful.**

2. **Please state how enzyme activity levels will be determined. Provide detailed information on the assays used to determine enzyme activity levels at the time of NDA submission.**

   You have stated in the protocol that inter-luminal samples will be analyzed for total protease, amylase, and lipase (p.4; Appendix 2). However, the summary of analytical methods to be used for this intubation study is not provided. It is not clear to us if the assay methods are of sufficient sensitivity and specificity to differentiate between the endogenous human pancreatic lipase (HPL) and the orally administered porcine pancreatic lipase (PPL). When the assay methods are validated, the accuracy and precision with respect to PPL should also be determined. Since Viokase is proposed for the treatment of patients with exocrine pancreatic insufficiency (associated with steatorrhea), the amount of *in vivo* lipase units recovered from the duodenum relative to the amount of labeled PPL in the given dose of Viokase tablet is of interest.

   Furthermore, if different assay methods are to be used for determining PPL in the tablets and in the duodenum, the conversion factor between the different assay methods should be determined.

   Additional Discussion:
   The sponsor clarified that the assays will not differentiate between porcine and endogenous human enzyme activity. However, the sponsor believes the study design will allow for adequate differentiation by comparing meal to meal+Viokase results. The Division stated that adequacy will be determined at the time of review of the results of the study, and will depend on the variability of the results in individual subjects.

3. Clearly define the inclusion/exclusion criteria for patients with chronic pancreatitis (CP) or pancreatic enzyme insufficiency (PEI) to be enrolled in this intubation bioactivity study, and how these patients will be diagnosed and screened for entry into the study. Ideally, patients enrolled in the study should have low levels of endogenous HPL.

   Additional Discussion:
   The sponsor clarified that patients will be selected for the study based on fecal elastase or serum tryptase results, and that only severely affected patients are planned for inclusion in this study.

4.T he proposed sampling time in your protocol outline for intra-duodenal aspiration using a modified Dreiling tube is every 15 minutes for the second and third hours (for only two hours after study treatment administration; p.4 of Appendix 2). A two-hour post-treatment period is likely to be inadequate to complete the collections of administered pancreatic enzyme in duodenal aspirations. We recommend that the collection period be extended to three hours.

Additional Discussion:
The sponsor clarified that based on review of the medical literature, advice from clinical consultants, and their experience with performing these tests; the two-hour post-treatment collection period is felt to be adequate. The sponsor will submit their supporting documentation for selecting a two-hour collection period. The sponsor also felt that longer periods of study will lead to increase risks to the patients, increased drop-outs, and problems with patient recruitment.

The sponsor additionally clarified stated that they will collect baseline measurements before the administration of Ensure or Ensure + Viokase on both treatment days of the study.

5.**P** lease clarify the following issues in the study protocol:

a. How are the Viokase tablets to be administered to patients in this study? Will intact tablets be administered?

Additional Discussion:
The Sponsor stated that the tablets will be administered intact.

b. Is there a balloon at the end of the modified Dreiling tube to be inflated for complete duodenal sample collections?

Additional Discussion:
The sponsor clarified that there is no balloon, and that they are concerned that intermittent occlusion of the gastrointestinal tract with the balloon would lead to increased risks to patients. The sponsor stated that in their experience and in the published literature where tubes without balloons are used, the results showed that 85 to 90% of perfusate is recovered. The sponsor will submit their supporting documentation for performing sampling with a tube without a balloon.

c. Please clearly state all procedures to be performed during the study. For example, a detailed description of all procedures and the timing of these procedures during each of the two treatment phases in the study need to be clearly delineated in the protocol.

b) Will positive results from the completed clinical safety and efficacy study VIO16EP107-01, in combination with supporting data from the literature, a summary of the post-marketing safety data for the product and the results of study STEA-VK00-US01, provide sufficient evidence of effectiveness and safety in support of the NDA for VIOKASE Tablets?

Response:
In general, your proposal for the overall NDA submission for the clinical data for Viokase appears to be adequate; however, a determination as to the adequacy of the submission overall, and of study V1016EPI07-01 in particular, in demonstrating substantial evidence of efficacy (and safety) of Viokase can only be made after a review of the data contained in the NDA submission.

Other Comments:

Please describe the proposed content and format of your NDA submission (e.g., will your submission will be electronic or paper, will it use eCTD or another format, and will electronic datasets for all variables necessary for the review of your submission be included?).

Given the importance of the content and format of your NDA submission in determining the fileability of your NDA, you may wish to consider requesting a pre-NDA meeting prior to submitting your NDA.

Additional Discussion:
The sponsor plans on requesting an additional pre-NDA meeting prior to submitting the NDA to the Division. The revised date of submission of the Viokase NDA is projected to be April 2008.

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/s/

Anne Pariser
8/8/2007 07:53:23 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,716

Axcan Scandipharm, Inc.
Attention: Nicole Brufatto, Ph.D., RAC
Project Leader, US Regulatory Affairs
22 Inverness Parkway
Birmingham, AL 35242

Dear Dr. Brufatto:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viokase® (pancrelipase, USP) tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2007. The purpose of the meeting was to discuss the responses provided in a Special Protocol Assessment on December 29, 2006.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: February 7, 2007
TIME: 11:00 AM – 12:00 PM
APPLICATION: IND 60,716
DRUG NAME: Viokase®
TYPE OF MEETING: Type B
CALL IN NUMBER: (b) (4)
MEETING CHAIR: Anne Pariser, M.D.
MEETING RECORDER: Maureen Dewey, M.P.H

FDA ATTENDEES:
Division of Gastroenterology Products
Brian E. Harvey, M.D., Ph.D., Director
Anne Pariser, M.D., Medical Team Leader
Virginia Elgin, M.D., Medical Reviewer
Michael Welch, Ph.D., Statistical Team Leader
Maureen Dewey, M.P.H., Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:
Axcan Scandipharm Inc.
Alexandre LeBeaut, M.D., Senior Vice President and Chief Scientific Officer
Manon Vezina, Ph.D., Programs Director, Pancreatic Enzymes and PSE
Guy Rousseau, Ph.D., Vice President, Regulatory Affairs
Jean-René Basque, Ph.D., Clinical Research Scientist
(b) (4)

CanReg Inc.
Anne Tomalin, B.A., B.Sc, Regulatory Consultant, President CanReg Inc.
Nicole Brufatto, Ph.D., Regulatory Consultant

BACKGROUND:
On July 26, 2000 Axcan, Inc. submitted IND 60,716 for Viokase® for the treatment of steatorrhea in patients with pancreatic enzyme insufficiency.

Axcan, Inc. submitted a Type A Meeting Request on January 12, 2007 to discuss the Agency's responses to the Special Protocol Assessment for Viokase Protocol VI016EP107-01.

MEETING OBJECTIVES:
The purpose of today's meeting is to clarify and discuss the Division's recommendations provided in the Special Protocol Assessment.

DISCUSSION POINTS:
Following introductions, Axcan's questions from the January 12, 2007, background package were addressed. The format of these minutes provides for Axcan's questions in italic typeface, followed by FDA's responses in regular print, followed by the February 7, 2007 meeting discussion in ***italic and bolded*** print.

Question 2
This study will be the only pivotal study carried out for VIOKASE. It is designed to compare a single dose of VIOKASE 16 with placebo. The goal is for 30 patients randomized in a 2:1 ratio (VIOKASE:Placebo) to complete the study. Given a drop-out rate of approximately 30%, it is expected that up to 42 patients will need to be enrolled in the study in order to get 30 completed patients. VIOKASE treatment will consist of 22 tablets of VIOKASE 16 per day, taken as 6 tablets with each meal and 2 tablets with each snack. The treatment duration of VIOKASE or Placebo will be one week.

Will the Agency confirm that this approach will be sufficient to support approval of VIOKASE 16 tablets?

Response:
No. The protocol seems to suggest that only subjects who complete the study will be included in the efficacy analyses. All subjects need to be included in the analyses of the ITT population. Please provide a plan that accounts for data missing due to non-completion of the study. Your sample size collections will need to reflect this plan. The inflation factor of 1/(1-0.3) implicitly assumes the treatment effect for non-completers is the same as that for those who complete the study. This will likely not be the case. For example, the treatment effect could be smaller than anticipated if non-completers are assigned their baseline value (i.e., no change in CFA%). The impact would be a sample size larger than 42.

Also note that if your treatment difference is less than 18.83%, your study will be underpowered. For example, your study will not have sufficient power to detect a difference of 15%.

Discussion Point:
This study involves a single baseline reading and end of treatment reading for %CFA. Axcan would like to discuss the statistical impact of carrying the baseline %CFA value forward for patients who are randomized but do not complete the study.

Additional Discussion on 02/07/2007:
The sponsor stated that carrying the baseline %CFA value forward for patients with no response is too conservative for such a small study. They are concerned that this will adversely affect the overall findings of the study. The sponsor proposes using the mean (or median) treatment value result for the placebo group as the treatment value for patients with missing data. The Division responded that the median imputation may be reasonable, but we would still like to see the non-responder analysis (i.e., use of baseline value carried forward for non-completers),

and recommended that the sponsor consider performing additional sensitivity analyses. The Division recommended that the sponsor anticipate the number of drop-outs and factor this into study size. Ultimately, an adequate sample size to demonstrate efficacy will be needed for NDA approval.

The Division also noted that in addition to achieving statistical significance, the percent change in CFA with treatment must be clinically meaningful. That is, for more severely affected patients (baseline %CFA ≤40), a change in %CFA of 30% is considered to be clinically meaningful. For less severely affected patients (%CFA <80 and >40), the percent change in CFA that is clinically meaningful has not been defined.

The sponsor stated that they plan to increase the sample size for this study.

Question 3
Will the agency confirm that the study population as described by the inclusion and exclusion criteria is acceptable to support approval of the proposed indication?

Response:
As noted in our answer to Question 1 (above), in general, your clinical trial design appears to be adequate to support the limited indication you have proposed, i.e., adult patients with chronic pancreatitis, pancreatectomy, (b) (4)

(b) (4)

In addition, we have the following comments regarding your inclusion and exclusion criteria for the study:

- Inclusion Criteria: Provide a definition for "recent alcohol consumption" in patients with chronic pancreatitis due to alcohol abuse, i.e., clarify the period of abstinence from alcohol needed in order to be eligible for study participation (e.g., six to twelve months).

Question 3a: Inclusion Criteria
Given the nature and prevalence of chronic pancreatitis (up to 80% of cases are due to chronic alcohol intake and the prevalence appears to be less than 200,000 in the United States), Axcan would like to discuss how best to define "recent alcohol consumption" and a reasonable period of abstinence from alcohol required for study participation.

Additional Discussion on 02/07/2007:
The sponsor stated that there is a high prevalence of alcohol use in the chronic pancreatitis population. They are concerned that overly restricting alcohol use will limit their ability to enroll patients in the trial. The sponsor is proposing that patients be permitted to use one drink of alcohol a day prior to inpatient treatment, and then no alcohol use will be allowed during the inpatient periods of the study. The Division stated that a reasonable time period of alcohol abstinence

is to be defined in the protocol at the sponsor's discretion. The Division's concern is that patients at risk of acute alcohol withdrawal will be entered into the study. This is a safety concern for the patients, and also a concern for non-compliance or a high study drop-out rate. The sponsor voiced agreement, and will include a defined time interval for absence of alcohol consumption in the protocol.

- Exclusion criteria:
    - Patients with insufficient body mass (e.g., BMI <18) should be considered for exclusion from study participation.
    - Patients with a history of fibrosing colonopathy, cirrhosis of the liver, or portal hypertension should be considered for exclusion from study participation.
    - Patients with AST or ALT greater than three times the upper limit of normal or other causes of liver disease (such as hepatitis), or patients with elevated uric acid levels should be considered for exclusion from study participation.

Question 3b: Exclusion Criteria
Axcan would like to discuss the exclusion of patients with elevated uric acid levels.

Additional Discussion on 02/07/2007:
The sponsor stated that concerns for elevated uric acid levels with the use of pancreatic enzyme products are mostly noted for patients with CF, and that, in all likelihood, the chronic pancreatitis population will have elevated uric acid due to other causes, such as alcohol use. They are concerned that being overly restrictive for uric acid levels will unnecessarily limit enrollment of patients. The Division stated that the exclusion of patients for a high uric acid level is a recommendation and is not mandatory. The Division suggests that the sponsor set an upper limit for uric acid at screening that is reasonable for the projected patient population.

As mentioned previously during the face-to-face meeting held between your company and the Agency on October 4, 2006, although pediatric data are not required at the time of the original NDA submission, the Pediatric Research Equity Act (PREA) of 2003 would likely require a pediatric study be performed in the post-approval time period (as a post-marketing commitment) as a requirement for approval. If you are not planning on developing your product for use in a pediatric (or Cystic Fibrosis) patient population, we recommend that you request a deferral of pediatric studies rather than a waiver of the PREA requirements. The granting of such a deferral regarding pediatric studies will be determined at the time of the NDA submission.

Question 3c: PREA
Based on the study design, Axcan will be limiting VIOKASE® to an indication of chronic pancreatitis. Axcan will apply for a deferral of pediatric studies until such time that data exist to suggest a medical need for a treatment for chronic pancreatitis in children.

Additional Discussion on 02/07/2007:
The Division agreed with the sponsor's proposal.

Question 4
The schematic for the study design is provided in Appendix 1 of the Protocol (Appendix 7.1).
Will the Agency confirm the acceptability of this approach?

Response:
In general, the overall design of the study appears to be acceptable. However, we have the following specific comments and recommendations for your proposed clinical protocol:

Study Procedures:

- The Study Flowchart in Appendix 1 is inadequate. Provide a flowchart that includes all study procedures to be performed by study day, rather than grouped by phase as currently depicted in the study flowchart. For example, during the inpatient periods of the Wash-out and Treatment phases, clearly delineate which protocol-defined treatments and procedures are to occur on each of the four to five days of this period.

- In the Study Procedures section of the protocol (section 9.0), clearly list and describe in detail, all protocol-related procedures that are to be performed and recorded. For example, describe how morning weight will be obtained, and on which days and at what time clinical laboratory testing will be performed.

- Ensure agreement between the study flowchart and the description of the study procedures in section 9.0. For example, vital signs are included in the flowchart during the inpatient period, but not in the listing of the study procedures.

- No protocol-defined procedures are noted for the Follow-up visit. Describe what information will be collected, and what procedures will be performed at this visit (e.g., collection of AEs).

- Include a pregnancy test for all female patients of child-bearing potential prior to the Wash-out and Treatment phases of the study.

Subpoint 5:
Regarding the inclusion of pregnancy tests for all female patients of child-bearing potential prior to the Wash-out and Treatment phases of the study, Axcan is proposing carrying out pregnancy tests on Day 3 (the first day of the inpatient period) of both the Wash-out and Treatment phases.

Additional Discussion on 02/07/2007:
The Division stated that urine pregnancy tests at Day 3 of the wash-out and treatment periods are acceptable.

- Vital signs and weight should be obtained, at minimum, at each study visit, and daily during the inpatient period.

- State the turn-around time for the safety laboratory tests to be performed during the study, and note in the protocol that all safety laboratory tests performed during the Wash-out and Treatment phases of the protocol will be reviewed by the Investigators prior to patient discharge from the inpatient treatment facility.

Subpoint 7:
Axcan would like to discuss the need for safety laboratory tests to be reviewed by the Investigators prior to patient discharge from the inpatient facility during the Wash-out and Treatment phases of the study.

Additional Discussion on 02/07/2007:
The sponsor stated that they plan on using a central laboratory for all laboratory tests, and that having the laboratory results available prior to discharge of the patients is not feasible. The Division stated that for safety reasons all patients should have a safety laboratory assessment (such as CBC and chemistry panel) performed and reviewed by the Investigator prior to discharge. A second set of safety laboratory samples can be sent to the clinical site's hospital laboratory in parallel with the safety sample being sent to the central laboratory, for the purpose of providing adequate patient safety monitoring prior to discharge. The sponsor agreed, and will incorporate laboratory monitoring prior to discharge into the study protocol.

- Define the length of time patients will be on double-blind study medication during the randomization phase prior to beginning the treatment phase of the study. Describe how a steady-state on double-blind medication will be established during this phase.

Subpoint 8:
During the Randomization phase, patients will take their own pancreatic enzyme supplements and their own PPI treatment. Upon initiation of the Treatment phase, patients will take VIOKASE® or Placebo. Given that pancreatic enzyme treatments act locally in the duodenum and are not at all or are very minimally absorbed, no carry over effects are expected from intake of the patient's pancreatic enzyme treatment during the Randomization phase. Axcan would like to discuss the Agency's comment regarding the establishment of a steady-state for the double-blind medication during the Treatment phase.

Additional Discussion on 02/07/2007:
The sponsor clarified the study procedures and provided a revised study flowchart (Attachment 1). The sponsor clarified that all patients are to initiate Viokase or placebo on Outpatient Day 1 of the treatment phase. Thus, all patients will have been receiving at least 72 hours of Viokase or placebo treatment prior to beginning the treatment phase stool collection. The Division

stated that the sponsor's explanation clarified the study procedures, and the sequence of events appears to be acceptable. Additionally, the Division noted that as this study is a fixed-dose treatment study with no dose titration, the sponsor runs the risk of having non-responders with this study design. The sponsor stated that the proposed dose of Viokase is relatively high, and that this is unlikely to happen.

- Clearly delineate where the two-day outpatient periods of the Wash-out and Treatment phases begin, and where the Screening and Randomization periods end. We recommend that patients be evaluated by the Investigators at the start of the Wash-out and Treatment phases (not currently listed as visits in the overall study schema).

Subpoint 9:
Regarding the introduction of patient evaluations at the beginning of the Wash-out and Treatment phases of the study, Axcan is proposing introducing these evaluations on Day 3 (the first day of the inpatient period) of both the Wash-out and Treatment phases.

Additional Discussion on 02/07/2007:
The sponsor clarified that patients will receive a phone-call on Day 1 of the Outpatient Treatment period marking the beginning of the treatment phase. Patients will not be seen in person on this day. Patients will monitor compliance and symptoms on diary cards. The Division stated that maintaining consistency and ensuring adequate data capture can be problematic with this study design. The sponsor stated that they plan to minimize the risk of experiencing these problems as much as possible through investigator education and training. They also stated that there is a possibility that some of the sites may house the patients for the entire treatment phase (for what are currently designated as the outpatient and inpatient periods.) The Division stated that as this is a multi-center study, consistency across sites is very important, and it is possible that different study sites using different study procedures may show large differences in the results obtained in the study. The Division requested that the sponsor develop a pooling plan by sites and by country. The sponsor will need to show consistency across sites and study centers in these analyses. Large discrepancies in the results between the study sites may impact the overall findings for the study.

- Define procedures to be used to verify compliance with all study-related procedures, such as compliance with PPI treatments, and with pancreatic enzyme product treatments during all phases of the study.

- Since a large number of study sites will be participating in the study (16 to 20 sites, for a total enrollment of approximately 42 patients, or two to three patients per site), describe how study conduct will be standardized across these sites.

- Clearly define all study endpoints in the study protocol, and provide a listing of all primary, secondary, and other variables to be collected, evaluated, and analyzed in this study. The study endpoints as listed in the Section 11.5.6 do not agree with the variables noted in Question 7 of your submission.

- Clarify whether patients or study personnel will be collecting and recording data, and administering all study-related treatments during the inpatient periods of the Wash-out and Treatment phases of the study. For example, who will be recording number of bowel movements, will patients be self-administering PPIs and double-blind study medication during these periods, and how will the 72-hour stool collection be performed?

- Discontinuation Criteria:
  - Define individual patient stop criteria, and stop criteria for the overall study based on objective criteria. Patients should be discontinued from the study for safety reasons only. For example, any patient developing an AST or ALT greater than eight times the upper limit of normal should be discontinued from treatment during the study. Such a patient should also be evaluated for the cause of the liver enzyme elevation (e.g. viral hepatitis).
  - We recommend that you describe standardized interventions for severe or serious Adverse Events (AEs) anticipated to occur during the study, e.g., gastrointestinal AEs, such as abdominal pain.

- Concomitant medications: Since FD&C Blue No. 2 and PPIs will be administered to all patients as part of study procedures, include information about their adverse reaction profiles in both the Investigators Brochure and the patient Informed Consent Form.

- Submit a copy of the Case Report, Forms (CRFs), sample Informed Consent form and Investigator's Brochure with the finalized study protocol.

Question 5
Will the Agency confirm the acceptability of the proposed concomitant use of PPIs to support approval of VIOKASE 16?

Response:
The proposed concomitant use of PPIs is acceptable; however, PPI treatment is to be standardized during the study. Define the dose ranges for all PPIs to be used in the study, and provide justification for the similarity in proton pump inhibition for these medications at these dosages, and their comparability to omeprazole 20 mg per day. In addition, describe how compliance with PPI use will be evaluated during all phases of the study. For example, provide clarification whether patients or study personnel will be collecting and recording data during all phases of the study.

Question 5 – PPI Therapy
Axcan would like to discuss the standardization of the PPI treatment.

Additional Discussion on 02/07/2007:
The sponsor stated that patients will document their compliance with PPIs on patient diary cards. The sponsor will also provide a listing of acceptable PPIs to be used during the study. The Division stated that as long as an approved PPI was being used in the recommended dosage range during the study, then this would be acceptable to the Division.

Question 6
Will the Agency confirm the acceptability of the primary endpoint and the statistical analysis to support approval of the proposed indication?

Response:
Please explain the purpose of the analysis that compares the CFA% means at wash-out and how it will impact the interpretation of the efficacy results. We will consider this to be an exploratory analysis.

We consider the parametric models to be primary. Non-parametric models should be undertaken only in the cases of gross violations of the parametric modeling assumptions. The NDA will need to document reasons for using a non-parametric model.

A plan for pooling study sites for the purpose of assessing site by treatment interactions should be specified prior to the start of the study. Given the expected number of subjects per site will be 2 or 3 subjects, results from analyses of pooled sites by treatment interactions may not be meaningful. We recommend an analysis that includes an interaction term for country (Poland or USA) and treatment, denoted by country*treatment.

As we understand your proposal, the ITT population will include only subjects who have a CFA% calculated at 72 hours. If so, we do not find this acceptable. The ITT population needs to include data from all subjects who are randomized.

In addition, "discontinuing study treatment" needs to be distinguished from "discontinuing the study". Keeping with the ITT principle, all subjects should remain in the study regardless of treatment status and their data included in the ITT analysis.

Other than a subject's choice to discontinue treatment or study participation, subjects should be discontinued for safety reasons only.

There is a large number of study sites planned for participation in the study, and the expected number of subjects per study site is about two or three. If the characteristics of study patients and standards of medical care vary across study sites or countries, the interpretation of the study results could be difficult.

Question 6 – Primary Endpoint
Axcan would like to discuss the comparison of the %CFA means at Wash-out for the treatment groups and the effects on the analysis of the efficacy endpoint.

Additional Discussion on 02/07/2007:
The sponsor concurred with the exploratory nature of the analysis and withdrew this question. The sponsor clarified that they would be using %CFA at baseline as a covariate in the analysis.

Question 7
Will the agency confirm the acceptability of the secondary endpoints as described in the draft protocol contained in Appendix 1 (and outlined above) to support approval of the proposed indication?

Response:
Provide a listing of the secondary endpoints and other variables to be analyzed in the study protocol. The study endpoints as currently listed in the Section 11.5.6 do not agree with the secondary endpoints as described in Question 7 above.

We consider analyses of the secondary endpoints you have described above to be exploratory only.

ACTION ITEMS:

- Axcan will submit a protocol amendment to the IND.
- Axcan will submit a Statistical Analysis Plan (SAP), and schedule a meeting to discuss its acceptability of the SAP with the Statistical Review Team.

ATTACHMENT:
Study Flowchart

STUDY FLOWCHART

Phase	Screening Phase	Wash-Out Phase						
		Outpatient Period		Inpatient Period				
Visit	V1	(2 Days)		V2 (4 to 5 Days)				
Duration	Up to 10 Days	D1	D2	D1[b]	D2	D3	D4[c]	D5[c]
Informed Consent	X							
Demographic Data	X							
Relevant Medical / Surgical History	X							
Physical Examination	X						X	X
Vital Signs	X			X	X	X	X	X
Weight	X			X	X	X	X	X
Inclusion/Exclusion Criteria	X							
Fecal Elastase 1 Test	X							
Clinical Laboratory Tests and Urinalysis	X						X	X
Serum Pregnancy Test (if necessary)	X							
Patient's Usual Pancreatic Enzymes Treatment	X	Off	Off	Off	Off	Off	Off	Off
PPI	X	X	X	X	X	X	X	X
Dietician Instructions	X							
Dispensing of the Diary[a]	X							
High-fat Diet		X	X	X	X	X	X	X
Diary Completion[c]		X	X	X	X	X	X	X
72-Hour Stool Collection					X	X	X	X
FD&C Blue No. 2 Dye (stool marker)[d]				X			X	X
Randomization								
Double-Blind Study Drug (VIOKASE® 16 or Placebo)								
Recording Adverse Events	X	X	X	X	X	X	X	X
Recording Concomitant Medication	X	X	X	X	X	X	X	X
Compliance Check								
Drug Accountability								

a Diary dispensed to patients will include food records, stool frequency and stool characteristic recordings.
b Patients will arrive to the clinical facility in the first morning of the inpatient period of the Wash-Out Phase.
c Diary completed to include food records, stool frequency and stool characteristic recordings.
d The FD&C Blue No. 2 dye be administered with breakfast on the first and fourth day of the Inpatient period. If the dye marker does not pass within 36 hours after first administration (by the second day of the inpatient period), administer the second dye marker 96 hours after the first administration (on the fifth day of the Inpatient period).

STUDY FLOWCHART (Continued)

Phase	Randomization Phase	Treatment Phase						
		Outpatient Period		Inpatient Period				
Visit	V3	(2 Days)		V4 (4 to 5 Days)				
Duration	Up to 10 Days	D1	D2	D1[b]	D2	D3	D4	D5
Informed Consent								
Demographic Data								
Relevant Medical / Surgical History								
Physical Examination							X	X
Vital Signs				X	X	X	X	X
Weight	X			X	X	X	X	X
Inclusion/Exclusion Criteria								
Fecal Elastase 1 Test								
Clinical Laboratory Tests and Urinalysis							X	X
Serum Pregnancy Test (if necessary)								X
Randomization[c]								
Patient's Usual Pancreatic Enzymes Treatment	X	Off	Off	Off	Off	Off	Off	Off
PPI	X	X	X	X	X	X	X	X
Dietician Instructions	X							
Dispensing of the Diary[a]	X							
High-fat Diet		X	X	X	X	X	X	X
Diary Completion[d]		X	X	X	X	X	X	X
72-Hour Stool Collection				X	X	X	X	X
FD&C Blue No. 2 Dye (stool marker)[e]				X			X	X
Double-Blind Study Drug (VIOKASE® 16 or Placebo)		X	X	X	X	X	X	X
Recording Adverse Events	X	X	X	X	X	X	X	X
Recording Concomitant Medication	X	X	X	X	X	X	X	X
Compliance Check								X
Drug Accountability								X

a Diary dispensed to patients will include food records, stool frequency and stool characteristic recordings.
b Patients will arrive to the clinical facility in the first morning of the Inpatient period of the Treatment Phase.
c Double blind randomization number assigned to patients.
d Diary completed to include food records, stool frequency and stool characteristic recordings.
e. The FD&C Blue No. 2 dye be administered with breakfast on the first and fourth day of the Inpatient period. If the dye marker does not pass within 36 hours after first administration (by the second day of the inpatient period), administer the second dye marker 96 hours after the first administration (on the fifth day of the Inpatient period).

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

/s/

Anne Pariser
2/27/2007 04:25:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,716

Axcan Scandipharm Inc.
Attention: Nicole Brufatto, Ph.D., RAC
Director of Regulatory Affairs, CanReg Inc.
22 Inverness Parkway, Suite 310
Birmingham, AL 35242

Dear Dr. Brufatto:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Viokase® 16 (pancrelipase).

We also refer to your November 13, 2006, serial number 012, for a special clinical protocol assessment, received November 15, 2006. The protocol is entitled "A Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled, Phase III Study to Assess the Safety and Efficacy of VIOKASE® 16 for the Correction of Steatorrhea in Patients with Exocrine Pancreatic Insufficiency."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

Question 1
Will the Agency confirm that the proposed clinical trial VIO16EPI07-01 meets the criteria of an adequate and well-controlled study in support of this indication?

Response:
In general, your proposed clinical trial design appears to be adequate. However, we note that your indication will be limited to the patient population included for study in your proposed protocol, i.e., adult patients with chronic pancreatitis, pancreatectomy, (b) (4) (b) (4)

Question 2
This study will be the only pivotal study carried out for VIOKASE. It is designed to compare a single dose of VIOKASE 16 with placebo. The goal is for 30 patients randomized in a 2:1 ratio (VIOKASE:Placebo) to complete the study. Given a drop-out rate of approximately 30%, it is expected that up to 42 patients will need to be enrolled in the study in order to get 30 completed patients. VIOKASE treatment will consist of 22 tablets of VIOKASE 16 per day, taken as 6

tablets with each meal and 2 tablets with each snack. The treatment duration of VIOKASE or Placebo will be one week.

Will the Agency confirm that this approach will be sufficient to support approval of VIOKASE 16 tablets?

Response:
No. The protocol seems to suggest that only subjects who complete the study will be included in the efficacy analyses. All subjects need to be included in the analyses of the ITT population. Please provide a plan that accounts for data missing due to non-completion of the study. Your sample size collections will need to reflect this plan. The inflation factor of 1/(1-0.3) implicitly assumes the treatment effect for non-completers is the same as that for those who complete the study. This will likely not be the case. For example, the treatment effect could be smaller than anticipated if non-completers are assigned their baseline value (i.e., no change in CFA%). The impact would be a sample size larger than 42.

Also note that if your treatment difference is less than 18.83%, your study will be underpowered. For example, your study will not have sufficient power to detect a difference of 15%.

Question 3
Will the agency confirm that the study population as described by the inclusion and exclusion criteria is acceptable to support approval of the proposed indication?

Response:
As noted in our answer to Question 1 (above), in general, your clinical trial design appears to be adequate to support the limited indication you have proposed, i.e., adult patients with chronic pancreatitis, pancreatectomy (b) (4)
(b) (4)

In addition, we have the following comments regarding your inclusion and exclusion criteria for the study:

- Inclusion Criteria: Provide a definition for "recent alcohol consumption" in patients with chronic pancreatitis due to alcohol abuse, i.e., clarify the period of abstinence from alcohol needed in order to be eligible for study participation (e.g., six to twelve months).

- Exclusion criteria:
    - Patients with insufficient body mass (e.g., BMI <18) should be considered for exclusion from study participation.
    - Patients with a history of fibrosing colonopathy, cirrhosis of the liver, or portal hypertension should be considered for exclusion from study participation.

- Patients with AST or ALT greater than three times the upper limit of normal or other causes of liver disease (such as hepatitis), or patients with elevated uric acid levels should be considered for exclusion from study participation.

As mentioned previously during the face-to-face meeting held between your company and the Agency on October 4, 2006, although pediatric data are not required at the time of the original NDA submission, the Pediatric Research Equity Act (PREA) of 2003 would likely require a pediatric study be performed in the post-approval time period (as a post-marketing commitment) as a requirement for approval. If you are not planning on developing your product for use in a pediatric (or Cystic Fibrosis) patient population, we recommend that you request a deferral of pediatric studies rather than a waiver of the PREA requirements. The granting of such a deferral regarding pediatric studies will be determined at the time of the NDA submission.

Question 4
The schematic for the study design is provided in Appendix 1 of the Protocol (Appendix 7.1).

Will the Agency confirm the acceptability of this approach?

Response:
In general, the overall design of the study appears to be acceptable. However, we have the following specific comments and recommendations for your proposed clinical protocol:

Study Procedures:

- The Study Flowchart in Appendix 1 is inadequate. Provide a flowchart that includes all study procedures to be performed by study day, rather than grouped by phase as currently depicted in the study flowchart. For example, during the inpatient periods of the Wash-out and Treatment phases, clearly delineate which protocol-defined treatments and procedures are to occur on each of the four to five days of this period.

- In the Study Procedures section of the protocol (section 9.0), clearly list and describe in detail, all protocol-related procedures that are to be performed and recorded. For example, describe how morning weight will be obtained, and on which days and at what time clinical laboratory testing will be performed.

- Ensure agreement between the study flowchart and the description of the study procedures in section 9.0. For example, vital signs are included in the flowchart during the inpatient period, but not in the listing of the study procedures.

- No protocol-defined procedures are noted for the Follow-up visit. Describe what information will be collected, and what procedures will be performed at this visit (e.g., collection of AEs).

- Include a pregnancy test for all female patients of child-bearing potential prior to the Wash-out and Treatment phases of the study.

- Vital signs and weight should be obtained, at minimum, at each study visit, and daily during the inpatient period.

- State the turn-around time for the safety laboratory tests to be performed during the study, and note in the protocol that all safety laboratory tests performed during the Wash-out and Treatment phases of the protocol will be reviewed by the Investigators prior to patient discharge from the inpatient treatment facility.

- Define the length of time patients will be on double-blind study medication during the randomization phase prior to beginning the treatment phase of the study. Describe how a steady-state on double-blind medication will be established during this phase.

- Clearly delineate where the two-day outpatient periods of the Wash-out and Treatment phases begin, and where the Screening and Randomization periods end. We recommend that patients be evaluated by the Investigators at the start of the Wash-out and Treatment phases (not currently listed as visits in the overall study schema).

- Define procedures to be used to verify compliance with all study-related procedures, such as compliance with PPI treatments, and with pancreatic enzyme product treatments during all phases of the study.

- Since a large number of study sites will be participating in the study (16 to 20 sites, for a total enrollment of approximately 42 patients, or two to three patients per site), describe how study conduct will be standardized across these sites.

- Clearly define all study endpoints in the study protocol, and provide a listing of all primary, secondary, and other variables to be collected, evaluated, and analyzed in this study. The study endpoints as listed in the Section 11.5.6 do not agree with the variables noted in Question 7 of your submission.

- Clarify whether patients or study personnel will be collecting and recording data, and administering all study-related treatments during the inpatient periods of the Wash-out and Treatment phases of the study. For example, who will be recording number of bowel movements, will patients be self-administering PPIs and double-blind study medication during these periods, and how will the 72-hour stool collection be performed?

- Discontinuation Criteria:
    - Define individual patient stop criteria, and stop criteria for the overall study based on objective criteria. Patients should be discontinued from the study for safety reasons only. For example, any patient developing an AST or ALT greater than eight times the upper limit of normal should be discontinued from treatment during the study. Such a patient should also be evaluated for the cause of the liver enzyme elevation (e.g. viral hepatitis).
    - We recommend that you describe standardized interventions for severe or serious Adverse Events (AEs) anticipated to occur during the study, e.g., gastrointestinal AEs, such as abdominal pain.

- Concomitant medications: Since FD&C Blue No. 2 and PPIs will be administered to all patients as part of study procedures, include information about their adverse reaction profiles in both the Investigators Brochure and the patient Informed Consent Form.

- Submit a copy of the Case Report, Forms (CRFs), sample Informed Consent form and Investigator's Brochure with the finalized study protocol.

Question 5
Will the Agency confirm the acceptability of the proposed concomitant use of PPIs to support approval of VIOKASE 16?

Response:
The proposed concomitant use of PPIs is acceptable; however, PPI treatment is to be standardized during the study. Define the dose ranges for all PPIs to be used in the study, and provide justification for the similarity in proton pump inhibition for these medications at these dosages, and their comparability to omeprazole 20 mg per day. In addition, describe how compliance with PPI use will be evaluated during all phases of the study. For example, provide clarification whether patients or study personnel will be collecting and recording data during all phases of the study.

Question 6
Will the Agency confirm the acceptability of the primary endpoint and the statistical analysis to support approval of the proposed indication?

Response:
Please explain the purpose of the analysis that compares the CFA% means at wash-out and how it will impact the interpretation of the efficacy results. We will consider this to be an exploratory analysis.

We consider the parametric models to be primary. Non-parametric models should be undertaken only in the cases of gross violations of the parametric modeling assumptions. The NDA will need to document reasons for using a non-parametric model.

A plan for pooling study sites for the purpose of assessing site by treatment interactions should be specified prior to the start of the study. Given the expected number of subjects per site will be 2 or 3 subjects, results from analyses of pooled sites by treatment interactions may not be meaningful. We recommend an analysis that includes an interaction term for country (Poland or USA) and treatment, denoted by country*treatment.

As we understand your proposal, the ITT population will include only subjects who have a CFA% calculated at 72 hours. If so, we do not find this acceptable. The ITT population needs to include data from all subjects who are randomized.

In addition, "discontinuing study treatment" needs to be distinguished from "discontinuing the study". Keeping with the ITT principle, all subjects should remain in the study regardless of treatment status and their data included in the ITT analysis.

Other than a subject's choice to discontinue treatment or study participation, subjects should be discontinued for safety reasons only.

There is a large number of study sites planned for participation in the study, and the expected number of subjects per study site is about two or three. If the characteristics of study patients and standards of medical care vary across study sites or countries, the interpretation of the study results could be difficult.

Question 7
Will the agency confirm the acceptability of the secondary endpoints as described in the draft protocol contained in Appendix 1 (and outlined above) to support approval of the proposed indication?

Response:
Provide a listing of the secondary endpoints and other variables to be analyzed in the study protocol. The study endpoints as currently listed in the Section 11.5.6 do not agree with the secondary endpoints as described in Question 7 above.

We consider analyses of the secondary endpoints you have described above to be exploratory only.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
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/

Joyce Korvick
12/29/2006 02:17:37 PM

From: Dewey, Maureen
Sent: Tuesday, October 31, 2006 12:31 PM
To: 'nbrufatto@canreginc.com'
Cc: Guo, Wei; Elgin, Virginia; Pariser, Anne; Johnson, Gibbes
Subject: FW: VIOKASE IND 60,716 - Request for Feedback

Hi Nicole,

Thank you for your inquiry regarding the dissolution test to be used for Viokase.

Question:
Viokase 8000 and Viokase 16000 tablets are immediate release, solid oral dosage form pancrelipase products. Viokase is to be administered to the patient in combination with a meal and our Clinical study is intended to be performed using a PPI drug. The combination of a meal and the PPI drug result in a stomach pH of approximately 4.5. Since the formulations are immediate release, Axcan Pharma Inc. is planning to perform the dissolution test using a phosphate buffer at pH 4.5 as the dissolution medium. Given the complexity of pancreatic extracts, UV spectroscopy will be used to quantify total protein released.

The main purpose of the dissolution test is to ensure that the enzymes are released from the tablet as per specification and to ensure batch to batch consistency during manufacture. With regards to enzyme activities, the activity of each enzyme is measured in the drug substance before compounding and retested on the finished product.

Does the Agency agree that the proposed dissolution method is appropriate for the purpose described?

Response from our Reviewer in the Division of Therapeutic Proteins:

It is acceptable to use Phosphate buffer at pH 4.5 in your proposed dissolution test. UV monitoring of the dissolution is also acceptable assuming the tablet is completely dissolved. If the tablet is not completely dissolved, assays to measure the activity of amylase, lipase and protease should be used.

Please let me know if you need further clarification .

Regards,

Maureen Dewey, MPH
Regulatory Project Manager
Division of Gastroenterology Products

From: Guo, Wei
Sent: Tuesday, October 31, 2006 10:07 AM
To: Dewey, Maureen
Subject: RE: VIOKASE IND 60,716 - Request for Feedback

Hi Maureen, here is our response to their dissolution test:

It is acceptable to use Phosphate buffer at pH 4.5 in your proposed dissolution test. UV monitoring of the dissolution is also acceptable assuming the tablet is completely dissolved. If the tablet is not completely dissolved, assays to measure the activity of amylase, lipase and protease should be used.

Please let me know if further clarifications are needed.
Thanks.
Wei

****

Wei Guo, Ph.D.
LCDR, US Public Health Service
Review Chemist, HFD-122
FDA/CDER/OPS/OBP/DTP
Room 2B24, Building 29A
e-mail: wei.guo@fda.hhs.gov
voice mail: 301-827-1789
fax: 301-480-3256
****

From: Nicole Brufatto PhD, RAC [mailto:nbrufatto@canreginc.com]
Sent: Thursday, October 26, 2006 3:50 PM
To: Dewey, Maureen
Subject: FW: VIOKASE IND 60,716 - Request for Feedback

Hi Maureen,
As per the voicemail I left for you, Axcan Scandipharm Inc. has the following question regarding the dissolution test that they will be using for Viokase. I was hoping that this issue might be straightforward enough to allow us to solicit a response via email or telephone. If not, simply let me know.

Thanks again for your ongoing support!
Nicole

Nicole Brufatto, PhD
CanReg Inc.
905-689-3980 ext. 346

Question:
Viokase 8000 and Viokase 16000 tablets are immediate release, solid oral dosage form pancrelipase products. Viokase is to be administered to the patient in combination with a meal and our Clinical study is intended to be performed using a PPI drug. The combination of a meal and the PPI drug result in a stomach pH of approximately 4.5. Since the formulations are immediate release, Axcan Pharma Inc. is planning to perform the dissolution test using a phosphate buffer at pH 4.5 as the dissolution medium. Given the complexity of pancreatic extracts, UV spectroscopy will be used to quantify total protein released.

The main purpose of the dissolution test is to ensure that the enzymes are released from the tablet as per specification and to ensure batch to batch consistency during manufacture. With regards to enzyme activities, the activity of each enzyme is measured in the drug substance before compounding and retested on the finished product.

Does the Agency agree that the proposed dissolution method is appropriate for the purpose described?

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

/s/

Maureen Dewey
10/31/2006 01:39:45 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 60,716

Axcan Scandipharm, Inc.
Attention: Nicole Brufatto, Ph.D., RAC
Project Leader, US Regulatory Affairs
22 Inverness Parkway
Birmingham, AL 35242

Dear Dr. Brufatto:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)/505(b) of the Federal Food, Drug, and Cosmetic Act for Viokase® (pancrelipase, USP) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on October 4, 2006. The purpose of the meeting was to discuss the design of your proposed Phase 3 clinical trials to satisfy requirements for NDA submission of Viokase® tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0845.

Sincerely,

[See appended electronic signature page]

Maureen Dewey
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MEETING MINUTES

MEETING DATE: October 4, 2006
TIME: 11:00 AM – 12:00 PM
APPLICATION: IND 60,716
DRUG NAME: Viokase®
TYPE OF MEETING: Type B
CALL IN NUMBER: [redacted] (b) (4)

MEETING CHAIR: Anne Pariser, M.D.
MEETING RECORDER: Maureen Dewey

FDA ATTENDEES:
Division of Gastroenterology Products
Brian E. Harvey, M.D., Ph.D., Director
Anne Pariser, M.D., Medical Team Leader
Virginia Elgin, M.D., Medical Reviewer
Ethan Hausman, M.D., Medical Reviewer
Maureen Dewey, Regulatory Project Manager

Office of Biotechnology Products (OBP) Division of Therapeutic Proteins
Wei Guo, Ph.D., Chemistry Reviewer
Gibbes Johnson, Ph.D., Supervisory Research Chemist

Division of Clinical Pharmacology-3
Capt E. Dennis Bashaw, Pharm.D, Director
Sue Chih Lee, Ph.D., Clinical Pharmacology Reviewer
Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:
Axcan Scandipharm Inc.
Alexandre LeBeaut, M.D., Senior Vice President and Chief Scientific Officer
Patrick Colin, Ph.D., Vice President, Research and Development
Manon Vezina, Ph.D., Programs Director, Pancreatic Enzyme and PSE
Carl Gauthier, Ph.D., Project Manager, Pharmaceutical Development
Yves Dumoulin, Ph.D., Senior Director, Pharmaceutical Development
[redacted] (b) (4)

CanReg Inc.
Becky Prokipcak, Ph.D., Regulatory Consultant
Nicole Brufatto, Ph.D., Regulatory Consultant
Stuart Wright, M.Sc., Regulatory Consultant

BACKGROUND:
On July 26, 2000 Axcan, Inc. submitted IND 60,716 for Viokase® for the treatment of steatorrhea in patients with pancreatic enzyme insufficiency.

Axcan, Inc. submitted a Meeting Request on July 21, 2006, received July 24, 2006. The meeting background package was sent on September 5, 2006. Pre-meeting responses were sent to Axcan's regulatory representative by facsimile on September 28, 2006 to provide focus for the meeting discussion. On October 2, 2006, the Agency received a request from Axcan's regulatory representative to change the face to face meeting to a teleconference.

MEETING OBJECTIVES:
The purpose of today's teleconference is to clarify and discuss FDA's September 28, 2006, responses, as needed.

Discussion Points: Following introductions, Axcan's questions from the September 5, 2006 background package were addressed. The format of these minutes provides for Axcan's questions in regular typeface, followed by FDA's responses in **bolded** print, followed by the October 4, 2006 teleconference discussion in ***italic and bolded*** print.

Viokase Meeting Questions

PRECLINICAL:

1. Axcan Scandipharm Inc. would like to confirm that the toxicology information presented in Appendix 1 will be sufficient to support the safety of the inactive ingredients present in VIOKASE® Tablets.

Response:
Yes, it is sufficient.

2. Axcan Scandipharm Inc. would like to confirm that the analysis of the exposure to each excipient in VIOKASE® Tablets presented in Appendix 1, in addition to an update of the literature on pancrelipase since the last approved pancrelipase NDA (i.e., since February 1996), will be sufficient for the preclinical section of the VIOKASE® Tablets NDA.

Response:
Yes, it is sufficient. However, the information you provide should be relevant to Viokase.

BIOPHARMACEUTICS:

3. Does the Agency agree that these studies provide sufficient data to support the necessary human biopharmaceutic studies for the *VIOKASE®* NDA?

Response:
The articles provided are not sufficient to support the application of the proposed drug product because of the following reasons:

Two articles (published in 1977) reported intraduodenal enzyme activities following oral administration of pancreatin. Although the name, Viokase, was mentioned in these

studies, the product studied does not appear to represent the proposed product. It is noted that the strength of the studied product was not specified in the articles and its enzyme activities as indicated by the authors (lipase <4,000 units and trypsin <15,000 units) were much lower than those for either strength of the proposed product. To support the Viokase NDA, it is necessary to generate data using the proposed Viokase tablets.

Please refer to the "Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs" (April, 2006) which provides general guidance on the conduct of *in vivo* bioavailability studies. Considering the recent publication of this Guidance, we are willing to work with you to address the information needed to determine luminal pancreatic enzyme (lipase, protease, and amylase) levels post dosing in patients with pancreatic enzyme insufficiency.

Additional Discussion:
Axcan acknowledges that there are limited in vivo bioavailability data with Viokase available in the literature, and Axcan is planning on conducting a bioavailability study. Axcan will submit a full protocol of the proposed study(ies) as an amendment to the IND.

CLINICAL SAFETY/EFFICACY

4. Axcan Scandipharm Inc. would like to confirm that this supporting data, along with positive efficacy data from proposed Study-V1016CP06-01, will be sufficient to address the requirement for dose response data referred to in the Agency's Final Guidance entitled, Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs.

Response:
A determination as to the adequacy of the entire clinical development program for Viokase (including this proposed clinical study, the completed study STEA-VK00-US01, and the published articles) cannot be made, as the results of the proposed study are not yet known, and the ability of these results to support a claim of clinical benefit cannot be determined at this time.

The results for the completed study STEA-VK00-US01, as described in your briefing packet, show that the primary endpoint was not met, and that a clinically meaningful benefit of Viokase treatment in reducing pancreatic steatorrhea in patients with chronic pancreatitis was not demonstrated. The supporting evidence provided in the published journal articles is insufficient on its own to address the requirements in the Guidance document without a beneficial effect of treatment on clinical outcomes having been demonstrated in a separate Axcan Pharma-sponsored clinical trial. Thus, the results of the proposed study (V1016CP06-01) must be able to show a substantial evidence of clinical benefit for the submission to be considered adequate.

5. Axcan Scandipharm Inc. would like to confirm whether a full study report will be required for Protocol STEA-VK00-US01 when filing the VIOKASE NDA or whether an abbreviated report

detailing a full safety analysis, but only a partial efficacy analysis (i.e., the dose response trend), will be sufficient.

Response:
A final study report, including full reports of the safety and efficacy results, with all appropriate analyses, and with the supporting electronic datasets for these data, is required at the time of filing of the NDA submission (under 21 CFR 314.50).

6. Is the use of home stool collection for fecal fat tests acceptable in a clinical trial carried out to support the efficacy of a pancrelipase product?

Response:
The quality of the data generated for a 72-hour fecal fat stool endpoint would benefit from a rigorous collection methodology. For these data to be meaningful, a standardized diet with complete measurements of fat intake, as well as measurements of fecal fat excretion, must be performed. We recommend that these types of studies be performed in an inpatient, controlled setting to ensure the consistency of the study procedures, adherence of the subjects with all protocol requirements, and the reliability of the results. However, we will consider an alternative proposal that utilizes outpatient collection of stool that also ensures adequate data quality.

Additional Discussion:
Axcan will submit the proposed protocol, with a detailed description of the collection procedures, in writing as an amendment to the IND.

7. Is the use of a (b) (4) to measure lipid absorption acceptable in a clinical trial carried out to support the efficacy of a pancrelipase product?

Response:
We are unable to answer this question without more detailed information on the role of the (b) (4) in the proposed study. We are uncertain as to how the (b) (4) will be performed and evaluated, and on whether you are planning on using the (b) (4) as an adjunctive or exploratory endpoint to measure fat absorption or as a stand-alone endpoint for the study.

We do not currently recognize the (b) (4) as a valid measure of clinical efficacy for lipid absorption. If you intend to use this test to establish the clinical efficacy of Viokase, then it will be necessary for you to provide evidence that this test has been validated for this purpose.

We encourage you to discuss (b) (4) issues with CDRH in order to generate data for independent clinical validation of this test. Please use the following site for additional information: http://www.fda.gov/cdrh/oivd/index.html

Additional Discussion:
We encourage you to explore the use and independent validation of the (b) (4) ***with the Center for Devices (CDRH).***

8. Axcan Scandipharm Inc. would like to confirm that the design of the proposed study constitutes an adequate and well-controlled clinical investigation which, in combination with supporting data from completed VIOKASE Study STEA-VK00-US01 and from the literature will be sufficient to support filing of the NDA for VIOKASE 8 and VIOKASE 16 Tablets.

Response:
The overall design of the study as outlined in the protocol synopsis appears to be adequate, with the exception of our concerns regarding outpatient collection of 72-hour fecal fat as outlined in our response to Question 6; however, insufficient details are available for us to fully comment on the design of the proposed study. We ask that you submit a full study protocol to us as soon as possible so that we may provide you with more specific comments on the protocol design, such as on the adequacy of endpoint determination.

As stated above in our response to Question 4, we are unable to make a determination as to the adequacy of the entire clinical development program for Viokase being sufficient to support an NDA for Viokase, as the results of the proposed study are not yet known. A determination of sufficiency of a submission for filing can only be made at the time of the NDA submission, and will be based on the completeness of the submission and our ability to review the information (e.g., format of the submission). Please have full details of the construct and content of your planned NDA submission available for our review at the time of the pre-NDA meeting.

Additional Discussion:
Axcan will submit a proposed protocol to the Division as a Special Protocol Assessment in the near future. Please contact the Regulatory Project Manager if there are any areas that may need clarification.

The concomitant use of proton pump inhibitors (PPIs) (b) (4) ***in the protocol in this patient population is acceptable, provided these agents are used in a standardized, controlled manner.***

9. Axcan Scandipharm Inc. proposes to request a waiver, relative to the required pediatric assessment, and will provide written support demonstrating that VIOKASE Tablets (1) do not represent a meaningful therapeutic benefit over existing enteric coated products for pediatric patients, and (2) are not likely to be used in a substantial number of pediatric patients.

Does the Agency agree that this is an acceptable strategy?

Response:
In the "Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs," it is recommended that because cystic fibrosis is primarily a pediatric disease, and as these products are likely to be used by a pediatric population

in the clinical setting, that both pediatric and adult patients be included in clinical trials conducted in support of the NDA. While a waiver can be requested, a determination as to the granting of this waiver will be made at the time of the NDA submission.

Although pediatric data is not required at the time of the original NDA submission, The Pediatric Research Equity Act (PREA) of 2003 would likely require a pediatric study be performed in the post-approval time period (as a post-marketing commitment) as a requirement of approval. Therefore, we recommend that you plan on designing and implementing clinical study(ies) that include pediatric patients over a broad range of ages, early in your development program. The development of a formulation suitable for administration to pediatric patients is also recommended.

Additional Discussion:
We recommend that you request a deferral for the pediatric studies rather than a waiver of the PREA requirements. A decision on the deferral (or waiver) of pediatric studies will be considered at the time of submission.

CHEMISTRY

10. Does the Agency agree that re-labeling the units of lipase from 8,000 to 10,440 and from 16,000 to 20,880, for VIOKASE® 8 and 16 respectively, is an acceptable strategy?

Response:
Yes, please be aware that the labeled potency must be maintained throughout the dating period.

11. Based on the data and analysis presented, does the Agency agree that a manufacturing overage of lipase activity of (b) (4), is acceptable?

Response:
Yes.

12. Does the Agency agree that the proposed stability data will be sufficient for filing the VIOKASE® NDA?

Response:
This question cannot be answered since no stability data were provided in the submission. Stability studies performed in accordance with ICH Q1A, Q1E, Q5C will be suitable for filing in NDA.

Additional Discussion:
Axcan is developing the impurity testing method and plans to file it with stability data. Please provide enzyme assay methods and impurity test methods at the time of filing.

13. If the data show sufficient product stability, will the data set be sufficient to support 24 months of shelf life at controlled room temperature?

Response:
This question cannot be answered since no stability data were provided in the submission. Twenty four months of stability data and 3 months of accelerated stability data performed in accordance with ICH Q1A, Q1E, Q5C will be sufficient to support the 24 months expiry.

REGULATORY

14. Is there an Agency established procedure or strategy for removal of products, which do not have approved NDAs by April 28, 2008, from the market?

Response:
Although there are general established procedures for product removal, we are actively working with all applicants to resolve the technical and clinical issues with the pancreatic enzyme products (PEPs), to ensure that there will not be a shortage in the US market. Any concerns regarding your PEP development plan should be submitted in a letter to your IND. We look forward to working with you, and please do not hesitate to contact us with any questions or concerns.

Additional Discussion:
Axcan plans to submit an NDA for Viokase Tablets and does not plan to file for the powder formulation. We look forward to working with you on your NDA and encourage you to consider submitting an application for the powder formulation.

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/s/

Anne Pariser
10/23/2006 12:37:58 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,716

Ms. Irma Monaco
Manager, US Regulatory Services
CanReg Inc.
7 Innovation Drive
Dundas, Ontario, Canada L9H 7P3

Dear Ms. Monaco:

Please refer to the teleconference between representatives of your firm and FDA on August 29, 2002. The purpose of the teleconference was to discuss medication errors that occurred with the use of Viokase. We acknowledge receipt of your minutes sent via email to Dr. Hye-Joo Kim on September 4, 2002.

The official minutes of the teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Dr. Kim at (301) 827-3242.

Sincerely,

{See appended electronic signature page}

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety (HFD-420)
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECON

DATE: August 29,2002

Re: IND 60-716
Viokase 8 and Viokase 16

BETWEEN: Axcan Pharma Inc. and FDA, Office of Drug Safety, Division of Medication Errors and Technical Support

Representing Axcan Pharma Inc.:

Dr. Fancois Martin, Vice President, Scientific Affairs
Dr. Patrick Colin, Director, Clinical Research
Patricia Anderson, Executive Director of Regulatory Operations, CanReg Inc. (Regulatory Consultant for Axcan)
Irma Monaco, Manager, US Regulatory Services, CanReg Inc. (Regulatory Consultant for Axcan)

Phone: 1-905-689-3980

Representing FDA/DMETS:

Jerry Phillips, R.Ph., Associate Director, Office of Drug Safety, HFD-420
Carol Holquist, R.Ph, Deputy Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
Hye-Joo Kim, Pharm.D., Safety Evaluator, DMETS, HFD-420

SUBJECT: Discussion of medication error report concerning confusion with the proprietary name, Viokase 8 and the inadvertent administration of Viokase powder through an IV line.

DISCUSSION:

DMETS briefly provided an overview of the trade name review process, which DMETS took over in 1999. This process looks for look-alike and sound-alike names when reviewing a proposed name, as well as misleading and promotional issues. The proprietary name Viokase was not reviewed by DMETS, because the product is a pre-38 drug. If Viokase 8 and 16 were subjected to DMETS trade name review process, they would have been rejected, because in general, DMETS discourages the use of numbers as a part of the proprietary name. DMETS received a potential medication error report concerning the numerical suffixes 8. In this report, the numerical suffix "8" was misrepresented as a "number of tablets" to be taken.

IND 60,716
Tcon Minutes
August 29, 2002

The sponsor stated that their competitor's product, Creon, has numerical suffixes as well: Creon 5, Creon 10, and Creon 15 (Solvay). Additionally Axcan manufactures the products Ultrase MT 12, 18, and 20.

DMETS did not feel that Ultrase MT products would be confused, since "MT" is not a medical terminology. However, DMETS will review the numerical suffixes used with the proprietary name Creon. DMETS emphasized that a trade name change was not advocated, however suggested that the Viokase products be identified as Viokase 8,000 and Viokase 16,000 rather than Viokase 8 and Viokase 16.

The sponsor responded that DMETS's suggestions will be considered and will consult with the company's marketing personnel. The sponsor also inquired as to whether or not the current supply of labels for Viokase 8 and Viokase 16 would have to be destroyed. The sponsor was not aware of how many months of Viokase 8 and 16 are currently available. This will be verified. DMETS agreed with the sponsor that the current labels of Viokase 8 and 16 do not have to be destroyed.

The sponsor will issue letters to health care providers notifying them that Viokase 8 and 16 will be renamed to Viokase 8,000 and Viokase 16,000. The sponsor asked the division if there was more than one report of this confusion, and was concerned whether or not the error is only theoretical. DMETS indicated that it is aware of only one report of medication error involving Viokase 8, but emphasized that other products with the numerical modifiers have been confused. For example, when Tylenol No. 3 was first approved, patients were instructed to take "three tablets" of Tylenol No.3. Another example involves Percocet 5; the sponsor deleted the numerical suffix "5" after it was confused with a "number of tablets" to be taken.

The sponsor is willing to collaborate with DMETS and agrees with DMETS that the current supply of Viokase does not have to be destroyed. The sponsor also agrees to follow up this teleconference with a letter to DMETS. The sponsor asked again if Creon would be under the same investigation. DMETS agreed to look into Creon and its numerical suffixes.

IND 60,716
Tcon Minutes
August 29, 2002

Action Items:

1. DMETS will investigate the proprietary names of other pancrelipase containing products, including Creon, and their use of numerical suffixes.
2. The sponsor will revise the proprietary name to Viokase 8,000 and Viokase 16,000 at the time of next printing.
3. The sponsor will notify the health care providers of the new name by sending "Dear Health Care Provider" letters.
4. The sponsor will send a copy of container label and carton labeling of Viokase (b) (4).
5. The sponsor will follow up this meeting with a letter to DMETS summarizing the above recommendations.

Minutes Prepared By:

Hye-Joo Kim, Pharm.D.
Safety Evaluator
HFD-420

Concur:

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
HFD-420

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/s/

Jerry Phillips
9/6/02 07:06:39 AM