

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-222Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Deferred requirement for development of an age appropriate formulation for Ultresa (pancrelipase) Delayed-Release Capsules: Develop an age appropriate formulation to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement for an age appropriate formulation by March 31, 2014

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: <u>Supplement Submission Date</u>	<u>03/31/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The low weight pediatric patients are a small subpopulation affected.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In order to give the proper dose of PEPs to low weight pediatric patients, a formulation needs to be developed which can dose them correctly without using partial doses.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor agrees to develop a formulation for Ultresa which will allow dosing to the youngest, lowest weight pediatric patients who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Development of a specific formulation for Ultresa which will allow lipase doses of 2,000 to 4,000 lipase units (per 120 mL of formula or per breast-feeding) to be administered to pediatric patients.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Development of a specific formulation for Ultresa which will allow lipase doses of 2,000 to 4,000 lipase units (per 120 mL of formula or per breast-feeding) to be administered to pediatric patients.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: A 10 year, observational study to prospectively evaluate the incidence of fibrosing colonopathy in patients with cystic fibrosis treated with Ultresa (pancrelipase) Delayed-Release Capsules in the U.S. and to assess potential risk factors for the event.

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/2012
Study/Trial Completion: 07/2022
Final Report Submission: 12/2022
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The safety of PEPS is well established based on ample information available in the medical literature. Fibrosing colonopathy has been reported following treatment with different pancreatic enzyme products. Fibrosing colonopathy is a rare, serious adverse reaction initially described in association with high-dose pancreatic enzyme use, usually over a prolonged period of time and most commonly reported in pediatric patients with cystic fibrosis.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In the drug class of Pancrelipase, there were cases of fibrosing colonopathy identified. Fibrosing colonopathy is a serious, rare condition that has been described in association with high-dose pancreatic enzyme use.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Ten year observational safety study to evaluate the incidence of a specific serious and severe adverse event (fibrosing colonopathy).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Ten year observational study to evaluate the incidence of a specific serious and severe adverse event (fibrosing colonopathy).
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Ultresa (pancrelipase) Delayed-Release Capsules compared with an appropriate control group.

PMR/PMC Schedule Milestones: Final Protocol Submission: 09//2012
Study/Trial Completion: 06/2015
Final Report Submission: 02/2016
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The safety of PEPS is well established based on ample information available in the medical literature; however, since all PEPs contain porcine viruses, there is a theoretical risk of transmission of selected porcine viruses to patients taking Ultresa.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Since all PEPs contain porcine viruses, there is a theoretical risk of transmission of selected porcine viruses to patients taking Ultresa.

There is a theoretical risk of transmission of selected porcine viruses to patients taking Ultresa, thus porcine viruses can potentially infect patients taking Ultresa. Infection with these viruses can potentially lead to illness.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Ultrasa compared with an appropriate control group.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Observational study to estimate the prevalence of antibody seropositivity to selected porcine viruses in patients taking Ultresa.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 22222 ULTRESA

PMR/PMC Description: To provide an assessment of the viral inactivation capability of the cleaning agents currently used in the facility.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 09/01/2012
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The sponsor needs to evaluate the ability of the cleaning agents used in the facility to inactivate viral agents. This assessment will take time to design and execute. Since the sponsor has assays in place that will be used to monitor for the presence of viral agents, the absence of a formal evaluation of the inactivation capability of the cleaning agents does not preclude approval of the application. The company currently uses detergents, (b) (4) to clean equipment. These agents are known to inactivate viral and microbial agents, and their use thus provide some assurance that viral agents will be inactivated.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

During the inspection of the drug substance manufacturing facility, the inspectors noted that the manufacturer cleaning procedures were not robust, which resulted in a citation. The manufacturer committed to improve the cleaning procedures, but did not provide an evaluation of the viruses-inactivation capability of the cleaning agents. Although the cleaning agents used by the sponsor have the potential to inactivate viral and microbial agents, a formal assessment is necessary to address this issue.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should assess the capability of the cleaning agents to inactivate viruses. This assessment can be conducted as a laboratory study or as a formal risk assessment that takes into consideration the chemical characteristic of the agent and the biology of the viral agents.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 22222 ULTRESA

PMR/PMC Description: To develop and validate an infectivity assay for PCV1.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>03/01/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The (b) (4) drug substance and all PEP products have been shown to contain PCV1 genome equivalents indicative of the presence of this virus. It is not clear how genome equivalents translate to infectious particles but live virus presents a theoretical risk to patient safety. Although the virus has not been reported to cause human disease (and is probably present in porcine products that are ingested by humans), it is well documented that in extremely rare cases viruses can change species tropism leading to an infectious disease. This risk can be further mitigated by ensuring drug product has minimal live virus present in each dose consistent with manufacturing process history and our understanding of the virus's biology. DTP has established a policy that a PCV 1 infectious assay should be developed and used for lot release for all PEP products as recommended in the advisory committee meeting on viral issues for PEP products. The risk is low and these assays take time to develop so we believe it is appropriate to address this issue as a PMC

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. PCV1 is a non enveloped virus that is likely to be present in these products yet the PEP manufacturing process demonstrates no capability to inactivate non enveloped viruses. Therefore (b) (4) should monitor for the virus and reject lots that contain unusual levels of the infectious agent and present a risk to patient safety.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<p>(b) (4) should develop a cell-based assay to monitor for infectious PCV1</p>

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 22222 ULTRESA

PMR/PMC Description: To establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 03/01/2013
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The ^{(b) (4)} drug substance and all PEP products have been shown to contain PPV and PCV2 virus. In order to establish appropriate and meaningful specifications, the sponsor will need to manufacture several lots of drug substance to fully understand the capability of the process to reduce the load of these two viruses. These viruses are not known to infect humans but there is a theoretical risk that mutations or genetic recombination events could change species specificity so control of these viruses is warranted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. PCV2 and PPV are non enveloped virus that are present in these products. PEP manufacturing process demonstrates little or no capability to inactivate non enveloped viruses. Therefore ^{(b) (4)} should monitor for the viruses and reject lots that do not meet specifications and contain unusual levels of the infectious agent and present a risk to patient safety. These virus are not associate with human infection and are likely present in porcine meat products consumed by humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement assays to monitor for infectious PPV and PCV2
--

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 22222 ULTRESA

PMR/PMC Description: To perform additional monitoring of viral load entering the manufacturing process. The control program will include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 05/13/2013
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current PCR assays sensitivity is sub optimal since the limit of detection is only (b) (4) genome equivalents per gram of drug substance. This level is beyond the capacity of the manufacturing process to inactivate some viruses. While this is an important issue, availability of these products is critical and the risk to product quality has already been greatly reduced as compared to current marketed product. Again the risk is theoretical in that no infectious diseases are known to have been transmitted by the unapproved PEPs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The (b) (4) process demonstrates no capability to inactivate non enveloped viruses. Therefore, the sponsor should monitor for the virus with sensitive assays and reject lots that contain the infectious agents beyond the processes capacity to inactivate these viruses.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should select viruses that have the potential to infect the source material and develop appropriate quantitative, PCR based assays to assess the viral load in incoming materials.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 22222 ULTRESA

PMR/PMC Description: To 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 will be submitted to the Agency.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 04/15/2013
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current PCR assays sensitivity is sub optimal since the limit of detection is only (b) (4) genome equivalents per gram of drug substance. The starting material for one lot is (b) (4) kg. Therefore, with the current assays, the sensitivity would be (b) (4) genome equivalent per lot. While this is an important issue, availability of these products is critical and the risk to product quality has already been greatly reduced as compared to current marketed product. The risk is theoretical in that no infectious diseases are known to have been transmitted by the unapproved PEPs.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The (b) (4) process demonstrates no capability to inactivate non enveloped viruses. Therefore, (b) (4) should monitor for the virus with sensitive assays and reject lots that contain the infectious agents. All of the virus in this PMC have the potential to cause human infections. This was a PMC for the Creon, Zenpep, and Pancrease products.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should improve the assays currently in use to increase sensitivity and propose new acceptance criteria based on the improved assays.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 22222 ULTRESA

PMR/PMC Description: To assess the risk to product quality associated with hokovirus, and to submit a control strategy for mitigating the risk to product quality.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 06/01/2012
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Hokovirus has only recently been identified in porcine material in south east Asia but has never been detected in the pig population on the US or Europe. The virus can infect humans, but has never be detected in humans in the US or Europe. Since the source material for pancrelipase is (b) (4), the risk to patients is low. However, the sponsor should work proactively and implement a surveillance program that routinely evaluates the risk from this virus in case it spreads to the (b) (4) pig population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. Hokovirus has only recently been identified in swine and therefore little information is available. The sponsor’s surveillance program should include continual monitoring of the literature to ensure that quality systems could be updated to control for this viurus (e.g. herd surveillance programs) and other emerging new viral agents that infect humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement a surveillance program to monitor for the emergence of hokovirus in the pig herds.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 22222 ULTRESA

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

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 03/15/2013
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Ebola virus has only recently been identified in porcine material in south east Asia but has never been detected in the pig population on the US or Europe. The virus can infect humans, but has never been detected in humans in the US or Europe. Since the source material for pancrelipase is (b) (4) the risk to patients is low. Additionally, Ebola is an enveloped virus and thus can be inactivated by the (b) (4) (b) (4) step in the process, further reducing the risk to patients. Regardless, the sponsor should implement a surveillance program that routinely evaluates the risk from this virus to emerge in the (b) (4) swine herds.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

ICH Q5A and the 2006 FDA PEP guidance have indicated that the pancrelipase manufacturing process should be robust to ensure removal of viral adventitious agents. The process does have the capability to inactivate enveloped viruses and thus should inactivate the Ebola virus. Ebola virus has only recently been identified in swine and therefore little information is available. The sponsor’s surveillance program should include continual monitoring of the literature to ensure that quality systems could be updated to control for this virus (e.g. herd surveillance programs) and other emerging new viral agents that infect humans.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor should implement a surveillance program to monitor for the emergence of Ebola virus in pig herds.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

MF #/Product Name: 22222 ULTRESA

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 06/01/2012
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4) drums are used for drug substance intermediate storage, for (b) (4). Although (b) (4) is a relatively inert material, metal ions could potentially leak into the drug substance. Metal ions have the potential to chemically react with the proteins in the pancrelipase drug substance. Therefore, although the risk to product quality is low, a study to evaluate the potential of metal ions to leak from the (b) (4) containers is warranted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to determine the extent of metal ions leaching into pancrelipase drug substance and to perform a risk assessment and if necessary, develop a control strategy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The type of study that is warranted is inductively coupled plasma mass spectrometry (ICP-MS) as a sensitive way to measure metal ions in pancrelipase drug substance under leachable conditions.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

MF #/Product Name: 22222 ULTRESA

PMR/PMC Description: ^{(b) (4)} commits to revise release specifications after 30 lots of 1208 and 1286 drug substance have been manufactured.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>05/15/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current release specifications for drug substance are adequate to ensure product quality but more robust programs should be developed to provide a better assurance of product quality. While the lots produced so far have shown acceptable results that are in-line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. To established process capability and reduce the risk to product quality, a larger number of product lots are necessary which could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assays used for release testing of drug substance are adequate for approval. Proposed acceptance criteria for drug substance release specifications are wide and should be based on manufacturing history and clinical experience, once the sponsor gains sufficient information through manufacturing of multiple lots.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<p>(b) (4) should re-evaluate the release specifications for drug substance and tighten acceptance criteria based on results of lots manufactured with the clinical and commercial processes.</p>

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 22222 ULTRESA

PMR/PMC Description: Revise release and stability specifications after 30 lots of drug product have been manufactured.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>July 2014</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current release and stability specifications for drug product are adequate to ensure product quality and stability but more robust programs should be developed to provide a better assurance of product quality. While the lots produced so far have shown acceptable results that are in-line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. To establish process capability and reduce the risk to product quality, a larger number of product lots are necessary which could not be accomplished during the review cycle.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Assays used for release and stability testing of drug product are adequate for approval. Proposed acceptance criteria for drug product release and stability specifications are wide and should be based on manufacturing history and clinical experience, once the sponsor gains sufficient information through manufacturing of multiple lots.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Aptalis should re-evaluate the release and stability specifications for drug product and tighten acceptance criteria based on results of lots manufactured with the clinical and commercial processes.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 22222 ULTRESA

PMR/PMC Description: Include accelerated and/or stressed stability conditions in the annual stability protocol.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>June 2012</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The current annual stability protocol for drug product provides for one lot of drug product to be entered on stability at the approved storage conditions. However, the approved storage conditions are not permissive for significant product degradation and therefore do not provide an adequate level of sensitivity to confirm that routine minor changes in operations or equipment do not have an impact on product quality. Because stress stability studies can detect subtle differences in product quality that may not be readily detectable by release tests or the proposed stability protocol, FDA requested the addition of a stress stability protocol that would be capable of detecting these differences in a timely manner. Considering that the stability protocol will be implemented during the next year and the fact the new protocol will be approved in a post approval supplement before implementation, there is no approval issue.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Release and real time stability testing confirm product quality but are less sensitive to detect minor changes that may occur from changes in manufacturing over time. Performing stress stability studies under accelerated and/or stressed conditions provides a bigger window in which to detect changes to product quality.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

No study is required to be agreed upon. A stability protocol will be updated to include stressing one lot of drug product under accelerated and/or stressed conditions.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Include a protocol to stress one lot of drug product per year.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: NDA 22222 ULTRESA

PMR/PMC Description: To 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 current manufacturing experience. Final report submission by:

PMR/PMC Schedule Milestones: Final Protocol Submission: June, 2012
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The stability data provided supports the drug substance and drug product dating periods and current cumulative data for drug product lots that will be marketed but does not include drug product produced with drug substance at the end of its expiry period. The concern is only for material that in the future could exceed current cumulative storage times for drug substance and drug product. Therefore to control this risk the applicant should propose a protocol that places on stability lots of drug product manufactured with drug substance aged past what the manufacturer experience has been.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor has used drug substance of various ages and established a stability profile and expiry for the drug product. However, the sponsor may receive drug substance close to its own expiry date and there is little information on what the cumulative stability of the drug substance might be. For protein products extrapolation of existing stability data is not appropriate and therefore real time, real condition studies should be performed. The goal of this protocol is to confirm that product manufactured with drug substance aged past what the manufacturer experience has been, maintains an adequate stability profile throughout its shelf life.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A stability study will be required each time the manufacturer exceeds the cumulative storage time of the drug substance/drug product. Data supporting the cumulative time will be submitted in the annual report as is typical for these types of studies using an agreed to protocol.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: NDA 022222 Ultresa (pancrelipase) Delayed-Release Capsules

PMR/PMC Description: Perform *in vitro* studies to determine the feasibility of administering the contents of Ultresa (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 03/2013
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Patients that require PEPs to be administered via gastrostomy tubes are a small subpopulation affected.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

PEPs, including Ultresa, are not approved for administration via gastrostomy tubes. However, a small number of patients may require PEPs to be given through this route. In order to evaluate the feasibility of administering Ultresa via gastrostomy tubes, the Applicant has committed to conducting *in vitro* testing.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant will conduct *in vitro* testing to evaluate the feasibility of administering Ultresa via gastrostomy tubes.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
The Applicant will conduct *in vitro* testing to evaluate the feasibility of administering Ultresa via gastrostomy tubes.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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
02/29/2012

ANIL K RAJPAL
02/29/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: February 22, 2012

From: Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Marjorie Dannis, MD, Clinical Reviewer
Anil Rajpal, MD, Clinical Team Leader
Division of Gastroenterology and Inborn Errors Products
(DGIEP)

Re: PREA PMR Language for Approval Letter

Sponsor: Aptalis Pharma, Inc.

Drug: Ultresa (pancrelipase)

NDA: 22-222

Submission Date: September 1, 2012

Sequence #: 076 ([\\CDSESUB1\EVSPROD\NDA022222\022222.enx](#))

Indication (proposed): treatment of exocrine pancreatic insufficiency due to cystic fibrosis (CF) or other conditions

Proposed Dose: To be titrated; 3-5 doses per day with meals and snacks

Proposed Pediatric Dose: Per CFF guidelines (See Appendix I)

Dosage form: delayed-release capsules

Dosage strengths: 13,800 USP, 20,700 USP and 23,000 USP units of lipase

Route of Administration: oral

Consult Question: DGIEP requests PMHS assistance with the language/text for the PREA section of the approval letter and associated PREA PMR.

Materials Reviewed:

- Ultresa proposed labeling (“Sponsor Version 7-14-09 with track changes from FDA version 4.27.10.doc”)
- Approved labeling and approval letters Creon[®] (NDA 20-725), Zenpep[®] (NDA 22-210) and Pancreaze[®] (22-523).
- PMHS Ultresa Consult (May 3, 2010)

Brief Regulatory Background:

Pancreatic Enzyme Products (PEPs):

Historically, PEPs were marketed without NDAs; however, the wide range of enzyme activity, the variety of dosage forms, and the uneven quality of the enteric coatings among PEPs resulted in underdosing and overdosing with pancreatic extracts; hence, the FDA determined that evaluation of the manufacturing of the formulations and preclearance of PEPs are necessary. In April 2004, the FDA announced that all orally administered PEPs are new drugs that will be approved for prescription use (69 FR 23410), and an April 2010 enforcement discretion of unapproved PEPs was established.

The Agency has determined that for enteric coated PEP products, the clinical experience and body of literature supporting PEP product use in pediatric patients with exocrine insufficiency due to cystic fibrosis (CF) are adequate to support labeling for pediatric patients of all ages when accompanied by data demonstrating short-term safety and efficacy in adult patients. Dosing recommendations are based on guidelines developed by the Cystic Fibrosis Foundation (See Appendix I: PEP Dosing in Pediatric Patients). In addition, the Agency has determined that administering a portion of fixed-dose capsule’s content is unacceptable. At the time of original NDA approval for Creon[®] (NDA 20-725, approved April 2009), Zenpep[®] (NDA 22-210, approved August 2009) and Pancreaze[®] (NDA 22-523, approved April 2010), the smallest capsule concentrations were 6,000, 5,000 and 4200 lipase units, respectively. Although these capsule concentrations were not considered age-appropriate formulations for infants for which the recommended dosage is 2000-4000 lipase units per 120 mL of formula or breast feeding, given that a formulation was not available to dose patients less than one year, dosing could be provided by administering half a capsule’s content (versus a smaller fraction of the capsule’s content) and that the current practice for providing appropriate dosing for the youngest pediatric patients was administering a portion of a capsule’s content, dosing recommendations were provided for all ages of pediatric patients for all three products. PREA PMRs were established to develop an age-appropriate formulation for patients 1 month to 1 year.

Reviewer Comment:

In June 2011, 3000 lipase unit capsules of Creon[®] and Zenpep[®] were approved. Given that both Creon[®] and Zenpep[®] have an age-appropriate formulation adequate for dosing all pediatric patients, including infants, if subsequent PEP products are approved, dosing should only be provided for those patients for which an age-appropriate formulation is available.

Ultresa:

The NDA for Ultresa (22-222), an enteric coated PEP, was initially submitted in August 2007. The product is in its 5th review cycle and an approval action is anticipated March 1, 2012.

The PREA requirements for the application were discussed by the Pediatric Review Committee (PeRC) in March 2010, and the PeRC agreed with a partial waiver in patients birth to one month (too few patients to study as the disease is not diagnosed) and a deferral in patients greater than one month to 12 months for the development of an age-appropriate formulation. The PeRC agreed that the PREA PMR for patients 1 year through 16 years was fulfilled based on the short-term safety and efficacy data submitted with the NDA, and the clinical experience and body of literature supporting the use of enteric coated PEP products in pediatric patients with CF.

Reviewer Comment:

The March 2010 PeRC discussions and recommendations for Ultresa, specifically the age group for which an age-appropriate formulation was deferred and the age group for which PREA was considered fulfilled, were consistent with the established PREA requirements for Creon[®], Zenpep[®] and Pancreaze[®]. However, the Agency has determined that unlike these PEP products, the proposed concentrations of the Ultresa capsules are not only inadequate for dosing patients less than 1 year, but also for dosing the youngest, lightest pediatric patients 1 year and older (more below).

Ultresa Dosing in Pediatric Patients:

The smallest capsule concentration of Ultresa is 13,800 lipase units. The Agency has determined that the formulations of Ultresa are not adequate to accommodate the doses recommended for infants up to age 12 months, i.e. 2000-4000 lipase units per feeding, as this would require administering a small fraction of a capsule. In addition, the Agency has determined that the appropriate meal dose for patients older than 12 months and less than 4 years, i.e. 1000 lipase units per kg. per meal, and the appropriate meal dose for patients 4 years and older, 500 lipase units per kg per meal, could only be provided for patients greater than 1 year and less than 4 years weighing 14 kg or more (starting meal dose 14,000 lipase units) and for patients greater than 4 years weighing 28 kg or more (starting meal dose 14,000 lipase units).

Hence, the Agency has determined that although a general indication for Ultresa will be granted, dosing recommendations will only be provided for patients older than 12 months and less than 4 years and weighing 14 kg or more, and for patients 4 years and older and weighing 28 kg or more. In addition, labeling will reflect the limitations in dosing for

pediatric patients and state that attempting to divide a capsule's content into small fractions is not recommended (See Appendix II: Dosage and Administration Section of Proposed Labeling).

Reviewer Comment:

Given that an age-appropriate formulation not only is needed for patients 1 month to 12 months, but also is needed for patients older than 12 months and less than 4 years (weighing less than 14 kg), and for patients 4 years and older (weighing less than 28 kg), PREA cannot be considered fulfilled in these pediatric patients.

Conclusions and Recommendations:

Because Ultresa does not have an age appropriate formulation for pediatric patients one month to one year, patients greater than 1 year to 4 years (weighing less than 14 kg), and patients 4 to 17 years (weighing less than 28 kg), an age-appropriate formulation is required and a deferral for the development of an age-appropriate formulation is appropriate for these patients. Because an age-appropriate formulation is not available for patients 1 year to 4 years (weighing less than 14 kg), and patients 4 to 17 years (weighing less than 28 kg), unlike the other recently approved PEP products, i.e. Creon[®], Zenpep[®] and Pancreaze[®], the PREA PMR cannot be considered fulfilled in patients one to 17 years. The PREA PMR can be considered fulfilled in pediatric patients greater than 1 year to less than 4 years (weighing 14 kg or more) and in patients 4 to 17 years (weighing 28 kg or more).

The Approval Letter must reflect the appropriate population for the deferral and for which the PREA requirement is fulfilled. Although the Division could consider choosing a specific age for which PREA is fulfilled and for which an age-appropriate formulation is required, given that patients with CF weigh less than otherwise healthy children,^{3,4} and therefore choosing an age for which the Ultresa formulations are adequate to support dosing may be subjective, PMHS recommends using language based on age and weight (See Appendix III: PMHS Suggested Language for Ultresa Approval Letter). In addition, the Approval Letter must document the day, month and year when the supplement for the age-appropriate formulation is due.

Given that the change in the population for the deferral for an age-appropriate formulation and the population for which PREA is considered fulfilled does not involve a change in clinical protocols or clinical study requirements, review by the Pediatric Review Committee is not necessary.

APPENDIX I: PEP Dosing in Pediatric Patients (Cystic Fibrosis Foundation Guidelines^{1,2})

Standard meal dosing

- Infants - 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding
- Children < 4 years old – starting dose of 1000 lipase units/kg per meal
- Children > 4 years old – starting dose of 500 lipase units/kg per meal (older children tend to ingest less fat per kilogram of body weight)

Snack dosing - ½ the standard dosing

Total daily dose - should reflect approximately three meals and two or three snacks per day². In addition, as mentioned above, to avoid fibrosing colonopathy, enzyme doses should not exceed 2500 lipase units/kg per meal, 10,000 lipase units/kg per day and 4000 lipase units/gram fat per day¹.

APPENDIX II: Dosage and Administration Section of Proposed Labeling

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

TRADENAME is not interchangeable with other pancrelipase products.

TRADENAME is orally administered. Therapy should be initiated at the lowest recommended dose and gradually increased. The dosage of TRADENAME should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet (see Limitations on Dosing below).

(b) (4)

Children Older than 12 Months and Younger than 4 Years and weight 14 kg or greater

Children older than 12 months and younger than 4 years, weighing under 14 kg should not be dosed with this product because capsule dosage strengths cannot adequately provide dosing for these children.

Enzyme dosing should begin with 1,000 lipase units/kg of body weight per meal for children less than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Children 4 Years and Older and Adults and weight 28 kg or greater

Children 4 years and older, weighing under 28 kg should not be dosed with this product because capsule dosage strengths cannot adequately provide dosing for these children.

Enzyme dosing should begin with 500 lipase units/kg of body weight per meal for those older than age 4 years to a maximum of 2,500 lipase units/kg of body weight per meal (or less than or equal to 10,000 lipase units/kg of body weight per day), or less than 4,000 lipase units/g fat ingested per day.

Usually, half of the prescribed TRADENAME dose for an individualized full meal should be given with each snack. The total daily dosage should reflect approximately three meals plus two or three snacks per day.

Enzyme doses expressed as lipase units/kg of body weight per meal should be decreased in older patients because they weigh more but tend to ingest less fat per kilogram of body weight.

Limitations on Dosing: Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines.^{1,2,3}

If symptoms and signs of steatorrhea persist, the dosage may be increased by a healthcare professional. Patients should be instructed not to increase the dosage on their own. There is great inter-individual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. If doses are to exceed 2,500 lipase units/kg of body weight per meal, further investigation is warranted. Doses greater than 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day) should be used with caution and only if they are documented to be effective by 3-day fecal fat measures that indicate a significantly improved coefficient of fat absorption. Doses greater than 6,000 lipase units/kg of body weight per meal have been associated with colonic stricture, indicative of fibrosing colonopathy, in children less than 12 years of age [see Warnings and Precautions (5.1)]. Patients currently receiving higher doses than 6,000 lipase units/kg of body weight per meal should be examined and the dosage either immediately decreased or titrated downward to a lower range.

Use of TRADENAME in children is limited by the available capsule dosage strengths and their ability to provide the recommended dose based on age and weight. Attempting to divide the capsule contents in small fractions to deliver small doses of lipase is not recommended.

APPENDIX III: Suggested Language for Ultresa Approval Letter

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 are waiving the pediatric study requirement for ages birth to 1 month because necessary studies are impossible or highly impracticable. This is because patients are not usually diagnosed before the age of 1 month, so there would not be enough eligible patients in this age range to study.

We note that you have fulfilled the pediatric study requirement for patients greater than 1 year to less than 4 years (weighing 14 kg or more) and patients 4 to 17 years (weighing 28 kg or more) for this application.

The pediatric requirement for patients 1 month to 1 year, patients greater than 1 year to less than 4 years (weighing less than 14 kg), and patients ages 4 to 17 years (weighing less than 28 kg) is not fulfilled due to the lack of an age appropriate formulation.

We are deferring submission of an age appropriate formulation for patients one month to one year, patients greater than 1 year to 4 years (weighing less than 14 kg), and patients 4 to 17 years (weighing less than 28 kg). The status must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This requirement is listed below.

1629-1. Deferred requirement for development of an age appropriate formulation for Ultresa (pancrelipase) Delayed-Release Capsules to allow for dosing to the youngest, lowest weight pediatric patients, including infants less than 12 months of age who will be administered 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Submit a supplement for an age appropriate formulation by March 31, 2014. Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "Required Pediatric Assessments".

REFERENCES

1. Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. *Journal of Pediatric Gastroenterology and Nutrition*. 2002;35:246–259.
2. Borowitz D, Grand RF, Durie PR and the Consensus Committee. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Peds*. 1995;127:681-84.
3. Lai H, Kosorok MR, Sondel SA, et al. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: Evaluation of various criteria used to identify malnutrition. *J Pediatr*. 1998;132:478-85.
4. Powers SW, Patton SR, Byars KC, et al. Caloric Intake and Eating Behavior in Infants and Toddlers With Cystic Fibrosis. *Pediatrics* 2002;109:e75.

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

/s/

ELIZABETH L DURMOWICZ
02/27/2012

LISA L MATHIS
02/28/2012



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW-Second Amendment

Application Number: NDA 22-222

Name of Drug: Ultresa™ (Pancrelipase) Capsules

Sponsor: Aptalis Pharma US, Inc. (Originally submitted under
AXCAN PHARMA, US, Inc.)

Material Reviewed: ULTRESA™ (Pancrelipase) Carton and Container Labels

Submission Dates: July 31, 2007, July 31, 2009, March 10, 2010, May 5,
2010, July 1, 2010, August 3, 2010, August 6, 2010,
January 9, 2012

EXECUTIVE SUMMARY

The carton and container labels for ULTRESA™ (Pancrelipase) Delayed-Release Capsules were reviewed and found to comply with the following regulations: 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27 through 2/1/11-4/30/12, USP 34/NF 28. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section. The labels are acceptable.

Background:

ULTRESA™ (Pancrelipase) Delayed-Release Capsules is a New Drug Application (NDA) indicated as a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

Labels Reviewed:

ULTRESA® (Pancrelipase) Container Label
13,800 Lipase Units -100 ct Trade Bottle, 12 ct Professional Sample
20,700 Lipase Units -100 ct Trade Bottle, 12 ct Professional Sample
23,000 Lipase Units -100 ct Trade Bottle, 500 ct Trade Bottle, 12 ct Professional

Sample
ULTRESA[®] (Pancrelipase) Carton Label
13,800 Lipase Units -100 ct Trade Carton, 12 ct Professional Sample
20,700 Lipase Units -100 ct Trade Carton, 12 ct Professional Sample
23,000 Lipase Units -100 ct Trade Carton, 500 ct Trade Carton, 12 ct Professional Sample

Review

I. Container

A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
Manufactured By: Eurand International, (b)(4), using its (b)(4) for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units. **This does not conform to the regulation.**
4. 21 CFR 201.6 Drugs; misleading statements- The proprietary name ULTRESA[™] appears on the label with the established name, pancrelipase. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, Pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA[®]. **This does not conform to the regulation.**
6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”, “Protect from moisture”, “Do

- not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the side of the label. This conforms to the regulation.
 8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the side of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
 9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. Per the United States Pharmacopeia ,12/1/09-5/1/10, USP 32/NF 27 monograph for Pancrelipase Delayed Release Capsules-the product should be labeled **Recommend removing the highlight from the lipase line, enclosing the ingredient listing in a box, and adding a statement to denote the product is dosed based on lipase units.**
 10. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents in terms of numerical count in units on the label, below the proprietary and established name. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count for the 23,000 lipase unit. This conforms to the regulation.
 11. 21 CFR 201.55 Statement of dosage- On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. This conforms to the regulation.
 12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements “Rx Only”, identifying lot number, storage conditions and a reference to the package insert. “Protect from moisture”, "Do not refrigerate” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
 13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This

conforms to the regulation. The statement, “ACCOMPANYING **MEDICATION GUIDE TO BE DISPENSED TO PATIENT**” appears on the side on the label.

Proposed Labels submitted March 30, 2010



1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



II. Carton

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:
Manufactured By: Eurand International, (b) (4), using its (b) (4) for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units. **This does not conform to the regulation.**
4. 21 CFR 201.6 Drugs; misleading statements - The proprietary name, ULTRESA™ appears with the established name, pancrelipase on the carton. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA®. **This does not conform to the regulation.**
6. 21 CFR 201.15 Drugs; prominence of required label statements-

All required statements (“Rx Only”, “Protect from moisture”, “Do not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**

7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date appears on the carton below the lot number. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of the side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. **Recommend removing the highlight from the lipase line, enclosing the ingredient listing in a box and adding a statement to denote the product is dosed based on lipase units.**
10. 21 CFR 201.51 Declaration of net quantity of contents - The label states the net quantity of contents in terms of numerical count in units at the top of the carton. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count configuration is available for the 23,000 lipase units. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage - The label states “For dosage and other information for use, see accompanying product literature. This conforms to the regulation. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for “Rx Only”, an identifying lot number, storage conditions, and a reference to the package insert. “Protect from moisture”, “Do not refrigerate” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation. The following statement appears on the container and carton label, “ACCOMPANYING

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

III. Conclusions

- A. The proposed carton and container labeling are acceptable only upon the following changes:
1. Container and carton (commercial labels)
 - a. Per 21 CFR 201.10, please revise the presentation of the established name and proprietary name. The established name shall have the prominence commensurate with the prominence of the proprietary name or such designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. It shall also be printed in letters that are at least half as large as the letters comprising proprietary name. **Changes made and acceptable.**
 - b. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the bolded statements, “Protect from moisture”, “Avoid excessive heat” and “Do not refrigerate” to the storage conditions listed. **Change made and acceptable.** The statement, “Do not refrigerate” was removed from both the PI, carton and container labels (submission August 3, 2010) for consistency with other Pancrelipase Enzyme Product labels.
 - c. Per the United States Pharmacopeia, 12/1/09-5/10/10, USP 32/NF 27 Monograph for Pancrelipase Delayed Release Capsules, please revise the dosage form from, “capsules” to

“Delayed Release Capsules” on all labeling. **Change made and acceptable.**

- d. Please revise the following statement, “Each capsule of enteric-coated pancrelipase minitabets contains:” to “Each enteric-coated delayed release capsule contains:” for consistency, clarity, and readability with the dosage form, delayed release capsule. **Change made and acceptable.**
 - e. Per 21 CFR 201.5, please remove the color highlight from the Lipase Unit presentation and add a statement that dosing is based on lipase units. **Highlight not removed. Dosing statement added. Acceptable.**
 - f. Please remove “(b) (4)” from the statement, “Where swallowing of capsules is difficult, capsules may be opened and contents added to small amount of yogurt, (b) (4) or applesauce at room temperature.” from all labeling due to lack of supporting clinical data. **Statement removed. Acceptable.**
2. Professional samples
 - a. Please see comments 1(a), (c), and (e). **Change made and acceptable.**
 - b. Per 21 CFR 201.10, 21 CFR 201.51, the label must provide the lipase, amylase, and protease USP units. **Change made and acceptable.**

Additional notes:

1. On August 5, 2010, an additional request was made to the applicant to revise the temperature storage conditions on the container and carton labels from, (b) (4) .” to “Store at room temperature 20-25°C (68-77°F) in a dry place.”. The applicant submitted revised labeling on August 6, 2010. **Change made is acceptable.**
2. On December 20, 2011 an information request from DMEPA was sent with the following requests:

Container Labels and Carton Labeling (100 count, 500 count, and 12 count)

- a. Revise the warning statement (b) (4) to read ‘Ultresa capsules should be swallowed whole. Do not crush or chew the capsules and the capsule contents.’ 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 capsules can be crushed or chewed. Additionally, ensure the statement is prominent by bolding the statement.

b. Include a statement under ‘Warnings’ on the container labels and carton labeling to warn patients to take Ultresa with food and plenty of fluid (as noted in the Prescribing Information and the Medication Guide), and ensure the statement is prominent by bolding the statement.

The statement may appear as follows:

‘Warnings:

Take Ultresa capsules with food and plenty of fluid.

See package insert.’

c. Revise the color of the proprietary name, Ultresa, to appear less prominent. As currently presented, the color green distracts attention from other important information such as the NDC number and the product 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).

d. 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 three 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.

e. Increase the prominence of the dosage form statement ‘Delayed-Release Capsules’, on all container labels and carton labeling. As currently presented, the statement lacks prominence.

f. Increase the prominence of the boxed strength statement on all container labels and carton labeling by increasing the font size. As currently presented, although color-coded, the strengths lack prominence and may increase the risk of medication errors due to incorrect product selection (i.e. selecting the incorrect strength).

g. Delete or reduce the prominence of the round graphic design next to the proprietary name, Ultresa, on the container labels and carton labeling. As currently presented, the graphic design is too prominent and distracts attention from the proprietary name and the NDC numbers.

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

Carton Labeling (100 counts and 500 counts)

a. Delete or reduce the prominence of the company name on the principal display panel. As currently presented, the company name is too prominent and distracts attention from the Medication Guide statement, as well as information such as the product name and product strength. Additionally, the company name also appears on the side panel and is duplicative.

3 of 3

Carton Labeling (12 counts)

- a. Relocate the statement '810D32-C Rev 05/10' from the top portion of the principal display panel to the back panel of the carton labeling to provide space for other important information.

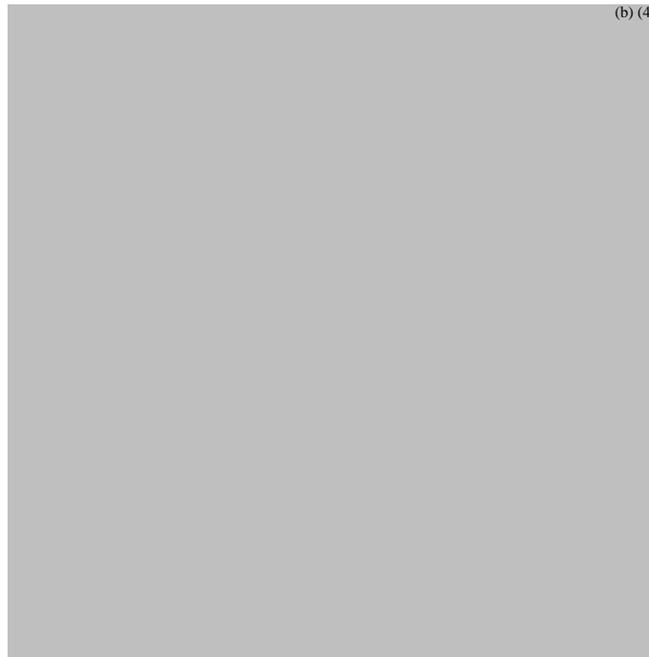
- b. Relocate the quantity statement 'Contents: 1 bottle of 12 capsules' to the left top portion of the principal display panel, in the space provided after relocating '810D32-C Rev 05/10'. Additionally, delete the word 'Contents'. The revised quantity statement should appear as follows: '1 bottle of 12 capsules'. As currently presented, the quantity statement is too close to the product strength and crowds the space.

Container Labels (12 counts)

- a. Relocate the 'Professional sample' statement from the top right hand side of the principal display panel to the area directly above the NDC number (similar to that displayed on the carton labeling of the 12 count sample product) to provide space for other information.

- b. Relocate the quantity statement '12 capsules' to the top right hand portion of the principal display panel in the space provided after relocating the 'Professional sample' statement. As currently presented, the quantity statement is too close to the product strength and crowds the area.

The revised labels submitted January 9, 2012 are acceptable.



6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

Richard Ledwidge, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP/

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

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

/s/

KIMBERLY M RAINS
02/07/2012

RICHARD LEDWIDGE
02/09/2012

BARRY W CHERNEY
02/15/2012

SEALD Director Sign-Off Memo and Labeling Review

Product Trade Name (Non-Propriety Name)	ULTRESA (pancrelipase) delayed-release capsules, for oral use
Application Number/Supplement Number	NDA 22222
Type of Application	Resubmission Class 2
Indication	For the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Applicant	Aptalis Pharma US, Inc.
Office/Division	ODE III/DGIEP
Division Project Manager	Jagjit Grewal, MPH
Submission Date	September 1, 2011
PDUFA Goal Date	March 1, 2012
SEALD Review Date	February 10, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie B. Burke, RPh, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
 - For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
 - Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
 - For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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.”
 - For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**
 - Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.

- **Patient Counseling Information**
 - This section is required and cannot be omitted.
 - Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ... (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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

/s/

JEANNE M DELASKO
02/10/2012

LAURIE B BURKE
02/10/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion
Division of Direct-to-Consumer Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 8, 2012

To: Jagjit Grewal, Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Twyla Thompson, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
OPDP

CC: Lisa Hubbard, Professional Group Leader, DDP/OPDP
Shefali Doshi, Direct-To-Consumer Group Leader, DDTCP/OPDP

Subject: NDA 022222
ULTRESA (pancrelipase) delayed-release capsules, for oral use [Ultresa]
OPDP Labeling Consult Response

In response to DGIEP's January 30, 2012, consult request, OPDP has reviewed the draft package insert (PI), carton/container labeling, and Medication Guide for Ultresa and offers the following comments.

OPDP's comments on the PI are based on version 9 of the proposed draft marked-up labeling titled, Proposed PI 8-12-10.doc, accessed via the e-Room (last modified February 3, 2012 at 8:24 am). OPDP used the Division of Medical Policy Programs' tracked changes version of the Medication Guide finalized on February 6, 2012 as the base document for review. OPDP's comments on the PI and Medication Guide are provided directly on the document attached below. Please also see below for OPDP's comments on the carton/container labeling.

If you have any questions regarding the PI or carton/container labeling, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Twyla Thompson at 301.796.4294 or Twyla.Thompson@fda.hhs.gov.

Carton/Container Labeling

OPDP has reviewed the following materials, accessed via the EDR (sequence 0076 dated 1/9/12; available at <\\CDSESUB1\EVSPROD\NDA022222\022222.enx>):

- Container (Bottle) Label for 500 Capsule Count 23,000 Lipase Units
- Carton (Box) Label for 100 Capsule Count 13,800 Lipase Units
- Carton (Box) Label for 100 Capsule Count 20,700 Lipase Units
- Carton (Box) Label for 100 Capsule Count 23,000 Lipase Units
- Carton (Box) Label for 500 Capsule Count 23,000 Lipase Unit
- Carton (Box) Label for 12 Capsule Count (Professional Sample) 13,800 Lipase Units
- Carton (Box) Label for 12 Capsule Count (Professional Sample) 20,700 Lipase Units
- Carton (Box) Label for 12 Capsule Count (Professional Sample) 23,000 Lipase Units
- Container (Bottle) Label for 12 Capsule Count (Professional Sample) 13,800 Lipase Units
- Container (Bottle) Label for 12 Capsule Count (Professional Sample) 20,700 Lipase Units
- Container (Bottle) Label for 12 Capsule Count (Professional Sample) 23,000 Lipase Units
- Container (Bottle) Label for 100 Capsule Count 13,800 Lipase Units
- Container (Bottle) Label for 100 Capsule Count 20,700 Lipase Units
- Container (Bottle) Label for 100 Capsule Count 23,000 Lipase Units

OPDP has no comments on these proposed materials.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

TWYLA N THOMPSON
02/08/2012

KATHLEEN KLEMM
02/08/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: February 3, 2012

To: Donna Griebel, MD, Director
Division of Gastrointestinal and Inborn Errors Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): ULTRESA (pancrelipase)

Dosage Form and Route: delayed-release capsules

Application Type/Number: NDA 22-222

Applicant: Aptalis Pharma US, Inc.

1 INTRODUCTION

This review is written in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for ULTRESA (pancrelipase) delayed-release capsules.

The Applicant submitted a Complete Response in response to a Complete Response (CR) letter issued by the Agency on November 28, 2010 for original New Drug Application (NDA) 22-222 for ULTRESA (pancrelipase) delayed-release capsules. The proposed indication for ULTRESA (pancrelipase) delayed-release capsules is for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

2 MATERIAL REVIEWED

- ULTRESA (pancrelipase) delayed-release capsules labeling comments sent to Applicant on August 5, 2010 and August 11, 2010.
- Draft ULTRESA (pancrelipase) delayed-release capsules Medication Guide (MG) received on August 12, 2010.
- DRISK (Labeling Review) Comments to Applicant dated August 25, 2010.
- Draft ULTRESA (pancrelipase) delayed-release capsules Prescribing Information (PI), revised by the Review Division throughout the current review cycle, and provided to DMPP on January 30, 2012.
- Approved Creon (pancrelipase) delayed-release capsules comparator labeling dated July 12, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- performed a side-by-side review of the MG submitted on August 12, 2010 to the MG comments sent to the Applicant on August 5, 2010 and August 11, 2010, and DRISK comments to Applicant dated August 25, 2010
- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SHARON R MILLS
02/03/2012

BARBARA A FULLER
02/06/2012

LASHAWN M GRIFFITHS
02/06/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: November 1, 2011

Reviewer(s): Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Ultresa (Pancrelipase) Delayed-release Capsules

13,800 USP units Lipase
27,600 USP units Amylase
27,600 USP units Protease
and
20,700 USP units Lipase
41,400 USP units Amylase
41,400 USP units Protease
and
23,000 USP units Lipase
46,000 USP units Amylase
46,000 USP units Protease

Application Type/Number: NDA 022222

Applicant/sponsor: Axcan Pharma

OSE RCM #: 2011-3389

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the container labels, carton labeling, Prescribing Information, and the Medication Guide for Ultresa (Pancrelipase) Tablets, in response to a consult from the Division of Gastroenterology Products to identify any areas of concern from a medication errors perspective.

1.1 REGULATORY HISTORY

Ultresa (Pancrelipase) Delayed-released Capsules (NDA 022222) is the subject of a Class-II resubmission dated September 1, 2011. On November 28, 2010 the Agency issued a Complete Response letter for this Application due to deficiencies identified. DMEPA reviewed the container labels and the Prescribing Information for Ultresa, as part of the Applicant's original submission pursuant to section 505(b)(2) on March 10, 2010, in OSE Review #2009-942, dated April 15, 2010. The Applicant submitted revised container labels (trade and professional samples) and carton labeling (trade and professional samples) on August 6, 2010, and Prescribing Information and Medication Guide on August 12, 2010, which will be evaluated in this review.

1.2 PRODUCT INFORMATION

Ultresa (Pancrelipase) Capsules is a combination of porcine-derived Lipases, Proteases, and Amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions. Ultresa is not interchangeable with other pancrelipase products. Ultresa is dosed by Lipase units, and is individualized and determined by the degree of steatorrhea present and the fat content of the diet. Therapy should begin with 500 lipase units/kg/meal (children 4 years and older and weight 28 kg or greater and adults) to 1000 Lipase units/kg/meal (children older than 12 months and younger than 4 years and weight 14 kg or greater) to a maximum of 2,500 Lipase units/kg/meal (or less than or equal to 10,000 Lipase units/kg/day), or less than 4,000 Lipase units/gram fat ingested/day. For children or patients unable to swallow intact capsules, the contents may be sprinkled on applesauce, yogurt, and other acidic food with pH 4.5 or less. Ultresa will be available in the following three formulations in bottles of 100 and 500 (only the 23,000 USP units Lipase):

- 1) 13,800 USP units of Lipase, 27,600 USP units of Amylase and 27,600 USP units of Protease;
- 2) 20,700 USP units of Lipase; 41,400 USP units of Amylase and 41,400 USP units of Protease;
- 3) 23,000 USP units of Lipase, 46,000 USP units of Amylase and 46,000 USP units of Protease.

2 METHODS AND MATERIALS

Because Pancrelipase, the active ingredient of Ultresa is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) to identify medication errors related to the use of Pancrelipase. We also evaluated the container labels (trade and professional samples), carton labeling (trade and professional samples), Prescribing Information, and the Medication Guide for Ultresa (Pancrelipase) Capsules 13,800 USP units Lipase, 20,700 USP units Lipase, and 23,000 USP units Lipase, to ensure all our label and labeling recommendations in OSE Review #2009-942 have been implemented, and to identify areas of vulnerability that can lead to medication errors.

2.1 IDENTIFICATION OF MEDICATION ERRORS IN AERS DATABASE

The October 7, 2011 AERS search used the following criteria: Active ingredient 'Pancrelipase', Verbatim term 'Pancrel%' as well as the MedDRA reaction terms 'Medication Errors' (HLGT),

‘Product Label Issues’ (HLT), and ‘Product Quality Issue’ (PT). The date limit was set from March 8, 2010 (the date of the last search conducted in OSE review #2009-942, dated April 15, 2010) to October 7, 2011. Those cases not pertaining to errors, pertaining to errors of concomitant drugs, and occurrence of adverse events not due to medication errors were excluded from further analysis.

2.2 LABELS AND LABELING

Using failure Mode and Effects Analysis¹, the principles of human factors, and the lessons learned from postmarketing experience, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the revised container labels (trade and professional samples), carton labeling (trade and professional samples), Prescribing Information, and Medication Guide, submitted on August 6, 2010 and August 12, 2010, to identify vulnerabilities that may lead to medication errors. The following were submitted for our evaluation (see Appendices A through C):

- Container labels for trade and professional samples (13,800 USP units Lipase, 20,700 USP units Lipase, and 23,000 USP units Lipase) submitted 8/6/10
- Carton labeling for trade and professional samples (13,800 USP units Lipase, 20,700 USP units Lipase, and 23,000 USP units Lipase) submitted 8/6/10
- Prescribing Information submitted 8/12/10
- Medication Guide submitted 8/12/10

3 RESULTS

The following sections describe the results of DMEPA’s medication error searches and label and labeling evaluation.

3.1 IDENTIFICATION OF MEDICATION ERRORS IN AERS DATABASE RESULTS

The October 7, 2011 AERS search identified 3 reports (ISR #'s 6900582, 7767629, and 7798907). After eliminating cases as described in Section 2, no cases remained for further evaluation.

3.2 LABELS AND LABELING RISK ASSESSMENT

Our evaluation of the container labels, carton labeling, Prescribing Information, and the Medication Guide noted that the Applicant implemented DMEPA’s recommendations from OSE review #2009-942, dated April 15, 2010. However, the statement ‘Ultresa capsules and capsule contents should not be crushed or chewed’ can be improved to include positive language (i.e. tell patients they should do something). Additionally, a warning statement on the container labels and carton labeling may be helpful in reminding patients to take Ultresa with food and plenty of fluid. Also, the ‘Rx only’ and the quantity statements on the container labels, as well as the company name ‘Axcan Pharma’ on the carton labeling are too prominent and distract attention from other important information on the container labels and carton labeling.

4 CONCLUSIONS

The container labels, carton labeling, Prescribing Information, and the Medication Guide noted that the Applicant implemented DMEPA’s recommendations from OSE review #2009-942, dated April 15, 2010. However, our further evaluation of the proposed labels and labeling identified areas of needed improvement in order to reduce the potential for medication errors. We provide

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004

recommendations to the Prescribing Information in Section 4.1 *Comments to the Division* for discussion during the labeling meetings. Section 4.2 *Comments to the Applicant* for the container labels and carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact OSE Regulatory Project Manager, Nitin Patel, at 301-796-5412.

4.1 COMMENTS TO THE DIVISION

In the Dosage and Administration Section in the Highlights and the Full Prescribing Information, as well as the Medication Guide, the warning statement ‘Do not crush or chew capsules (or Ultresa capsules) and capsule contents.’ or ‘Ultresa capsules and capsule contents should not be crushed or chewed.’ contain negative language. This statement may have the opposite effect of the intended meaning. Patients may overlook the words ‘Do not’ and interpret this statement to mean the capsules can be crushed or chewed. We recommend revising the warning statement to include a positive language. The statement may appear as follows:

‘Ultresa capsules should be swallowed whole. Do not crush or chew the capsules and the capsule contents.’

Additionally, the Dosage and Administration Section in the Highlights of the Prescribing Information does not include the warning statement ‘Ultresa should be taken during meals or snacks.’

4.2 COMMENTS TO THE APPLICANT

A. Container Labels and Carton Labeling (100 count, 500 count, and 12 count)

1. Revise the warning statement (b) (4) to read ‘Ultresa capsules should be swallowed whole. Do not crush or chew the capsules and the capsule contents.’ 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 capsules can be crushed or chewed. Additionally, ensure the statement is prominent by bolding the statement.
2. Include a statement under ‘Warnings’ on the container labels and carton labeling to warn patients to take Ultresa with food and plenty of fluid (as noted in the Prescribing Information and the Medication Guide), and ensure the statement is prominent by bolding the statement. The statement may appear as follows:

‘Warnings:
Take Ultresa capsules with food and plenty of fluid.
See package insert.’
3. Revise the color of the proprietary name, Ultresa to appear less prominent. As currently presented, the color green distracts attention from other important information such as the NDC number and the product 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).
4. 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 three 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.

5. Increase the prominence of the dosage form statement 'Delayed-Release Capsules', on all container labels and carton labeling. As currently presented, the statement lacks prominence.
6. Increase the prominence of the boxed strength statement on all container labels and carton labeling by increasing the font size. As currently presented, although color-coded, the strengths lack prominence and may increase the risk of medication errors due to incorrect product selection (i.e. selecting the incorrect strength).
7. Delete or reduce the prominence of the round graphic design next to the proprietary name, Ultresa, on the container labels and carton labeling. As currently presented, the graphic design is too prominent and distracts attention from the proprietary name and the NDC numbers.

B. Carton Labeling (100 counts and 500 counts)

Delete or reduce the prominence of the company name 'Axcan Pharma' on the principal display panel. As currently presented, the company name is too prominent and distracts attention from the Medication Guide statement, as well as information such as the product name and product strength. Additionally, the company name also appears on the side panel and is duplicative.

C. Carton Labeling (12 counts)

1. Relocate the statement '810D32-C Rev 05/10' from the top portion of the principal display panel to the back panel of the carton labeling to provide space for other important information.
2. Relocate the quantity statement 'Contents: 1 bottle of 12 capsules' to the left top portion of the principal display panel, in the space provided after relocating '810D32-C Rev 05/10'. Additionally, delete the word 'Contents'. The revised quantity statement should appear as follows: '1 bottle of 12 capsules'. As currently presented, the quantity statement is too close to the product strength and crowds the space.

D. Container Labels (12 counts)

1. Relocate the 'Professional sample' statement from the top right hand side of the principal display panel to the area directly above the NDC number (similar to that displayed on the carton labeling of the 12 count sample product) to provide space for other information.
2. Relocate the quantity statement '12 capsules' to the top right hand portion of the principal display panel in the space provided after relocating the 'Professional sample' statement. As currently presented, the quantity statement is too close to the product strength and crowds the area.

5 REFERENCES

1. ADVERSE EVENTS REPORTING SYSTEM (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. PREVIOUS OSE REVIEW

OSE Review #2009-942, Ultresa Label and Labeling Review, Baugh, D.V,
April 15, 2010.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MANIZHEH SIAHPOUSHAN
11/01/2011

ZACHARY A OLESZCZUK
11/01/2011

CAROL A HOLQUIST
11/02/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 25, 2010

To: Donna Griebel, MD Director
Division of Gastroenterology Products (DGP)

Through: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader

From: Steve L. Morin, RN, BSN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Ultresa (pancrelipase) Delayed Release Capsules

Application Type/Number: NDA 22-222

Applicant/sponsor: Axcan Pharma US Inc.

OSE RCM #: 2009-1000

1 INTRODUCTION

This Memo is written in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review Axcan Pharma US Inc. responses to DRISK's review of the proposed Medication Guide (MG) for New Drug Application NDA 22222 Ultresa (pancrelipase) Delayed Release Capsules that was completed on March 23, 2009. DRISK's comments were provided to DGP by email, as requested, on July 23, 2010. Further changes were made to the MG and agreed upon by DGP and DRISK at a labeling meeting on July 30, 2010. DGP sent the agreed upon MG revisions to the Applicant on August 5, 2010, and copied DRISK on the correspondence.

Please let us know if additional DRISK input is needed when the Applicant responds to the Agency's MG revisions and comments.

2 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

10 Page(s) 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-22222	ORIG-1	AXCAN PHARMA US INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

STEVE L MORIN
08/25/2010

SHARON R MILLS
08/26/2010



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW-Second Amendment

Application Number: NDA 22-222

Name of Drug: Ultresa™ (Pancrelipase) Capsules

Sponsor: AXCAN PHARMA

Material Reviewed: ULTRESA™ (Pancrelipase) Delayed-Release Capsules
Carton and Container Labels

Submission Dates: July 31, 2007, July 31, 2009, March 10, 2010, May 5,
2010, July 1, 2010, August 3, 2010, August 6, 2010

EXECUTIVE SUMMARY

The carton and container labels for ULTRESA™ (Pancrelipase) Delayed-Release Capsules were reviewed and found to comply with the following regulations : 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section. The labels are acceptable.

Background:

ULTRESA™ (Pancrelipase) Delayed-Release Capsules is a New Drug Application (NDA) indicated as a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

Labels Reviewed:

ULTRESA® (Pancrelipase) Container Label
13,800 Lipase Units -100 ct Trade Bottle, 12 ct Professional Sample
20,700 Lipase Units -100 ct Trade Bottle, 12 ct Professional Sample
23,000 Lipase Units -100 ct Trade Bottle, 500 ct Trade Bottle, 12 ct Professional Sample

ULTRESA® (Pancrelipase) Carton Label

13,800 Lipase Units -100 ct Trade Carton, 12 ct Professional Sample

20,700 Lipase Units -100 ct Trade Carton, 12 ct Professional Sample

23,000 Lipase Units -100 ct Trade Carton, 500 ct Trade Carton, 12 ct Professional Sample

Review

The carton and container labels for ULTRESA® (Pancrelipase) were reviewed using the following regulations: 21 CFR 201.1 through 21 CFR 201.18; 21 CFR 201.25; and 21 CFR 201.50 through 21 CFR 201.55 through 21 CFR 200.57; 21 CFR 201.100 and United States Pharmacopeia, 12/1/10-5/1/10, USP 32/NF27. Please see comments in the conclusions section.

I. Container**A. Bottle Label**

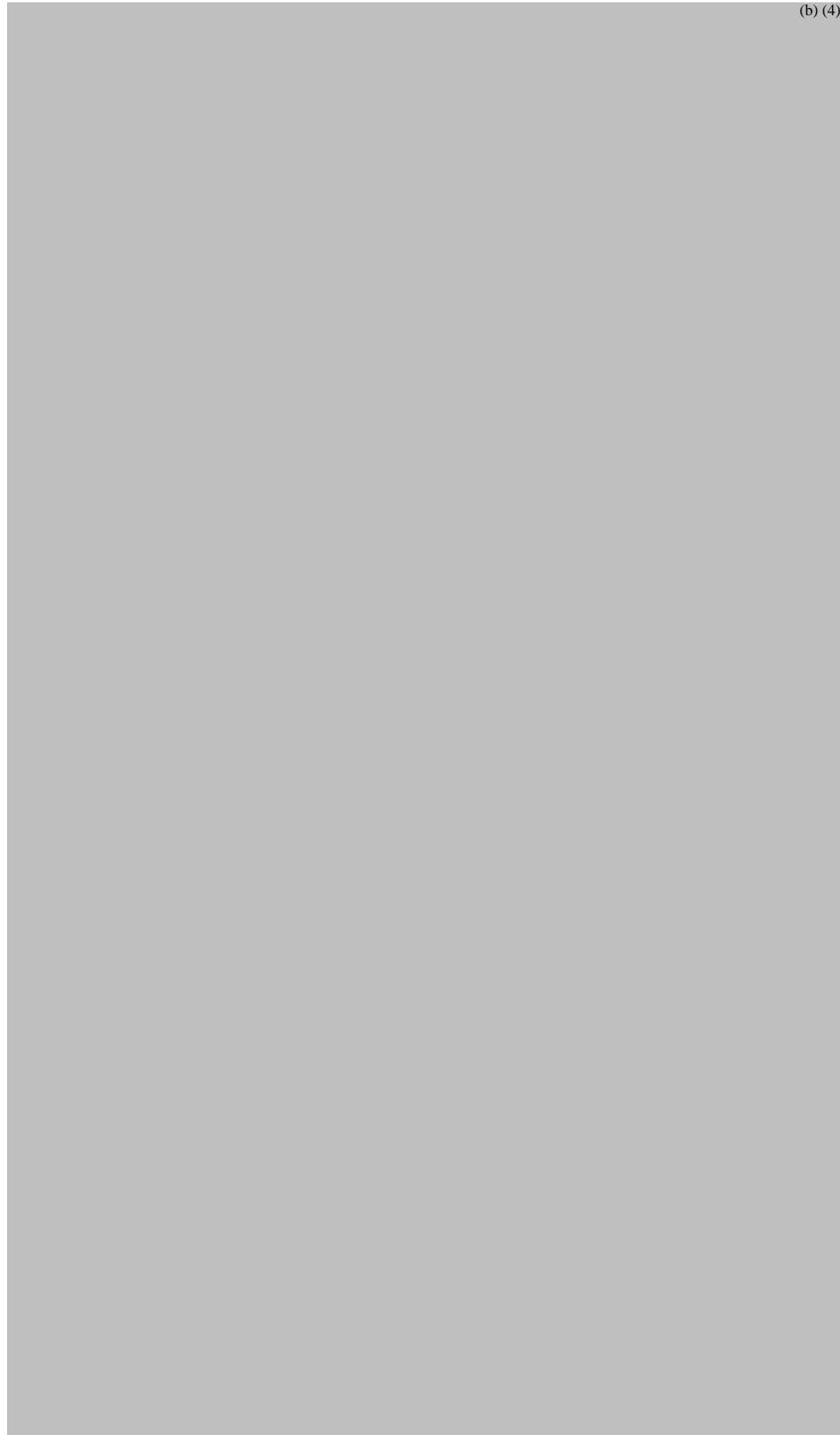
1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
Manufactured By: Eurand International, (b)(4), using its (b)(4) for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers-
The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units.
This does not conform to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements- The proprietary name ULTRESA™ appears on the label with the established name, pancrelipase. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, Pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA®.
This does not conform to the regulation.
6. 21 CFR 201.15 Drugs; prominence of required label statements-

All required statements (“Rx Only”, “Protect from moisture”, “Do not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**

7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the side of the label. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the side of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. Per the United States Pharmacopeia ,12/1/09-5/1/10, USP 32/NF 27 monograph for Pancrelipase Delayed Release Capsules-the product should be labeled **Recommend removing the highlight from the lipase line, enclosing the ingredient listing in a box, and adding a statement to denote the product is dosed based on lipase units.**
10. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents in terms of numerical count in units on the label, below the proprietary and established name. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count for the 23,000 lipase unit. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage- On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements “Rx Only”, identifying lot number, storage conditions and a reference to the package insert. “Protect from moisture”, "Do not refrigerate" and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small,

the required statement may be placed on the package label. This conforms to the regulation. The statement, “**ACCOMPANYING MEDICATION GUIDE TO BE DISPENSED TO PATIENT**” appears on the side on the label.

Proposed Labels submitted March 30, 2010
100 count



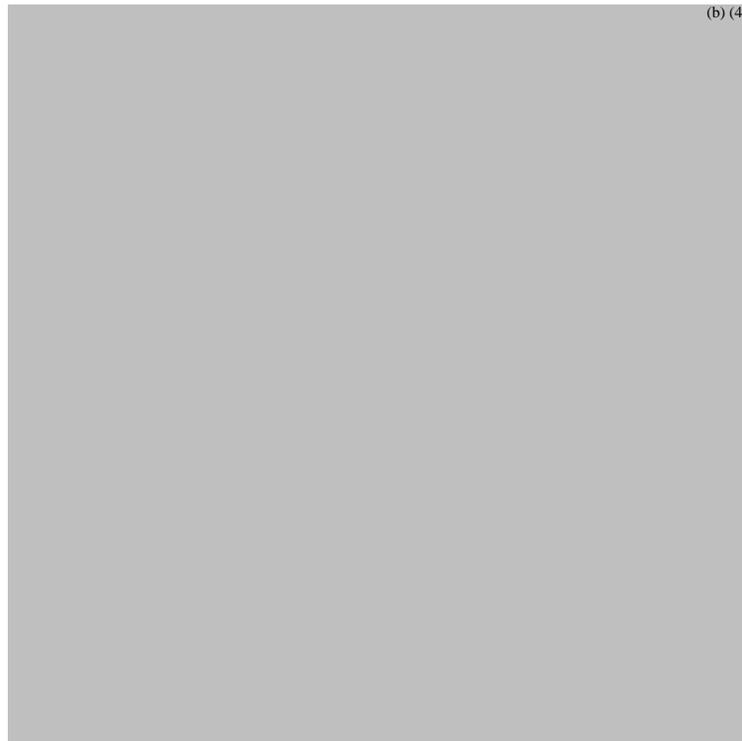
II. Carton

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:
Manufactured By: Eurand International, ^{(b) (4)}, using its ^{(b) (4)} ⁽⁴⁾ for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units. **This does not conform to the regulation.**
4. 21 CFR 201.6 Drugs; misleading statements - The proprietary name, ULTRESA™ appears with the established name, pancrelipase on the carton. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA®. **This does not conform to the regulation.**
6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”, “Protect from moisture”, “Do not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date appears on the carton below the lot number. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of the side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. **Recommend removing the highlight from the lipase line, enclosing the ingredient listing in a box and adding a statement to denote the product is dosed based on lipase units.**
10. 21 CFR 201.51 Declaration of net quantity of contents - The label states the net quantity of contents in terms of numerical count in units at the top of the carton. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count configuration is available for the 23,000 lipase units. This conforms to the regulation.

11. 21 CFR 201.55 Statement of dosage - The label states “For dosage and other information for use, see accompanying product literature. This conforms to the regulation. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for “Rx Only”, an identifying lot number, storage conditions, and a reference to the package insert. “Protect from moisture”, “Do not refrigerate” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation. The following statement appears on the container and carton label, “**ACCOMPANYING MEDICATION GUIDE TO BE DISPENSED TO THE PATIENT**”.

Proposed Labels submitted March 30, 2010



III. Conclusions

- A. The proposed carton and container labeling are acceptable only upon the following changes:
1. Container and carton (commercial labels)
 - a. Per 21 CFR 201.10, please revise the presentation of the established name and proprietary name. The established name shall have the prominence commensurate with the prominence of the proprietary name or such designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. It shall also be printed in letters that are at least half as large as the letters comprising proprietary name. **Changes made and acceptable.**
 - b. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the bolded statements, “Protect from moisture”, “Avoid excessive heat” and “Do not refrigerate” to the storage conditions listed. **Change made and acceptable.** The statement, “Do not refrigerate” was removed from both the PI, carton and container labels (submission August 3, 2010) for consistency with other Pancrelipase Enzyme Product labels.
 - c. Per the United States Pharmacopeia, 12/1/09-5/10/10, USP 32/NF 27 Monograph for Pancrelipase Delayed Release Capsules, please revise the dosage form from, “capsules” to “Delayed Release Capsules” on all labeling. **Change made and acceptable.**
 - d. Please revise the following statement, “Each capsule of enteric-coated pancrelipase minitabets contains:” to “Each enteric-coated delayed release capsule contains:” for consistency, clarity, and readability with the dosage form, delayed release capsule. **Change made and acceptable.**
 - e. Per 21 CFR 201.5, please remove the color highlight from the Lipase Unit presentation and add a statement that dosing is based on lipase units. **Highlight not removed. Dosing statement added. Acceptable.**
 - f. Please remove “^{(b) (4)}” from the statement, “Where swallowing of capsules is difficult, capsules may be opened and contents added to small amount of yogurt, ^{(b) (4)} or applesauce at room temperature.” from all labeling due to lack of supporting clinical data. **Statement removed. Acceptable.**
 2. Professional samples

- a. Please see comments 1(a), (c), and (e). **Change made and acceptable.**
- b. Per 21 CFR 201.10, 21 CFR 201.51, the label must provide the lipase, amylase, and protease USP units. **Change made and acceptable.**

On August 5, 2010, an additional request was made to the applicant to revise the temperature storage conditions on the container and carton labels from, “Store below 25°C (77°F) in a dry place.” to “Store at room temperature 20-25°C (68-77°F) in a dry place.”. The applicant submitted revised labeling on August 6, 2010. **Change made is acceptable.**

Revised Labels submitted August 6, 2010
100 Count Containers



5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

Wei Guo, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP/

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN PHARMA US INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

KIMBERLY M RAINS
08/11/2010

WEI GUO
08/11/2010

BARRY W CHERNEY
08/11/2010



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW-Amendment

Application Number: NDA 22-222

Name of Drug: Ultresa™ (Pancrelipase) Capsules

Sponsor: AXCAN PHARMA

Material Reviewed: ULTRESA™ (Pancrelipase) Delayed-Release Capsules
Carton and Container Labels

Submission Dates: July 31, 2007, July 31, 2009, March 10, 2010, May 5,
2010, July 1, 2010, August 3, 2010

EXECUTIVE SUMMARY

The carton and container labels for ULTRESA™ (Pancrelipase) Delayed-Release Capsules were reviewed and found to comply with the following regulations : 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopoeia, 12/1/09-10/1/10, USP 32/NF 27. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section. The labels are acceptable.

Background:

ULTRESA™ (Pancrelipase) Delayed-Release Capsules is a New Drug Application (NDA) indicated as a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

Labels Reviewed:

ULTRESA® (Pancrelipase) Container Label
13,800 Lipase Units -100 ct Trade Bottle
20,700 Lipase Units -100 ct Trade Bottle
23,000 Lipase Units -100 ct Trade Bottle

ULTRESA® (Pancrelipase) Carton Label

4,200 Lipase Units -100 ct Trade Bottle

21,000 Lipase Units -100 ct Trade Bottle

16,800 Lipase Units -100 ct Trade Bottle

10,500 Lipase Units -100 ct Trade Bottle

Review

The carton and container labels for ULTRESA® (Pancrelipase) were reviewed using the following regulations: 21 CFR 201.1 through 21 CFR 201.18; 21 CFR 201.25; and 21 CFR 201.50 through 21 CFR 201.55 through 21 CFR 200.57; 21 CFR 201.100 and United States Pharmacopeia, 12/1/10-5/1/10, USP 32/NF27. Please see comments in the conclusions section.

I. Container

A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
Manufactured By: Eurand International, (b)(4), using its (b)(4) for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers-
The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units.
This does not conform to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements- The proprietary name ULTRESA™ appears on the label with the established name, pancrelipase. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established

name, Pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA®. **This does not conform to the regulation.**

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”, “Protect from moisture”, “Do not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the side of the label. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the side of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. Per the United States Pharmacopeia ,12/1/09-5/1/10, USP 32/NF 27 monograph for Pancrelipase Delayed Release Capsules-the product should be labeled **Recommend removing the highlight from the lipase line, enclosing the ingredient listing in a box, and adding a statement to denote the product is dosed based on lipase units.**
10. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents in terms of numerical count in units on the label, below the proprietary and established name. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count for the 23,000 lipase unit. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage- On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements “Rx Only”, identifying lot number, storage conditions and a reference to the package insert. “Protect from moisture”, "Do not refrigerate” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation. The statement, “**ACCOMPANYING MEDICATION GUIDE TO BE DISPENSED TO PATIENT**” appears on the side on the label.

Proposed Labels submitted March 30, 2010



II. Carton

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:
Manufactured By: Eurand International, (b) (4), using its (b) (4) for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units. **This does not conform to the regulation.**
4. 21 CFR 201.6 Drugs; misleading statements - The proprietary name, ULTRESA™ appears with the established name, pancrelipase on the carton. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA®. **This does not conform to the regulation.**
6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”, “Protect from moisture”, “Do not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date appears on the carton below the lot number. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of the side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. **Recommend removing the highlight from the lipase line, enclosing the ingredient listing in a box and adding a statement to denote the product is dosed based on lipase units.**
10. 21 CFR 201.51 Declaration of net quantity of contents - The label states the net quantity of contents in terms of numerical count in units at the top of the carton. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count configuration is available for the 23,000 lipase units. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage - The label states “For dosage and other information for use, see accompanying product literature. This conforms to the regulation. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for “Rx Only”, an identifying lot number, storage conditions, and a reference to the package insert. “Protect from moisture”, “Do not refrigerate” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation. The following statement appears on the container and carton label, “**ACCOMPANYING MEDICATION GUIDE TO BE DISPENSED TO THE PATIENT**”.

III. Conclusions

- A. The proposed carton and container labeling are acceptable only upon the following changes:
1. Container and carton (commercial labels)
 - a. Per 21 CFR 201.10, please revise the presentation of the established name and proprietary name. The established name shall have the prominence commensurate with the prominence of the proprietary name or such designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. It shall also be printed in letters that are at least half as large as the letters comprising proprietary name. **Changes made and acceptable.**
 - b. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the bolded statements, “Protect from moisture”, “Avoid excessive heat” and “Do not refrigerate” to the storage conditions listed. **Change made and acceptable.** The statement, “Do not refrigerate” was removed from both the PI, carton and container labels (submission August 3, 2010) for consistency with other Pancrelipase Enzyme Product labels.
 - c. Per the United States Pharmacopeia, 12/1/09-5/10/10, USP 32/NF 27 Monograph for Pancrelipase Delayed Release Capsules, please revise the dosage form from, “capsules” to “Delayed Release Capsules” on all labeling. **Change made and acceptable.**
 - d. Please revise the following statement, “Each capsule of enteric-coated pancrelipase minitabets contains:” to “Each enteric-coated delayed release capsule contains:” for consistency, clarity, and readability with the dosage form, delayed release capsule. **Change made and acceptable.**
 - e. Per 21 CFR 201.5, please remove the color highlight from the Lipase Unit presentation and add a statement that dosing is based on lipase units. **Highlight not removed. Dosing statement added. Acceptable.**
 - f. Please remove “^{(b) (4)}” from the statement, “Where swallowing of capsules is difficult, capsules may be opened and contents added to small amount of yogurt, ^{(b) (4)} or applesauce at room temperature.” from all labeling due to lack of supporting clinical data. **Statement removed. Acceptable.**
 2. Professional samples

- a. Please see comments 1(a), (c), and (e). **Change made and acceptable.**
- b. Per 21 CFR 201.10, 21 CFR 201.51, the label must provide the lipase, amylase, and protease USP units. **Change made and acceptable.**

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

Wei Guo, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP/

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN PHARMA US INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

KIMBERLY M RAINS
08/04/2010

WEI GUO
08/04/2010

BARRY W CHERNEY
08/04/2010



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: NDA 22-222

Name of Drug: Ultresa™ (Pancrelipase) Capsules

Sponsor: AXCAN PHARMA

Material Reviewed: ULTRESA™ (Pancrelipase) Delayed-Release Capsules
Carton and Container Labels

Submission Dates: July 31, 2007, July 31, 2009, March 10, 2010, May 5, 2010

EXECUTIVE SUMMARY

The carton and container labels for ULTRESA™ (Pancrelipase) Delayed-Release Capsules were reviewed and found to comply with the following regulations : 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopoeia, 12/1/09-5/1/10, USP 32/NF 27. Labeling deficiencies were identified and mitigated. Please see comments in the conclusions section.

Background:

ULTRESA™ (Pancrelipase) Delayed-Release Capsules is a New Drug Application (NDA) indicated as a combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

Labels Reviewed:

ULTRESA® (Pancrelipase) Container Label
13,800 Lipase Units -100 ct Trade Bottle
20,700 Lipase Units -100 ct Trade Bottle
23,000 Lipase Units -100 ct Trade Bottle

ULTRESA® (Pancrelipase) Carton Label

- 4,200 Lipase Units -100 ct Trade Bottle
- 21,000 Lipase Units -100 ct Trade Bottle
- 16,800 Lipase Units -100 ct Trade Bottle
- 10,500 Lipase Units -100 ct Trade Bottle

Review

The carton and container labels for ULTRESA® (Pancrelipase) were reviewed using the following regulations: 21 CFR 201.1 through 21 CFR 201.18; 21 CFR 201.25; and 21 CFR 201.50 through 21 CFR 201.55 through 21 CFR 200.57; 21 CFR 201.100 and United States Pharmacopeia, 12/1/10-5/1/10, USP 32/NF27. Please see comments in the conclusions section.

I. Container

A. Bottle Label

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer or distributor-
Manufactured By: Eurand International, (b)(4), using its (b)(4) for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers-
The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units.
This does not conform to the regulation.
4. 21 CFR 201.6 Drugs; misleading statements- The proprietary name ULTRESA™ appears on the label with the established name, pancrelipase. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established

name, Pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA®. **This does not conform to the regulation.**

6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”, “Protect from moisture”, “Do not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs: location of expiration date-The expiration date appears under the lot identification number on the side of the label. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements – The bar code is located on the side of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.
9. 21 CFR 201.50 Statement of identity- The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. Per the United States Pharmacopeia ,12/1/09-5/1/10, USP 32/NF 27 monograph for Pancrelipase Delayed Release Capsules-the product should be labeled **Recommend removing the highlight from the lipase line and enclose the ingredient listing in a box and adding a statement to denote the product is dosed based on lipase units.**
10. 21 CFR 201.51 Declaration of net quantity of contents – The label prominently states the net quantity of contents in terms of numerical count in units on the label, below the proprietary and established name. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count for the 23,000 lipase unit. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage- On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. This conforms to the regulation.
12. 21 CFR 201.100 Prescription drugs for human use- The label bears statements “Rx Only”, identifying lot number, storage conditions and a reference to the package insert. “Protect from moisture”, "Do not refrigerate" and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**

13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation. The statement, “**ACCOMPANYING MEDICATION GUIDE TO BE DISPENSED TO PATIENT**” appears on the side on the label.

Proposed Labels submitted March 30, 2010



II. Carton

1. 21 CFR 201.1 Drugs; name and place of business of manufacturer, packer, or distributor- The label states:
Manufactured By: Eurand International, (b) (4), using its (b) (4) for AXCAN PHARMA US, Inc., 22 Ivenerness Center Parkway, Birmingham, AL 35242 USA. This conforms to the regulation.
2. 21 CFR 201.2 Drugs and devices; National Drug Code numbers- The National Drug Code (NDC) number is located above the proprietary name at the top of the label. It is noted as NDC 58914-XXX-XX. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
3. 21 CFR 201.5 Drugs; adequate directions for use-On the side of the label “For dosage and other information for use, see accompanying product literature.” appears on the container labels. The strength presentation of the Lipase Units is highlighted, but the label does not indicate that dosing is based on lipase units. **This does not conform to the regulation.**
4. 21 CFR 201.6 Drugs; misleading statements - The proprietary name, ULTRESA™ appears with the established name, pancrelipase on the carton. This conforms to the regulation.
5. 21 CFR 201.10 Drugs; statement of ingredients- The established name, pancrelipase is not used in type at least half as large as the most prominent presentation of the proprietary name, ULTRESA®. **This does not conform to the regulation.**
6. 21 CFR 201.15 Drugs; prominence of required label statements- All required statements (“Rx Only”, “Protect from moisture”, “Do not refrigerate”) appear on the label. “Protect from moisture”, “Do not refrigerate”, and “Avoid excessive heat” do not appear on the label. **This does not conform to the regulation.**
7. 21 CFR 201.17 Drugs; location of expiration date - The expiration date appears on the carton below the lot number. This conforms to the regulation.
8. 21 CFR 201.25 Bar code label requirements - The bar code is located at the bottom of the side panel of the carton with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

9. 21 CFR 201.50 Statement of identity - The ingredients, Lipase, Amylase and Protease are listed with corresponding units per capsule per 21 CFR 201.10. This conforms to the regulation. **Recommend removing the highlight from the lipase line and enclose the ingredient listing in a box and adding a statement to denote the product is dosed based on lipase units. .**
10. 21 CFR 201.51 Declaration of net quantity of contents - The label states the net quantity of contents in terms of numerical count in units at the top of the carton. Each strength is available in a 12 count Professional sample, 100 count, and a 500 count for the 23,000 lipase unit. This conforms to the regulation.
11. 21 CFR 201.55 Statement of dosage - The label states “For dosage and other information for use, see accompanying product literature. This conforms to the regulation. Per the United States Pharmacopeia
12. 21 CFR 201.100 Prescription drugs for human use - The label bears statements for “Rx Only”, an identifying lot number, storage conditions, and a reference to the package insert. “Protect from moisture”, “Do not refrigerate” and “Avoid excessive heat” are not listed on the label. **This does not conform to the regulation.**
13. 21 CFR 208.24 Distribution and dispensing of a Medication guide- If a Medication Guide is required under part 208 of chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. This conforms to the regulation. The following statement appears on the container and carton label, “**ACCOMPANYING MEDICATION GUIDE TO BE DISPENSED TO THE PATIENT**”.

III. Conclusions

- A. The proposed carton and container labeling are acceptable only upon the following changes:
1. Container and carton (commercial labels)
 - a. Per 21 CFR 201.10, please revise the presentation of the established name and proprietary name. The established name shall have the prominence commensurate with the prominence of the proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. It shall also be printed in letters that are at least half as large as the letters comprising proprietary name. **Changes made and acceptable.**
 - b. Per 21 CFR 201.15 and 21 CFR 201.100 - Please add the bolded statements, "Protect from moisture", "Avoid

excessive heat” and “Do not refrigerate” to the storage conditions listed. **Change made and acceptable.**

- c. Per the United States Pharmacopeia, 12/1/09-5/10/10, USP 32/NF 27 Monograph for Pancrelipase Delayed Release Capsules, please revise the dosage form from, “capsules” to “Delayed Release Capsules” on all labeling. **Change made and acceptable.**
 - d. Please revise the following statement, “Each capsule of enteric-coated pancrelipase minitablets contains:” to “Each enteric-coated delayed release capsule contains:” for consistency, clarity, and readability with the dosage form, delayed release capsule. **Change made and acceptable.**
 - e. Per 21 CFR 201.5, please remove the color highlight from the Lipase Unit presentation and add a statement that dosing is based on lipase units. **Highlight not removed. Dosing statement added. Acceptable.**
 - f. Please remove “^{(b) (4)}” from the statement, “Where swallowing of capsules is difficult, capsules may be opened and contents added to small amount of yogurt, ^{(b) (4)} or applesauce at room temperature.” from all labeling due to lack of supporting clinical data. **Statement removed. Acceptable.**
2. Professional samples
 - a. Please see comments 1(a), (c), and (e). **Change made and acceptable.**
 - b. Per 21 CFR 201.10, 21 CFR 201.51, the label must provide the lipase, amylase, and protease USP units. **Change made and acceptable.**

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

Wei Guo, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP/

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN PHARMA US INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

KIMBERLY M RAINS

06/22/2010

Final revisions are acceptable.

WEI GUO

06/23/2010

BARRY W CHERNEY

08/04/2010

SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22-222
APPLICANT	Axcan Pharma US, Inc.
DRUG NAME	ULTRESA (Pancrealipase)
SUBMISSION DATE	May 28, 2010
PDUFA DATE	November 28, 2010
SEALD REVIEW DATE	August 2, 2010
SEALD LABELING REVIEWER(S)	Jeanne M. Delasko, RN, MS

Outlined below are the following outstanding labeling issues that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), "none" is stated. If clearly inapplicable sections are omitted from the FPI, "not applicable" is stated. In addition, "not applicable" is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

The following comments delineate major deficiencies noted in the label. Please note that all reviewers' comments are noted in *italics*.

Highlights (HL):

- **Highlights Limitation Statement:** *None*
- **Product Title Line:** *None*
- **Initial U.S. Approval:** *Enter 4-digit year (i.e., 2010) for initial U.S. approval date; do not leave blank.*
- **Boxed Warning:** *Not applicable*
- **Recent Major Changes:** *Not applicable*
- **Indications and Usage:** *None*
- **Dosage and Administration:** *The statement "Dosing should not exceed the recommended maximum dosage set forth by the Cystic Fibrosis Foundation Consensus Conferences Guidelines" should not be a 'Limitation on Dosing.' Include this statement*

SEALD LABELING REVIEW

as the last sentence under the first block of text for D&A to be consistent with the approved CREON label.

- **Dosage Forms and Strengths:** *None*
- **Contraindications:** *None*
- **Warnings and Precautions:** *None*
- **Adverse Reactions:** *None*
- **Drug Interactions:** *Not applicable*
- **Use in Specific Populations:** *Delete the following two statements: (1) [REDACTED] (b) (4)*
[REDACTED] (b) (4)
- **Patient Counseling Information Statement:** *None*
- **Revision Date:** *Enter revision date in month/year (i.e., November/2010) format. Do not leave blank.*

Table of Contents (TOC):

None

Full Prescribing Information:

Boxed Warning: *Not applicable*

1 Indications and Usage: *None*

2 Dosage and Administration: *None*

3 Dosage Forms and Strengths: *None*

4 Contraindications: *None*

5 Warnings and Precautions: *None*

6 Adverse Reactions: *Delete all extra spaces in Table 1. For the last statement under Clinical Trials Experience, "Adverse reactions that occurred during ULTRESA treatment were neck pain, nasal disorder, and nasal congestion," include the incidence rate.*

SEALD LABELING REVIEW

7 Drug Interactions: *None*

8 Use in Specific Populations: *None*

9 Drug Abuse and Dependence: *Not applicable*

10 Overdosage: *None*

11 Description: *None*

12 Clinical Pharmacology: *None*

13 Nonclinical Toxicology: *None*

14 Clinical Studies: *None*

15 References: *None*

16 How Supplied/Storage and Handling: *Delete the following statement: "Keep out of reach of children." This statement should appear in the Medication Guide, not prescribing information.*

17 Patient Counseling Information: *None*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN PHARMA US INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

JEANNE M DELASKO
08/02/2010

LAURIE B BURKE
08/03/2010

For Internal Use Only

Meeting Request Granted Form**
 (Use this form to document the meeting granted via telephone.)

Complete the information below and check form into DFS.

Application Type	NDA
Application Number	022222
DATE Sponsor informed of meeting granted	April 28, 2010
Sponsor was informed of: <ul style="list-style-type: none"> • date/time & meeting location • expected FDA attendees • meeting briefing package due date • number of copies 	<input type="checkbox"/> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes (date: _____) <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Other: please indicate <hr style="width: 20%; margin-left: 0;"/>
Project Manager	Elizabeth A.S. Ford, R.N.

Any follow-up letter must be checked into DFS as an advice letter, **NOT as a meeting request granted letter.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22222

GI-1

AXCAN
SCANDIPHARM
INC

ULTRASE MT 12, 18, 20
CAPSULES

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

/s/

ELIZABETH A FORD
05/05/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: May 3, 2010

From: Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Ali Niak, MD, Clinical Reviewer
Anil Rajpal, MD, Clinical Team Leader
Division of Gastroenterology Products (DGP)

Re: Labeling

Sponsor: Axcen Pharma, Inc.

Drug: Ultresa™ (pancrelipase)

NDA: 22-222

Supporting Doc: #51

Submission Date: April 6, 2010

Indication (proposed): treatment of exocrine pancreatic insufficiency caused by cystic fibrosis or other conditions

Proposed Dose: To be titrated; 3-5 doses per day with meals and snacks

Proposed Pediatric Dose: Per CFF guidelines (See Appendix I)

Dosage form: delayed-release capsules

Dosage strengths: 13,800 USP, 20,700 USP and 23,000 USP units of lipase

Route of Administration: oral

Consult Question:

Because the smallest dose capsule of this pancreatic enzyme replacement product (PEP) is 13,800 USP units of lipase, DGP requests guidance on labeling this product in younger/lighter pediatric patients.

Materials Reviewed:

- Ultresa™ proposed labeling
- Approved labeling Creon® (NDA 20-725), Pancreaze™ (22-523) and Zenpep® (NDA 22-210)
- PMHS Pancrease MT Consult (IND 74,893) December 2008

Regulatory Background:

Ultresa™, a PEP, is currently under NDA review with a PDUFA date of May 5, 2010.

In response to Agency request, the Sponsor submitted revised labeling and justification for the administration of Ultresa™ to infants on April 6, 2010.

Dosing of PEPs in Pediatric Patients:

Dosing recommendations for PEPs, including the three PEP products approved under the NDA process, Creon® (NDA 20-725), Pancreaze™ (22-523) and Zenpep® (NDA 22-210), are based on guidelines published after Cystic Fibrosis Foundation (CFF) Consensus Conferences^{1,2} and are based on age and weight (See Appendix I: PEP Dosing in Pediatric Patients).

Dosing in Infants up to 12 Months

Although infants and children less than 12 months require doses of 2000-4000 units of lipase per feeding, none of the available and approved PEP products has a formulation that is adequate to administer this quantity of lipase. Although Creon®, Pancreaze™ and Zenpep® have postmarketing requirements (PMRs) under PREA to develop a formulation that is able to deliver this quantity of lipase, the smallest Creon®, Pancreaze™ and Zenpep® formulations contain 6000, 4200 and 5000 units of lipase respectively. Therefore, to deliver PEPs to patients requiring doses less than 4200-6000 units of lipase, the current practice is to administer a portion of a capsule's contents².

Reviewer Comment:

Although FDA has determined that using a portion of the contents of a fixed-dose formulation is not acceptable, until a formulation is available that permits the administration of smaller quantities of lipase, administering half of a capsule of the smallest formulations of the currently approved products is a necessity to provide pancreatic enzyme replacement in some pediatric patients. However, attempting to divide a capsule in smaller fractions is impractical and potentially dangerous as discussed below.

Dosing of Ultresa™ in Infants:

The Sponsor states that each Ultresa™ contains 13,800 USP units of lipase distributed in 18-24 minitabets, and therefore, one third (approximately 6-8 minitabets) of the capsule contents approximates 4,000 lipase units and half of this amount (approximately 3-4 minitabets) of the capsule contents approximates 2,000 lipase units. The Sponsor concludes that the number of minitabets is sufficient to allow for counting and portioning of capsule contents.

Reviewer Comment:

Attempting to divide the smallest Ultresa™ capsule contents to deliver 2000-4000 units of lipase, the recommended PEP dose for infants, would involve dividing the capsule contents into sixths and is not acceptable. Because of the small size of the minitabets (approximately 2 mm), counting the minitabets and administering 3 or 4 individual tablets is not practical, and may result in inaccurate dosing, including overdosing, secondary to the need to administer only small fractions of the capsule contents. In addition, although unused portions of the capsule contents should be discarded after dosing, because a large percentage of the minitabets will not be administered, the remaining minitabets are likely to be saved for later use. Per the review team, stability data are not available for the minitabets, and therefore, because the minitabets are likely to have been released from the capsule in order to be portioned, the remaining capsule content potency may be reduced and less effective.

(b) (4)

Dosing in Children 12 months of age and older:

Weight based dosing is recommended by the CFF beginning at age 12 months. Patients older than 12 months and younger than 4 years are to receive starting doses of 1000 lipase units/kg of body weight per meal, but because the fat content of the diet tends to decrease after age 4 years², children older than 4 years should begin with 500 lipase units/kg per body weight per meal. The recommended snack dose for both age groups is half of the recommended meal dose.

Reviewer Comment:

As discussed, although administering a portion of a capsule has been determined by the Agency to be unacceptable, until PEP products are available in formulations that are able to deliver smaller quantities of lipase, the administration of half of a capsule's contents may be necessary for some pediatric patients. For use of Ultrase™ to be acceptable, a patient's recommended starting meal dose must be ~13,800 units of lipase, the quantity of lipase in the smallest capsule, as the snack dose will be half the meal dose, or ~6,400 units, or half the contents of the smallest Ultrase™ formulation. Because patients older than 12 months to 4 years must be at least 14 kg to receive 14,000 units of lipase as a starting meal dose, Ultrase™ would not be an appropriate product for use in patients weighing <14 kg in this age group. Similarly, because patients 4 years and older must weigh at least 28 kg to receive 14,000 units of lipase as a starting meal dose, Ultrase™ would not be appropriate for patients weighing <28 kg in this age group (Please see Appendix II Recommended Starting PEP Dosing for Girls 1-10 Years).

Labeling should reflect the limitations of the Ultrase™ formulations in providing adequate dosing in these age and weight cohorts, specifically, Ultrase™ should not be used in patients older than 12 months to 4 years weighing <14 kg, and in patients 4 years and older and weighing <28kg.

Conclusions and Recommendations:

The current formulations of Ultrase™ do not appear to be adequate to accommodate the doses recommended for infants up to age 12 months, patients older than 12 months weighing less than 14 kg, and patients 4 years and older weighing less than 28 kg. Until an age appropriate formulation is developed, as outlined in the PREA PMR, labeling should reflect these limitations in dosing and that attempting to divide a capsule's contents into small fractions is not recommended.

PMHS participated in labeling meetings, reviewed the draft labeling and agrees with the pediatric labeling information included.

APPENDIX I: PEP Dosing in Pediatric Patients (Cystic Fibrosis Foundation Guidelines^{1,2})

Standard meal dosing

- Infants - 2000 to 4000 lipase units per 120 ml of formula or per breast-feeding
- Children < 4 years old – starting dose of 1000 lipase units/kg per meal
- Children > 4 years old – starting dose of 500 lipase units/kg per meal (older children tend to ingest less fat per kilogram of body weight)

Snack dosing - ½ the standard dosing

Total daily dose - should reflect approximately three meals and two or three snacks per day². In addition, as mentioned above, to avoid fibrosing colonopathy, enzyme doses should not exceed 2500 lipase units/kg per meal, 10,000 lipase units/kg per day and 4000 lipase units/gram fat per day¹.

APPENDIX II: Recommended Starting PEP Dosing for Girls 1-10 Years*

*Based on CFF Guidelines²

Age (yrs)	Weight* (kg)	Weight Based Dosing ¹	Recommended Starting Dose per Meal	Recommended Starting Dose per Snack (½ meal dose)
			Lipase Units	Lipase Units
1	9.5	1000 lipase units/kg per meal	9,500	4,750
2	12	“	12,000	6,000
3	14	“	14,000	7,000
4	16	500 lipase units/kg per meal	8,000	4,000
5	18	“	9,000	4,500
6	20	“	10,000	5,000
7	23	“	11,500	5,750
8	26	“	13,000	6,500
8.5	28	“	14,000	7,000
9	29	“	14,500	7,250
10	33	“	16,500	8,250

*Girls' weights are based on the 50% weight for age³ and were chosen as girls typically weigh less than boys' of the same age.

REFERENCES

1. Borowitz D, Baker RD, Stallings V. Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis. *Journal of Pediatric Gastroenterology and Nutrition*. 2002;35:246–259.
2. Borowitz D, Grand RF, Durie PR and the Consensus Committee. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Peds*. 1995;127:681-84.
3. CDC Growth Charts page. Center for Disease Control Web site. <http://www.cdc.gov/growthcharts/>. Accessed April 27, 2010.

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

/s/

ELIZABETH L DURMOWICZ
05/03/2010

HARI C SACHS
05/04/2010
I agree with the labeling recommendations contained within this consult

LISA L MATHIS
05/12/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 15, 2010

To: Donna Griebel, MD
Director, Division of Gastroenterology Products

Through: Todd Bridges, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Ultresa (Pancrelipase) Delayed-release Capsules
Lipase 13,800 USP units;
Amylase 27,600 USP units; and
Protease 27,600 USP units

Ultresa (Pancrelipase) Delayed-release Capsules
Lipase 20,700 USP units;
Amylase 41,400 USP units; and
Protease 41, 400 USP units

Ultresa (Pancrelipase) Delayed-release Capsules
Lipase 23,000 USP units;
Amylase 46,000 USP units; and
Protease 46,000 USP units

Application Type/Number: NDA# 022222

Applicant: Axcan Pharma US, Inc.

OSE RCM #: 2009-942

1 INTRODUCTION

This review is written in response to a request from the Division of Gastroenterology Products for assessment of the labels and labeling for Ultresa (Pancrelipase) Delayed-release Capsules for their vulnerability to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) in our evaluation of the container labels, carton and insert labeling submitted March 10, 2010 (see Appendices A through D).

2.1 FDA'S ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

Because Pancrelipase is currently marketed, DMEPA conducted a search of the Adverse Events Reporting System (AERS) database to determine if medication errors related to the use of this product have been reported. DMEPA previously performed an AERS search for Pancrelipase in OSE review # 2008-1231, dated May 5, 2009. At that time, there were no cases of medication errors involving Pancrelipase. For this review, DMEPA performed an updated AERS search on March 8, 2010 for medication errors submitted for Pancrelipase since the aforementioned review using the following terms: Established Name "Pancrelipase", Verbatim Name "Pancrel%" and the MedDRA reactions, "Medication Errors" (HLGT) and "Product Quality Issues" (HLGT). The updated AERS search did not retrieve any cases of medications errors involving Pancrelipase.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 (*Comments to the Division*) for discussion during the review team's label and labeling meetings. Section 3.2 (*Comments to the Applicant*) contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Nitin M. Patel, OSE Regulatory Project Manager, at 301-796-5412.

3.1 COMMENTS TO THE DIVISION

- A. DMEPA notes in the Dosage and Administration Section of the Highlights of Prescribing Information and Full Prescribing Section that reference is made to (b) (4)
[REDACTED]
[REDACTED] this information should be deleted along with the statements which address appropriate administration of this drug product in this patient population. As of the team meeting March 24, 2010, we note that the final disposition of dosing in this population has not been resolved.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

DMEPA also notes that the strengths proposed may not cover all children older than 12 months and younger than 4 years. Some doses may require a lower strength than supplied (e.g., lower than 13,800 units of lipase). As such, there would be instances where the lipase dose for this age group may not be feasible with this product as well. At the labeling meeting held April 14, 2010, a suggestion was made to allow dosing in this population but to avoid dosing below 13,800 units USP lipase. DMEPA would be in agreement with this decision.

3.2 COMMENTS TO THE APPLICANT

- A. All Container Labels and Carton Labeling (100 count, 500 count, 12 count professional)
- 1) We note that the logo to the left of the proprietary name is more prominent than other more important information such as the established name and statements of strength. Decrease the prominence of this logo.
 - 2) We note that the white and grey text is difficult to read. To improve the readability, revise the labels and labeling so that there is greater contrast between the text and the background.
 - 3) The green font color used for the proprietary name is also used as the differentiating color for the 23,000 unit lipase product. This color overlap lessens the impact of using different colors as a tool to identify different strengths. Therefore, we recommend that you ensure that the color of the proprietary name is not the same as any color used for product strength differentiation.
 - 4) We note the established name lacks prominence. Increase the prominence of the established name such that it is at least half as large as the letters comprising the proprietary name and with a prominence commensurate to the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features pursuant to 21 CFR 201.10 (g)(2).
 - 5) Revise all labels and labeling so they contain the dosage form, “Delayed-release Capsules”.
 - 6) Include the bolded statement: “Ultresa capsules and capsule contents should not be crushed or chewed”.
 - 7) The amylase and protease strengths should be presented in the same size, type and weight font as that of lipase.
 - 8) In areas where the proprietary and established names are presented, the statements of strength should also be stated. For example, on the 100 count carton labeling, the proprietary and established names are presented on the side and back panels without statements of strength for lipase, amylase and protease.
 - 9) Where space allows, ensure that the Medication Guide statement is located on the principle display panel as to be in a prominent and conspicuous location pursuant to 21 CFR 208.24 (2)(d).
 - 10) Although your labels and labeling contain the required statement alerting the dispenser to provide the Medication Guide with the product for all strengths, we recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- a. “Dispense the enclosed Medication Guide to each patient.” or
 - b. “Dispense the accompanying Medication Guide to each patient.”
- 11) Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:
- a. A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily (a monthly supply is 30 tablets).
 - b. A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
- 12) To simultaneously emphasize the importance of the active ingredients along with the use of lipase-based dosing, add a box around the strengths and maintain the color block for the lipase content.

B. Container Labels and Carton Labeling (100 count and 500 count)

- 1) We note that the statement ‘Keep out of Reach of Children’ is stated twice, which is redundant. Revise the label to present the statement once. This will decrease label clutter and allow space so that other statements can be increased in size.
- 2) We note that you have included some product administration instructions on the side panel for patients who have difficulty swallowing. However, the instructions are not complete. Revise to include all administration instructions or delete this incomplete information.

(b) (4)

APPEARS THIS WAY ON ORIGINAL

4 REFERENCES

ADVERSE EVENTS REPORTING SYSTEM (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

7 Page(s) 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-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

DENISE V BAUGH
04/15/2010

DENISE P TOYER
04/15/2010

CAROL A HOLQUIST
04/15/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

******Pre-decisional Agency Information******

Memorandum

Date: March 9, 2010

To: Elizabeth Ford, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Shefali Doshi, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Robert Dean, DTC Group Leader
Wayne Amchin, Regulatory Health Project Manager
DDMAC

Subject: NDA 22-222

DDMAC labeling comments for Ultresa[®] (pancrelipase) delayed release capsules

In response to DGP's November 18, 2009, consult request, DDMAC has reviewed the draft labeling (PI, Carton and Container labeling and Medication Guide) for Ultresa[®] (pancrelipase) delayed release capsules (NDA 22-222). DDMAC's comments on the PI and Medication Guide are based on the proposed draft marked-up labeling titled "sponsor version 7-14-09 with track changes from FDA version 9-9-09.doc" that was modified in the DGP e-room on March 2, 2010, at 9:55 am.

DDMAC's comments on the PI and Medication Guide are provided directly in the marked-up document attached (see below). Please also see below for DDMAC's comments on the Carton and Container labeling.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI or Carton and Container labeling, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

Carton and Container Labeling

DDMAC has reviewed the following materials, accessed via the DGP e-room on March 9, 2010. These documents were last modified on July 15, 2009:

- labels-ultresa.pdf
- labels-^{(b) (4)}.pdf

General Comments

- The proposed labels state, ^{(b) (4)}
" We recommend that this statement be revised to be consistent with the final approved PI.

13 Page(s) 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-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

KATHLEEN KLEMM

03/09/2010

We hid track changes and other reviewer's comments so that our comments are easier to read.

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-222
APPLICANT	Axcan Scandipharm, Inc.
DRUG NAME	TRADENAME (pancrealipase)
SUBMISSION DATE	November 5, 2009
SEALD REVIEW DATE	March 4, 2010
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

15 pages of draft labeling have been withheld as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22222	ORIG-1	AXCAN SCANDIPHARM INC	ULTRASE MT 12, 18, 20 CAPSULES

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

/s/

JEANNE M DELASKO
03/04/2010

LAURIE B BURKE
03/04/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 3, 2009

To: Anna Simon, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Shefali Doshi, Regulatory Review Officer, DDMAC
Robert Dean, DTC Group Leader, DDMAC
Lisa Hubbard, Professional Group Leader, DDMAC
Wayne Amchin, Project Manager, DDMAC

Subject: NDA 22-222

DDMAC labeling comments for Ultrase MT (pancrelipase) Delayed Release Capsules
(Ultrase MT)

We acknowledge receipt of your May 21, 2009, consult request for the proposed product labeling for Ultrase MT, NDA 22-222. DDMAC was notified on July 28, 2009, by Anna Simon that final labeling negotiations would not be initiated during the current review cycle and that a Complete Response letter would be issued. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Katie Klemm at 301.796.3946 or
Kathleen.Klemm@fda.hhs.gov.

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

/s/

KATHLEEN KLEMM
09/03/2009

Review of Consultation Request

Consultation Sent By: Anna Simon, RPM/DGP
Anil Rajpal, MO/DGP

Date Sent: May 21, 2009

Date Received by MO: May 27, 2009

Date Review Completed: June 1, 2009

Background: The Division of Gastroenterology Products is performing an evaluation of Ultrase MT, a pancreatic enzyme product (PEP), with microbial contamination. PEPs are used to treat exocrine pancreatic insufficiency in patients with various diseases and conditions; two of the most common are cystic fibrosis (CF) and chronic pancreatitis. Many of the patients may be chronically ill and thus potentially immunocompromised. The drug product is a PO capsule, and patients typically take two to seven capsules, four to six times a day. The inspection of an API manufacturer identified the presence of several types of bacteria (*Bacillus cereus*, *B. thuringiensis*, *B. sphaericus*, *Eikenella corrodens*, and *Enterobacter cloacae*). Some of the counts exceeded particular specifications, so DGP is requesting advice from DAIOP regarding the possible risks associated with use of the contaminated product.

Comments: *Bacillus cereus* is well known as an etiologic agent of two distinct food poisoning syndromes: an emetic type (short-incubation) and a diarrheal type (long-incubation). Both syndromes occur following ingestion of contaminated food even after normal cooking. When the food is improperly stored, the surviving spores germinate, and manifestation of symptoms is the result of toxin production. Significant numbers of the organism (typically on the order of $>10^5$ colony forming units [CFU]/g, but as little as 10^3 have been observed as well) and detection of the emetic toxins and/or enterotoxins in consumed food are often observed in foodborne-illness investigations. Food poisoning may occur in normal and immunocompromised hosts. In normal hosts, *B. cereus* does not typically disseminate when ingested orally and the illness is usually self-limited (beginning as early as 1-6 hours of exposure and lasting usually no longer than 24 hours); however, rarely and in opportunistic situations (neutropenia, catheter-related or other major immune compromise), infection with *Bacillus* spp. may present with bacteremia and/or multisystem involvement.

Certain strains of *B. thuringiensis*, which are grouped together taxonomically with *B. cereus*, may also produce diarrheogenic toxins. Descriptions of the clinical significance of *B. sphaericus* are limited to case reports of bacteremia in patients with neutropenia, cancer and in bone marrow transplant patients.

Eikenella corrodens is classically described as a member of the "HACEK" group of organisms, which are fastidious organisms that have a propensity for infecting the heart valves, and is part of the endogenous flora in the mouth and upper respiratory tract. Infection with *E. corrodens*

typically occurs from human bite wounds or needle contamination (soft tissue infections or osteomyelitis).

Enterobacter cloacae strains are endogenous to intestinal flora, and infections (usually nosocomial; e.g., pneumonia, UTI, wound infections or catheter-related bloodstream infections) are common in patients receiving antimicrobial therapy. Although many strains of *E. cloacae* are capable of acquiring resistance to multiple antibiotics, its intrinsic virulence, especially when inoculation occurs perorally, has not yet been described in much detail.

Conclusions: The contamination by these organisms varied by lot and stage of processing. The consequence of ingesting this drug product orally with the levels of contamination found is difficult to predict. Since most of these organisms are likely residua of the extraction process from the pancreas of pigs, it is not surprising the array of organisms that were found. These organisms are also typically found endogenously in the oral cavity, upper respiratory and gastrointestinal tracts of humans, so it may not necessarily constitute a significant risk for most immunocompetent individuals. Of the organisms found, the most concerning are the *Bacillus* spp., the effects of which might only predictably produce mild diarrhea. However, in patients with neutropenia, other major immunocompromise or anatomic derangements (as may be the case in patients with cancer or chronic pancreatitis), the risk could entail systemic illness. Since manufacturing levels exist for these particular organisms, and potentially immunocompromised patients may be exposed, the appropriate measures should be instituted to rectify this. Consider testing the final product for microbial and toxin contamination as well.

Benjamin Lorenz, M.D.
Medical Officer, HFD-520

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

/s/

Benjamin Lorenz
6/1/2009 02:28:13 PM
MEDICAL OFFICER

Thomas Smith
6/1/2009 02:29:27 PM
MEDICAL OFFICER

Kathrine Laessig
6/5/2009 09:21:32 AM
MEDICAL OFFICER

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

CLINICAL INSPECTION SUMMARY

DATE: February 21, 2008

TO: Maureen Dewey, M.P.H., Regulatory Project Manager
Joanna Ku, M.D., Clinical Reviewer
Division of Gastroenterology Products, HFD-180

FROM: Khairy W. Malek, M.D.

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: # 22-222

APPLICANT: Axcan Scandipharm, Inc.

DRUG: Ultrase MT (pancrelipase, USP) Capsule

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of exocrine pancreatic insufficiency caused by cystic fibrosis,
Chronic pancreatitis or other conditions.

CONSULTATION REQUEST DATE: November 21, 2007

DIVISION ACTION GOAL DATE: February 15, 2008

PDUFA DATE: April 1, 2008

I. BACKGROUND:

This NDA for Ultrase TM which is a pancrelipase enzyme product intended for the treatment of exocrine pancreatic insufficiency caused by cystic fibrosis and chronic pancreatitis.

Cystic fibrosis is a genetic disease which often results in exocrine pancreatic insufficiency (PI) which leads to non-digestion of fats and proteins. This leads to malabsorption of these nutrients and measurable steatorrhea (excessive amount of fat in the feces).

The drug is on the market for a long time and the submission of a new NDA follows FDA requirement due to substantial variations in drug potency among enzymes currently on the market. The proposed study was conducted to demonstrate the clinical efficacy and to investigate the safety of HP55, which is a new solvent-based coating agent used in the coating of the minitables. In this study, protocol # UMT20CF05-01, the efficacy and safety of Ultrase TM20 is compared to placebo. The primary efficacy endpoint is the coefficient of fat absorption between study drug and placebo.

Two sites were selected for inspection:

1. Site # 02: Theodore Liou, M.D., University of Utah School of Medicine, Salt Lake City, UT.
2. Site # 03: Steven Strausbaugh, M.D., Rainbow Babies and Children's Hospital Cleveland, OH.

Summary Report of U.S. Inspections

RESULTS:

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Theodore Liou, M.D., Site 02	Salt Lake City, UT	UMT20CF 05-01	January, 08 15-18	2/08/08	VAI
Steven Strausbaugh, M.D. Site 03	Cleveland, OH	UMT20CF 05-01	January, 08 14-18	1/30/08	NAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Protocol # UMT20CF05-01

1. Theodore Liou, M.D.

Site 02, Salt Lake City, UT-University of Utah.

- a. What was inspected: At this site seven subjects were randomized. The field investigator reviewed the records of all the subjects in the study.
- b. There was no limitations to the inspection.
- c. General Observations:
Inspection revealed many protocol violations for just 7 subjects in the study. Four subjects were allowed in the study before getting their fecal elastase results as a sign of pancreatic insufficiency: # 0201, 0202, 0203 and 0204. At the beginning of the study, the dietician was sick and clinical investigator allowed the study to proceed before getting another dietician. This resulted in poor dietary control and deviation from the protocol required 2 g of fat/per kg body weight (\pm 15%) for many subjects. In addition three subjects # 0204; 0205; and 0203 had poor dietary compliance during various Stabilization and Treatment periods.
- d. These violations would not affect the validity of the data or markedly affect the calculation of the coefficient of fat absorption which is the primary efficacy parameter.

The data from this site can be used in support of the NDA.

2. Steven Strausbaugh, M.D.

Site 03, Cleveland, OH.-Rainbow Babies and Children's Hospital
Pediatric Pulmonary Division

- a. What was inspected: At this site 6 subjects were enrolled, but 4 only completed the study. One subject on placebo dropped out because of discomfort and the other subject was discontinued by the CI because a stool collection was missed during the Comparison Phase. The field investigator reviewed the records of all subjects in the study.
- b. There was no limitation to the inspection.

c. General Observations:

The inspection revealed minor protocol violation: two subjects were enrolled before the results of the fecal elastase tests were received. The results were found later to be within the protocol requirement.

d. The data from this site can be used in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The violations described above will not affect the validity or reliability of the data. The data from the 2 inspected sites can be used in support of the NDA.

No follow-up is needed at this time.

{See appended electronic signature page}

GCPB Reviewer: Khairy W. Malek
Medical Officer

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Khairy Malek
2/21/2008 11:05:13 AM
MEDICAL OFFICER

Constance Lewin
2/21/2008 11:14:44 AM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-222 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Ultrase MT
Established Name: pancrelipase, USP
Strengths: MT 12, MT 18, MT 20 Capsules

Applicant: Axcan Scandipharm, Inc.
Agent for Applicant (if applicable): CanReg, Inc.

Date of Application: 9/28/2007
Date of Receipt: 10/1/2007
Date clock started after UN:
Date of Filing Meeting: 11/14/2007
Filing Date: 11/30/2007
Action Goal Date (optional): 3/15/2008 User Fee Goal Date: 4/1/2008

Indication(s) requested: **treatment of patients with exocrine pancreatic insufficiency caused by Cystic Fibrosis, chronic pancreatitis, or other related conditions**

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 7
Other (orphan, OTC, etc.) Fast Track

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

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

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

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

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

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

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

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

The applicant included a statement certifying that there are no relevant patents.

- Exclusivity requested? YES, Years **3** NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or **request for deferral**/partial waiver/full waiver of pediatric studies) included? YES NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

Deferral Request is not quite complete – additional information requested in 74 Day Letter.

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 41,387

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 3/13/2006 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 7/27/2006; 3/12/2007 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO

- | | | | | |
|--|-----|-------------------------------------|----|--------------------------|
| If no, did applicant submit a complete environmental assessment? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| If EA submitted, consulted to EA officer, OPS? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| ● Establishment Evaluation Request (EER) submitted to DMPQ? | YES | <input checked="" type="checkbox"/> | NO | <input type="checkbox"/> |
| ● If a parenteral product, consulted to Microbiology Team? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/18/2007

NDA #: 22-222

DRUG NAMES: ULTRASE MT

APPLICANT: Axcan Scandipharm, Inc,

BACKGROUND: Ultrase MT (pancrelipase) Capsules are orally administered capsules containing enteric-coated minitabets of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. The activities of the constituent enzymes in Ultrase MT Capsules are similar to endogenous pancreatic enzyme activities in that they hydrolize fats, proteins, and carbohydrates into smaller units to facilitate absorption.

ATTENDEES:

Julie Beitz, M.D., Office Director, ODE III
 Daniel Shames, M.D., Acting Division Director
 Anne Pariser, M.D., Clinical Team Leader
 Joanna Ku, M.D., Medical Officer
 Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader
 Tien-Mien Chen, Ph.D., Clinical Pharmacology Reviewer
 Gibbes Johnson, Ph.D., Chief, Laboratory Supervisor, TBP
 Wei Guo, Ph.D., Product Reviewer
 Ennan Guan, Ph.D., Product Reviewer
 Mike Welch, Ph.D., Biostatistical Team Leader
 David Joseph, Ph.D., Pharmacology Reviewer
 Sushanta Chakder, Ph.D., Supervisory Pharmacologist
 Stephen Langille, Ph.D., Microbiology Reviewer
 Sally Loewke, M.D., Office of Unapproved Drugs
 Nancy Boocker, J.D., Office of Regulatory Policy

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

Discipline/Organization

Medical:
 Secondary Medical:
 Statistical:
 Pharmacology:
 Statistical Pharmacology:
 Chemistry:
 Environmental Assessment (if needed):

Reviewer

Joanna Ku, M.D.

 Mike Welch, Ph.D.
 David Joseph, Ph.D.

 Wei Guo, Ph.D. & Ennan Guan, Ph.D.

Biopharmaceutical:	Tien-Mien Chen, Ph.D.
Microbiology, sterility:	Stephen Langille, Ph.D.
Microbiology, clinical (for antimicrobial products only):	
DSI:	Khairy Malek, M.D.
OPS:	
Regulatory Project Management:	Maureen Dewey, MPH
Other Consults:	505(b)2: Don Hare; Kim Colangelo, Nancy Boocker DMETS/DDMAC Office of Unapproved Drugs: Sally Loewke, M.D.

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

CLINICAL FILE REFUSE TO FILE

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

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
If yes, was microbiology consulted for validation of sterilization?
YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):
Microbiology, Biopharmaceutics and PLR Labeling comments.

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

REQUEST FOR INFORMATION:
(Conveyed in 74 Day Letter)

1. Product Quality Microbiology

Provide a list of revised microbial limit specifications as well as the procedures and results of analytical method verification studies for microbial limits testing. Section 3.2.P.5 – Microbial Limits Tests – specifies a total plate count of no more than (b) (4) CFU/gram and the absence of *E. coli* and *Salmonella* species. Microbial limits specifications for nonaqueous preparations for oral use should comply with the USP <1111> recommended acceptance criteria of 10³ CFU/g for total aerobic microbial counts and 10² CFU/g for total combined yeast and mold count. Because the USP monograph for Pancrelipase capsules specifies the absence of *E. coli* and *Salmonella* species, these specifications should be retained.

2. Clinical Pharmacology:

We refer to our information request letter dated October 16, 2007. We acknowledge receipt of your responses to our letter on November 6, 2007. Based on your response, we recommend that you conduct *in vitro* stability testing with the foods that will be used for mixing that you intend to specify in the labeling, and that you test the stability at various time points following mixing to allow for better instructions to patients. Even if the mixture is to be “swallowed immediately,” stability testing is still necessary.

In your proposed labeling it is not clear to us what kinds of food, other than applesauce and gelatin, will be used for mixing. Not all foods may be compatible with your product, and some food may cause breakdown of your product during mixing. Only the types of food that have undergone stability testing may be included in the labeling.

3. Pediatric Studies

We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients younger than two years of age. You are requesting this deferral as the pediatric studies have not yet been completed.

Before we can make a decision on your deferral request, we need the following additional information:

- a. A description of your planned study/studies in pediatric patients two years of age and younger. This description should include a synopsis of the planned study protocol, which should contain information such as the study design (e.g., cross-over, open-label), number of patients to be included in the study, length of treatment, and endpoints to be assessed, among others.
- b. A projected date for the submission of the pediatric assessment.

Maureen Dewey, M.P.H.
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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

1. Does the application reference a listed drug (approved drug)? YES NO
The applicant lists a Reference Listed Drug NDA 20-580 Cotazym, however, the Agency will not rely on findings of that NDA for approval of this application.

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 20-580 Cotazym, however, the Agency will not rely on findings of that NDA for approval of this application.

3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

Ultrase MT (pancrelipase) Capsules are orally administered capsules containing enteric-coated minitablets of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease.

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

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

As discussed with ORP representative, the NDA 20-580 Cotazym is not considered “very similar.” YES NO

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

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

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

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

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

The applicant provided published literature for the Non-clinical Study Reports, however, the applicant does not per say rely on this literature to support approval.

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO
10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO
11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) **No relevant patents.** YES NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- Not applicable (e.g., solely based on published literature. See question # 7)
 - 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):
- NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
 - Written statement from patent owner that it consents to an immediate effective date upon

approval of the application.
Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES N/A

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES N/A

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

**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
12/6/2007 12:55:19 PM
CSO

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 22-222
Name of Drug: Ultrase MT 12, MT 18, MT 20
Applicant: Axcan Scandipharm Inc. / CanReg Inc.

Material Reviewed:

Submission Date(s): September 28, 2007

Receipt Date(s): October 1, 2007

Submission Date of Structure Product Labeling (SPL): September 28, 2007

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues have been identified in your proposed labeling.

Highlights Section:

- Remove the period after the required statement “**See 17 for PATIENT COUNSELING INFORMATION**”. [21 CFR 201.57(a)(14)]
- A revision date must appear at the end of the highlights. However, for a new NDA, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval. Please delete “Revised: 07/2007”. [21 CFR 201.57(a)(3)]

Full Prescribing Information (FPI):

- Regarding Contraindications, “theoretical” possibilities must not be listed (i.e., hypersensitivity). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. [See 21 CFR 201.57(a)(9) and (c)(5)]
- Do not refer to adverse reactions as “adverse events.” [see Section 6.6] Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
- Please change the subheading to title case **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**, not **13.1 Carcinogenesis, Mutagenesis, and Impairment Fertility**. [See 21 CFR 201.57(c)(14)]
- The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610) should be located after the Patient Counseling Information section, at the end of the labeling.

Recommendations

Please address the identified issues and re-submit labeling by January 8, 2008. This updated version of labeling will be used for further labeling discussions.

Maureen Dewey, MPH
Regulatory Project Manager

Supervisory Comment/Concurrence:

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: MDD/November 26, 2007

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

NDA 22-222

CSO Labeling Review

CSO LABELING REVIEW OF PLR FORMAT

**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
12/3/2007 04:17:23 PM
CSO

Julieann DuBeau
12/4/2007 04:19:52 PM
CSO