DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022222

NDA APPROVAL

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

Dear Dr. Rousseau:

Please refer to your New Drug Application (NDA) dated September 28, 2007, received October 1, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ultresa (pancrelipase) Delayed Release Capsules.

We acknowledge receipt of your amendments dated October 23, 2007; October 26, 2007; December 11, 2007; December 20, 2007; December 21, 2007; January 8, 2008; January 21, 2008; February 1, 2008; February 14, 2008; March 10, 2008; April 17, 2008; May 9, 2008; July 4, 2008; August 6, 2008; September 16, 2008; October 20, 2008; April 7, 2009; May 7, 2009; June 2, 2009; June 12, 2009; July 7, 2009; July 13, 2009; July 14, 2009; July 31, 2009; August 4, 2009; August 17, 2009; September 8, 2009; September 15, 2009; September 28, 2009; October 30, 2009; November 5, 2009; November 19, 2009; November 27, 2009; February 19, 2010; March 8, 2010; March 10, 2010; March 12, 2010; March 29, 2010; April 6, 2010; April 28, 2010; May 4, 2010; May 5, 2010; May 6, 2010; May 11, 2010; May 27, 2010; May 28, 2010; June 21, 2010; July 1, 2010; July 12, 2010; July 20, 2010; August 3, 2010; August 6, 2010; August 12, 2010; August 27, 2010; October 1, 2010; October 19, 2010; October 21, 2010; October 26, 2010; November 9, 2010; November 15, 2010; November 18, 2010; November 23, 2010; December 21, 2010; September 1, 2011; September 29, 2011; October 12, 2011; October 14, 2011; October 17, 2011; November 16, 2011; December 5, 2011; December 29, 2011; January 9, 2012; January 12, 2012; January 24, 2012; February 3, 2012; February 6, 2012; February 7, 2012; February 13, 2012; and February 28, 2012.

The September 1, 2011, submission constituted a complete response to our November 28, 2010, action letter.

This new drug application provides for the use of Ultresa (pancrelipase) Delayed Release Capsules for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on January 9, 2012, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022222**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 your pediatric study for patients 1 month to 1 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 of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This requirement is listed below.

1877-1 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.

Reports of this required pediatric postmarketing study must be submitted as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the serious risk of fibrosing colonopathy and the unexpected serious risk of transmission of viral disease to patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1877-2 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.

The timetable you submitted on February 28, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2012
Study Completion:	July 2022
Final Report Submission:	December 2022

1877-3 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.

The timetable you submitted on February 28, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2012
Study Completion:	June 2015
Final Report Submission:	February 2016

Submit the protocols to your IND 041387, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitments in your submission dated February 28, 2012. These commitments are listed below.

Drug Substance:

1877-4 Provide an assessment of the viral inactivation capability of the cleaning agents currently used in the drug substance manufacturing facility.

Final Report Submission by September 1, 2012

1877-5 Develop and validate an infectivity assay for PCV1 (Porcine Circovirus 1).

Final Report Submission by March 1, 2013

1877-6 Establish lot release specifications for PPV (Porcine Parvovirus) and PCV2 (Porcine Circovirus 2) for the drug substance.

Final Report Submission by March 1, 2013

1877-7 Perform additional monitoring of viral load entering the drug substance manufacturing process. The control program should include the selection of human pathogenic viruses for monitoring by qPCR. An appropriate control strategy should be proposed.

Final Report Submission by May 15, 2013

1877-8 Improve the sensitivity of the qPCR assays used for drug substance release testing in order to provide adequate assurance that released drug substance will not contain EMCV, HEV, PEV-9, Reo1/3, Rota, Influenza, VSV-IND, and VSV-NJ viruses. The revised assays, assay validation data, and acceptance criteria should be submitted to the Agency.

Final Report Submission by April 15, 2013

1877-9 Assess the risk to product quality associated with hokovirus, and submit a control strategy for mitigating the risk to product quality.

Final Report Submission by June 1, 2012

1877-10 Revise the animal surveillance program and the risk assessment evaluation for source animals to capture new and emerging viral adventitious agents. The proposed program should include an example using Ebola virus, recently described in pigs from the Philippines, to illustrate how these programs will be implemented.

Final Report Submission by March 15, 2013

1877-11 Provide the results of leachable/extractable studies for the intermediate storage containers, a risk assessment evaluation and a proposed strategy to mitigate the risk to product quality.

Final Report Submission by June 1, 2012

1878-12 Revise release specifications after 30 lots of 1208 and 1286 drug substance have been manufactured.

Final Report Submission by May 15, 2013

Drug Product:

1877-13 Revise release and stability specifications after 30 lots of drug product have been manufactured.

Final Report Submission by July 2014

1877-14 Include accelerated and/or stressed stability conditions in the annual stability protocol.

Final Protocol Submission by June 2012

1877-15 Submit a stability protocol used to evaluate and extend the maximum cumulative storage time of the drug substance and drug product. The protocol will provide for placing on stability the first lot of drug product manufactured using drug substance aged beyond drug product manufacturing experience.

Final Protocol Submission by June 2012

1877-16 Perform *in vitro* studies to determine the feasibility of administering the contents of Ultresa (pancrelipase) Delayed-Release Capsules through a gastrostomy tube.

Final Report Submission by March 2013

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The

status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated June 2, 2009, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Ultresa (pancrelipase) Delayed Release Capsules to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Package Insert and Medication Guide

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

/s/

JULIE G BEITZ
03/01/2012