# CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**125151/0**

# APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125151/0

Shire Human Genetic Therapies, Inc.
Attention: Nikhil S. Mehta, PhD
Vice President, Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Mehta:

We are issuing Department of Health and Human Services U.S. License No. 1593 to Shire Human Genetic Therapies, Inc., Cambridge, Massachusetts, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Idursulfase. Idursulfase is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). Idursulfase has been shown to improve walking capacity in these patients.

Under this license, you are approved to manufacture Idursulfase at your facility in Cambridge, Massachusetts. You may label your product with the proprietary name ELAPRASE, and will market it in 5 mL single-use vials containing 6 mg Idursulfase per 3 mL of solution.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and the submitted labeling (immediate container and carton labels submitted July 17, 2006). Marketing product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

The dating period for Idursulfase shall be 24 months from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be when stored at . We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Idursulfase to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Idursulfase, or in the manufacturing facilities.

We acknowledge your written postmarketing commitments as described in your letters of July 17, 2006, and July 19, 2006, as outlined below:

**Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.**

1. Shire commits to evaluating long-term safety and efficacy data in an observational survey (the Hunter Outcome Survey, HOS) of patients with Hunter syndrome being treated with ELAPRASE. In addition to clinical and laboratory tests that are part of standard medical care for patients with Hunter syndrome, the survey will collect data from patients on the six-minute walk test, from a subset of centers that will have the training and facilities to collect the data in a standardized and reproducible manner, and urinary GAG levels approximately every 6 to 12 months for at least 15 years. Assessments and data collected in the HOS will include those listed in Table 1 of the Hunter Outcome Survey protocol summary version 1.0, dated October 31, 2005, and in the Safety Specification and Pharmacovigilance Plan documented in the ELAPRASE BLA. For pediatric patients in the HOS, data to be collected will include standardized and replicated height, weight, and head circumference measurements in conjunction with deformity assessments and patients method of feeding. The survey will be designed to take advantage of any opportunity to evaluate the effect of ELAPRASE on female reproduction, pregnancy, and lactation. The HOS data will be analyzed at yearly intervals and the results will be submitted in annual reports for BB-IND — A study protocol will be submitted to FDA by November 30, 2006, for concurrence, and the study will be initiated by March 31, 2007. The final study report under this survey will be submitted to FDA by September 30, 2022.

2. Shire commits to conducting a study to evaluate pharmacokinetics, pharmacodynamics, and safety in at least 18 children 5 years of age and under treated with ELAPRASE for at least 6 months. In this population, pharmacodynamics will include urinary GAG levels and changes in liver and spleen volumes. The study will assess routine developmental milestones and growth. The study will collect data on respiratory infections, surgical interventions (e.g., PE tubes and adenoidectomy), hearing loss, serious or severe infusion reactions, and other serious adverse events. The study may be conducted as a separate study or as a sub-study under a special protocol within the Hunter Outcome Survey. A study protocol will be submitted to FDA by November 30, 2006, for concurrence. The study will be initiated by March 31, 2007, enrollment will be completed by December 31, 2007, and a final study report will be submitted to FDA by June 30, 2009.

3. Shire commits to submit the final study report from study TKT018, titled "An Open-Label Maintenance Clinical Study of Iduronate-2-Sulfatase Replacement Therapy in Patients with MPS-II," to FDA by December 31, 2007.

4. Shire commits to completing study TKT024EXT, titled "An Open Label Extension study of TKT024 Evaluating Long-term Safety and Clinical Outcomes of MPS II Patients Receiving I2S Enzyme Replacement Therapy." This study is to be completed by December 31, 2007, and a final study report will be submitted to FDA by August 31, 2008. Safety data will be submitted in annual reports under BB-IND — until study completion.

5. Shire commits to test and provide data from study TKT024 and from the first 2 years of study TKT024EXT from patient samples that are positive in the screening assay, in the inhibition-of-entry neutralization assay. The information will be submitted to FDA by September 30, 2007.

6. Shire commits to track binding and neutralizing antibodies using sensitive and validated assays over an extended time period to assess the loss of antibodies (immunologic tolerance) to ELAPRASE. Individual patient data should be provided as a function of time and a correlation of antibody status with clinical efficacy and GAG levels provided. This information will be submitted to FDA by December 31, 2008.

7. Shire commits to initiate a Segment III prenatal and postnatal study in rats by January 31, 2007, and submit the full report of the study to FDA by January 31, 2008. This study should be preceded by a dose ranging study. The highest dose selected should either produce mild toxicity of or should be the maximum feasible dose. Prior to initiating the Segment III study, Shire will determine (1) the tissue distribution of the product in pregnant rats to determine its placental and fetal disposition, and (2) its excretion in milk of lactating rats. This information is pivotal in the interpretation of the results of the Segment III study.

**Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.**

8. Shire commits to develop, describe, and provide validation data for a neutralizing assay that can detect the presence of antibodies that inhibit the entry of idursulfase into cells. This information will be submitted to FDA by May 31, 2007.

9. Shire commits to provide complete validation data for the Conformation Specific Assay (CSA), particularly as regards sensitivity (ng/ml) and specificity in terms of anti-idursulfase antibodies. This information will be submitted to FDA by December 31, 2006.

10. Shire commits to fully validate an IgE assay for detection of anti-idursulfase antibodies. This information will be submitted to FDA by June 30, 2007.

11. Shire commits to investigate and provide data on the nature of the genetic mutations of iduronate-2 sulfatase in a subset of patients in studies TKT024, titled "A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Clinical Study Evaluating the Safety and Efficacy of Weekly and Every Other Week Dosing Regimens of Iduronate-2-Sulfatase Enzyme Replacement Therapy in Patients with MPS II" and TKT024EXT, titled "An Open Label Extension study of TKT024 Evaluating Long-term Safety and Clinical Outcomes of MPS II Patients Receiving I2S Enzyme Replacement Therapy" and to correlate findings with

the level of endogenous enzyme levels, the antibody response (binding, neutralizing and IgE), and clinical outcome. This information will be submitted to FDA by January 31, 2008.

12. Shire commits to develop and implement an improved — assay for drug product release and stability testing. Results and proposed specifications will be submitted to CDER by May 31, 2007.

13. Shire commits to develop and implement an improved enzyme potency assay which The assay will be used for drug substance and product release and stability testing. Results and proposed specifications will be submitted by January 31, 2008.

14. Shire commits to a laboratory scale study to support the maximum cumulative hold time for all in-process intermediates in the commercial purification process of the drug substance. Results from this study will be submitted by January 31, 2007.

15. Shire commits that an action limit for the appearance of any new — will be added to the — assay. The revised drug product specification will be submitted by January 31, 2006.

16. Shire commits that an — will be added to the drug product release specifications. The revised specifications will be submitted by September 30, 2006.

17. Shire commits that a qualification study will be conducted to assess the sensitivity of the currently employed — test method for — against the — test. The report will be submitted by June 30, 2007.

18. Shire commits that the analytical methods for the qualification and release of future reference standards will be re-evaluated and the acceptance criteria revised and tightened. The revised protocol will be submitted as a supplement by June 30, 2009.

19. Shire commits that all acceptance criteria for release of idursulfase drug substance and product manufactured at commercial scale will be evaluated and revised as necessary. The results together with any revisions to the specifications for drug substance and product will be submitted by September 30, 2008.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125151. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125151. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**

- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug

Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Sincerely,

Julie Beitz MD 7-24-06

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