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

APPLICATION NUMBER:

125151/0

MICROBIOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: May 12, 2006
To: Administrative File, **STN 125151** / 0
From: Patricia F. Hughes, Ph.D., CSO, CDER/OC/DMPQ TFRB, HFD-328
Through: Brenda Uratani, Ph.D., Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328
Subject: **Review of Biological License Application (BLA):** New BLA for the — treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPSII)
US License #1593
Applicant **Shire Human Genetic Therapies (formerly, Transkaryotic Therapies, Inc.), FEI 1000513202**
Product **Idursulfase**
Indication Treatment of patients with Hunter syndrome
Due date: 25 May 2005

Recommendation: The application, as amended, is recommended for approval from a CMC microbiology product quality perspective.

Review Summary

Shire Human Genetic Therapies (formerly, Transkaryotic Therapies, Inc.) (TKT) submitted a BLA for the license Idursulfase (iduronate-2-sulfatase). The drug substance is manufactured at by Shire at the TK3 facility, 205 Alewife Brook Parkway, Cambridge, MA 02138, USA. Quality control, in-process testing, lot release and stability testing are performed by Shire's Quality Control Department or by audited contract laboratories listed in the BLA Table 2.3.S.2-1.

Drug Product is manufactured by an —). The drug product is tested for release at Shire (TK8), 700 Main Street, Cambridge, MA 02139, USA.

The BLA was submitted in an electronic Common Technical Document (CTD) format.

The review covers the microbiological control aspects of the drug substance manufacturing process and drug product and includes an evaluation of microbial test methods used to manufacture and release product. The stability of the drug product is also evaluated from a microbiology product quality perspective.

Two amendments were submitted to respond to requests for information during this review (record of telephone conversations are attached to the review) and another amendment was submitted in response to 483 observations made during the inspection of the drug substance manufacturer, TKT, in Cambridge, MA. The amendments related to this review are:

BLA 125151/0/0002 dated 18 Jan 2006 for information on the Pre-license inspection
BLA 125151/0/008 dated 19 Apr 2006 in response to 483 observations
BLA 125151/0/009 dated 05 April 2006 for CMC information
BLA 125151/0/014 dated 15May 2006 for CMC information

The inspection of the facility(s) was conducted by Patricia F. Hughes, Ph.D., OC/DMPQ/TFRB, Serge Beaucage, Ph.D. and Kathy Lee from OBP/DTP. FDA Form 483 was issued to the firm on March 24, 2006 with six (6) observations. A response to the 483 observation was received on 19 April 2006 in amendment BLA125151/0/008, reviewed, and deemed adequate by the Agency. The inspection observations are described in the EIR. See the Conclusion section of this review for the individual inspectional items.

Review Narrative

Drug Substance

Idursulfase is a recombinant form of the human lysosomal enzyme iduronate-2-sulfatase (I2S). Idursulfase is produced in a — human cell line —
— The enzyme —
—
a 525 amino acid glycoprotein with a molecular weight of approximately 76 kDa. The enzyme contains 8 N-linked glycosylation sites occupied by a complex, — oligosaccharide chains.

Manufacturers

The drug substance is manufactured by:

Shire at the TK3 facility,
205 Alewife Brook Parkway,
Cambridge, MA 02138,
USA.
FEI 1000513202

Quality Control and Analytical Departments of Shire are located at:

TK8
700 Main Street
Cambridge, MA 02139
USA

Warehouse Operations are located at:

TK9
33 Brighton Street

Belmont, MA 02478
USA

Offices in support of manufacturing and quality operations are located at:

TK4
185 Alewife Brook Parkway
Cambridge, MA 02138
USA

TK8
700 Main Street
Cambridge, MA 02139
USA

Quality control testing is performed by Shire's Quality Control Department or by the following contract laboratories:

Compliance checks were conducted by DMPQ/IPCB on 12/22/05 regarding the facilities:

"The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the compliance check request below. There are no pending or ongoing compliance actions that would prevent approval of STN 125151/0 at this time. The inspection and compliance history has been reviewed and found to be acceptable for the sites listed below:"

Firm	Classification	Inspection Date	Profile
	NAI	05/06/05	
	VAI	04/02/03	
	VAI	08/09/05	
	NAI	05/12/05	
	VAI	08/10/05	
	NAI	05/19/04	
	NAI	02/08/04	

The following firms had no inspectional data in FACTS or EES:

—, Registration number is pending
Transkaryotic Therapies, Inc. FEI 1000513202 was inspected March 20-24, 2006

Review comments: The compliance checks are adequate for all facilities involved in Idursulfase manufacturing. The registration number for the — facility is pending and this facility is engaged in —

Satisfactory

27 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling