

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

APPLICATION NUMBER:

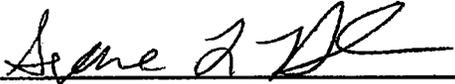
125151/0

**ADMINISTRATIVE DOCUMENTS AND
CORRESPONDENCE**



Debarment Certification Statement

This certifies that Transkaryotic Therapies, Inc., a wholly owned subsidiary of Shire Pharmaceuticals Group plc, 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.



Suzanne L. Bruhn, PhD
Vice President, Global Regulatory Affairs

12/2/05
/Date

700 Main Street
Cambridge, MA 02139



08 Nov 2005

Re: Debarment Certification

Dear _____

Shire Human Genetic Therapies, formerly Transkaryotic Therapies, Inc. ("TKT") is in the process of preparing various regulatory submissions in support of idursulfase (I2S) for the treatment of Hunter Syndrome. We at Shire appreciate your role in the achievement of this milestone. We respectfully request your acknowledgement of the statement below, as part of our effort to demonstrate our ongoing commitment to compliance.

Sincerely,

A handwritten signature in cursive script, appearing to read "Andrea Kean".

Andrea Kean
QA Manager, Contract Manufacturing

Neither _____ nor any of its employees or agents performing activities in support of idursulfase, is under investigation by any regulatory authority, including the FDA, for debarment action or is presently debarred.

Acknowledged and Agreed: _____

By: _____

Name: _____

Title: _____

700 Main Street
Cambridge, MA 02139



07 Nov 2005

Re: Debarment Certification

Dear _____

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QA Manager, Contract Manufacturing

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Acknowledged and Agreed:

By _____

Name: _____

Title: _____

BLA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

BLA 125151/0	Efficacy Supplement Type	Supplement Number	
Drug: Idursulfase		Applicant: _____	
RPM: Cristi Stark		HFD-180	Phone # (301)796-1007
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) N/A (BLA's are under the PHS Act)</p> <p>(This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	
❖ Application Classifications:			
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
• Chem class (NDAs only)		N/A	
• Other (e.g., orphan, OTC)		Orphan	
❖ User Fee Goal Dates		August 24, 2006	
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart E <input type="checkbox"/> 21 CFR 601.41 (accelerated approval) <input type="checkbox"/> 21 CFR 601.42 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
• User Fee		<input type="checkbox"/> Paid UF ID number _____	
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)			
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

<ul style="list-style-type: none"> This application is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Exception for review (Center Director's memo) 	
<ul style="list-style-type: none"> OC clearance for approval 	Compliance check complete
<ul style="list-style-type: none"> ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. 	<input checked="" type="checkbox"/> Verified
<ul style="list-style-type: none"> ❖ Patent 	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input type="checkbox"/> Verified (N/A under PHS Act)
<ul style="list-style-type: none"> Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified (N/A under PHS Act) 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) (N/A under PHS Act)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> (N/A under PHS Act)
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified <input type="checkbox"/> (N/A under PHS Act) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> (N/A under PHS Act) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> (N/A under PHS Act) <input type="checkbox"/> Yes <input type="checkbox"/> No

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

(N/A under PHS Act)

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

(N/A under PHS Act)

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(N/A under PHS Act)

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	N/A – only orphan exclusivity under the PHS Act
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Project manager – 1/19/06 (filing meeting)

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA () CR
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release (X) Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	7/14/06
• Original applicant-proposed labeling	11/23/05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	DMETS – 4/18/06 DMETS – 6/30/06 DDMAC – 5/11/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Naglazyme, Aldurazyme, Cerezyme, Fabrazyme, Myozyme
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	11/23/05, 7/17/06
• Reviews	Project manager – 7/18/06 (see project management review tab)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See AP letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	5/9/06, 5/11/06, 5/26/06, 6/6/06, 6/15/06, 6/23/06, 6/30/06, 7/11/06 (2), 7/13/06, 7/14/06 (3), 7/17/06
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Ack letter, 60-day letter, 74-day letter, major amendment letter
❖ Memoranda and Telecons	1/3/06, 4/5/06
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	12/10/02
• Pre-BLA meeting (indicate date)	10/26/05
• Pre-Approval Safety Conference (indicate date; approvals only)	7/17/06 (no minutes)
• Other	Pre-IND – 7/1/99
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Dir pharm/tox – 5/9/06 Sup pharm/tox – 5/7/06 Clin team leader – 7/24/06 Div Dir – 7/24/06 Off Dir – 7/24/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	DPAP – 4/4/06 Peds – 4/24/06 Clinical – 7/24/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Incorporated in clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	OSE/PP – 4/13/06
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A – orphan product
❖ Demographic Worksheet (NME approvals only)	Not required yet
❖ Statistical review(s) (indicate date for each review)	5/9/06
❖ Biopharmaceutical review(s) (indicate date for each review)	5/19/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	4/3/06
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	Immunogenicity – 7/3/06 Drug substance – 7/18/06 Drug product – 7/18/06 Potency – 7/18/06 CellBanks – 5/17/06 ProdCellLine – 7/18/06
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Incorporated in facility review
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	TFRB – 5/28/06
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed – under facility review () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	5/7/06
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125151/0 Product: Idursulfase Applicant: TKT

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 1/10/06 Committee Recommendation (circle one): File RTF

RPM: [Signature] 1/18/06
(Signature/date)

Attachments:

Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

Part A – RPM

Part B – Product/CMC/Facility Reviewer(s): _____

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____

Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____

Memo of Filing Meeting

STN 125151/0

Product 1 durvulfase

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?		If not, justification, action & status
Cover Letter	<input checked="" type="radio"/>	N	
Form 356h completed	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/>	N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	Y	<input checked="" type="radio"/>	N/A
Comprehensive Table of Contents	<input checked="" type="radio"/>	N	
Debarment Certification with correct wording (see * below)	<input checked="" type="radio"/>	N	
User Fee Cover Sheet	<input checked="" type="radio"/>	N	
User Fee payment received	Y	<input checked="" type="radio"/>	not needed - orphan
Financial certification &/or disclosure information	<input checked="" type="radio"/>	N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/>	N	(claims categorical exclusion)
Pediatric rule: study, waiver, or deferral.	Y	<input checked="" type="radio"/>	not needed - orphan
Labeling:	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> PI -non-annotated	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> PI -annotated	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> PI (electronic)	<input checked="" type="radio"/>	N	(did include SPL)
<input type="checkbox"/> Medication Guide	Y	<input checked="" type="radio"/>	N/A
<input type="checkbox"/> Patient Insert	Y	<input checked="" type="radio"/>	N/A
<input checked="" type="checkbox"/> package and container	<input checked="" type="radio"/>	N	(carton & container)
<input type="checkbox"/> diluent	Y	<input checked="" type="radio"/>	N/A
<input checked="" type="checkbox"/> other components	<input checked="" type="radio"/>	N	(vial & risk management plan)
<input checked="" type="checkbox"/> established name (e.g. USAN)	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> proprietary name (for review)	<input checked="" type="radio"/>	N	requesting tradename review - ELA (TRASE)

* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. 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 the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,..."

Examples of Filing Issues	Yes?		If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> legible	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> compatible file formats	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/>	N	
<input checked="" type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/>	N	

STN 125151/0

Product *Idursulfase*

Examples of Filing Issues	Yes?		If not, justification, action & status
<input checked="" type="checkbox"/> protocols for clinical trials present	<input checked="" type="checkbox"/> Y	N	
<input checked="" type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="checkbox"/> Y	N	
companion application received if a shared or divided manufacturing arrangement	Y	<input checked="" type="checkbox"/> N	N/A
if CMC supplement: <input type="checkbox"/> description and results of studies performed to evaluate the change <input type="checkbox"/> relevant validation protocols <input type="checkbox"/> list of relevant SOPs	Y Y Y	<input checked="" type="checkbox"/> N N N	N/A - this is an original application
if clinical supplement: <input type="checkbox"/> changes in labeling clearly highlighted <input type="checkbox"/> data to support all label changes <input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	Y Y Y	<input checked="" type="checkbox"/> N N N	N/A - this is an original application
if electronic submission: <input checked="" type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	<input checked="" type="checkbox"/> Y	N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? _____

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: _____

Recommendation (circle one) File RTF

RPM Signature: *[Signature]* Branch Chief concurrence: *[Signature]*
for B. Strongin
 1/19/06

A

17 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y N	
Non-clinical overview [2.4]	<input checked="" type="radio"/> Y N	
Non-clinical summary [2.6]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Pharmacology	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Pharmacokinetics	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Toxicology	<input checked="" type="radio"/> Y N	

CTD Module 4 Contents	Present?	If not, justification, action & status
Module Table of Contents [4.1]	<input checked="" type="radio"/> Y N	
Study Reports and related info. [4.2]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Pharmacology	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Pharmacokinetics	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Toxicology	<input checked="" type="radio"/> Y N	
Literature references and copies [4.3]	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	<input checked="" type="radio"/> Y N	
for each non-clinical laboratory study, either a statement that the study was conducted in compliance with the good laboratory practice requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance	<input checked="" type="radio"/> Y N	

STN 125151/0Product Idursulfase

Part D Page 1

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical)**Reviewers**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	(Y) N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	(Y) N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	(Y) N	
<input type="checkbox"/> Clinical Safety	(Y) N	
<input type="checkbox"/> Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
<input type="checkbox"/> Biopharmaceutic	(Y) N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y) N	
<input type="checkbox"/> Pharmacokinetics (PK)	(Y) N	
<input type="checkbox"/> Pharmacodynamic (PD)	(Y) N	
<input type="checkbox"/> Efficacy and Safety	(Y) N	
<input type="checkbox"/> Postmarketing experience	Y (N)	N/A
<input type="checkbox"/> Case report forms	(Y) N	
<input type="checkbox"/> Individual patient listings (indexed by study)	(Y) N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
<input type="checkbox"/> legible	(Y) N	
<input type="checkbox"/> English (or certified translation into English)	(Y) N	
<input type="checkbox"/> compatible file formats	(Y) N	
<input type="checkbox"/> navigable hyper-links	(Y) N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes/	No/Action & Status
<input type="checkbox"/> summary reports reference the location of individual data and records	(Y) N	
<input type="checkbox"/> protocols for clinical trials present	(Y) N	
<input type="checkbox"/> all electronic submission components usable	(Y) N	
statement for each clinical investigation:		
<input type="checkbox"/> conducted in compliance with IRB requirements	(Y) N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y (N)	N/A; As with other enzyme replacement therapies, drug-drug interactions are not expected. Therefore, no in vitro and no in vivo drug interaction studies were performed.
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Billing Issues	Yes?	Final action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y) N	Following pivotal phase II/III study TKTO24 scale increased to commercial-scale, comparability studied in TKTO24EXT, commercial-scale product introduced into TKTO18 also.
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electronic datasets complete & usable?	BIMO sites identified?
TKTO08	(Y) N	Y N NR	(Y) N	Y N NR
TKTO24	(Y) N	Y N NR	(Y) N	Y N NR
TKTO18-2yr	(Y) N	Y N NR	(Y) N	Y N NR
TKTO24EXT	(Y) N	Y N NR	(Y) N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

STN 125151/0

Product Idursulfase

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

Clinical Review

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y	<input type="radio"/> N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Study Reports and related information [5.3]	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Biopharmaceutic	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Pharmacokinetics (PK)	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Pharmacodynamic (PD)	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Postmarketing experience	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Case report forms	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> Individual patient listings (indexed by study)	<input type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y	<input type="radio"/> N	
Literature references and copies [5.4]	<input type="radio"/> Y	<input type="radio"/> N	

? ←

Examples of Filing Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y	<input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y	<input type="radio"/> N	

Examples of Filing Issues	Yes?	If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	(Y) N	
<input type="checkbox"/> protocols for clinical trials present	(Y) N	
<input type="checkbox"/> all electronic submission components usable	(Y) N	
statement for each clinical investigation:		
<input type="checkbox"/> conducted in compliance with IRB requirements	(Y) N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N N/A	None studied
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	<input checked="" type="radio"/> Y	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/> Y	N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/> Y	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/> Y	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
TKT024	<input checked="" type="radio"/> Y	N	Y	N	NR	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR
TKT024EXT	Y	<input checked="" type="radio"/> N	Y	N	NR	<input checked="" type="radio"/> Y	N	<input checked="" type="radio"/> Y	N	NR
TKT008	<input checked="" type="radio"/> Y	N	Y	N	NR	<input checked="" type="radio"/> Y	N	Y	<input checked="" type="radio"/> N	NR
TKT018	Y	<input checked="" type="radio"/> N	Y	N	NR	<input checked="" type="radio"/> Y	N	Y	<input checked="" type="radio"/> N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

STN 125151

Product Idursulfase

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Multiple horizontal lines for text entry.

Is clinical site(s) inspection (BiMo) needed?

Yes: We recommend Brazil, UNC, & Oakland.

3 sites to be inspected by DSI,

Is an Advisory Committee needed?

No

Recommendation (circle one): File RTF

Reviewer: [Signature] 01/19/06 Type (circle one): Clinical Clin/Pharm Statistical

Concurrence: Joanna Ku, MD

Branch Chief: [Signature] 1-10-06 Division Director: _____ (signature/ date)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: January 10, 2006
From: *Marlene G. Swider, RPM, ODE III, OGP, HFD-180*
To: The file (*STN 125151/0*)
Subject: Filing Meeting Minutes

Meeting Date: January 10, 2006

Time: 9:00 – 10:00

Location: WO Conf Room 5266

Firm: Transkaryotic Therapies, Inc. (TKT)

Product: Idursulfase (iduronate-2-sulfatase, I2S, DRX006A)

Proposed Use: For ~~the~~ treatment of patients with Hunter syndrome (*Mucopolysaccharidosis II, MPS II*).

Type of meeting: Filing Meeting

Meeting Purpose: To determine if BLA Supplement STN 125151/0 contains all the appropriate information for filing.

Discussion Items and Concerns:

All participants in the meeting introduced themselves.

Dr. Joanna Ku gave a well summarized description of the clinical data and pivotal study for this BLA in a handout provided to the participants during the meeting. She also detailed in her handout the nine sites selected: 3 of the sites provide only infusion to the patients; Brazil and Germany sites received the most funds and have the most data but already have being inspected. She suggested that the sites in North Carolina (UNC), Brazil and at Baylor College should be the ones inspected.

According to Dr. Ku, UNC has the highest enroller, principal investigator enroller, the most thorough testing and

Brazil site has the highest main site enroller,

Baylor College has an unusual pattern of “discarding” patients, i.e. 50% of the patients were enrolled but not selected to be randomized (6 out of 12 patients were enrolled but not randomized to enter into the study). This site has never been inspected.

Due dates for the submission were reminded to the reviewers as summarized in the agenda.

All participants agreed on filing the BLA but no form was received during the meeting. Also, Dr. Brian Harvey agreed on this being a 6-month review but no agreement was signed during the meeting. Clin/pharma commented on the commercial scale data submitted to be appropriate. Statistics was please with the excellent job done for the randomization of the data.

A 74-day letter in lieu of a 60-day letter was recommended by the product reviewers since they already have identified some deficiencies but would not be able to have the comments for this letter ready by January 23, 2006 (60 days from the submission date – November 23, 2005). Among the deficiencies identified was the need for more comparability and rigorous data.

No Advisory Committee is needed at this time. However, consults for pediatrics, pulmonary, safety and labeling need to be requested per Dr. Joyce Korvick and Dr. Brian Harvey request.

Dr. Joyce Korvick also requested that all the review memos be finalized soon since an office level signature is needed. April 13, 2006 was agreed as the date for the final reviews with the exception of Therapeutics Facility Review Branch (TFRB) review. Ms. Carolyn Renshaw requested more time for finalizing the Establishment Inspection Report since the inspection(s) are not being scheduled but by the end of March – after the mid-February mid cycle meeting.

Site for inspection –

TFRB agreed that they will be conducting the inspection at UNC Chapel Hill by the end of March.

Ms. Dianne Tesch requested to proceed with the scheduling of the inspection to Brazil but did not committed DFS since it depends on funds available.

Recommendations: Filing BLAs STN 103773/5138.

Issues Requiring Further Discussion:

Inspections sites and confirmation of inspections dates.

Action Items:

- 1) RPMs will follow up with the consult requests.
- 2) All the teleconference members not present during the meeting would receive

from the RPMs a copy of the handout given by Dr. Ku.

- 3) Product reviewers would provide an attendance list with their names and addresses where the handout can be sent to by the RPMs.
- 4) RPM would notify reviewers about the mid-cycle meeting date.
- 5) Reviewers need to provide their parts of the filing memo as soon as possible.
- 6) Dr. Brian Harvey's signature is needed for the approval of the 6-mo review granted.

Attendee List & Handout

Division of Gastroenterology Products
PROJECT MANAGER'S REVIEW

Application Number: STN 125151/0

Name of Drug: Idursulfase

Sponsor: Shire Human Genetic Therapies, Inc.

Material Reviewed:

Submission Date:

November 23, 2005 – original Carton and Vial Draft Labeling
April 26, 2006 – revised Carton and Vial Draft Labeling
June 2, 2006 – revised Carton and Vial Draft Labeling
July 17, 2006 – revised Carton and Vial Draft Labeling

Receipt Date:

November 23, 2005 – original Carton and Vial Draft Labeling
April 27, 2006 – revised Carton and Vial Draft Labeling
June 5, 2006 – revised Carton and Vial Draft Labeling
July 18, 2006 – revised Carton and Vial Draft Labeling

Background and Summary

STN 125151/0 for Idursulfase is an original application with a proposed indication for use as a treatment for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

Review

For the April 26, 2006 submissions of the carton and vial draft labeling:

I. Vial

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:
 - a. The proper name of the product – Idursulfase is displayed along with the proprietary name, Elaprase. This conforms to the regulation.
 - b. The name, address, and license number of the manufacturer – Shire Human Genetic

Therapies, Inc is the manufacturer of drug substance. The final drug product fill is handled through a contract manufacturer. The correct address per the 356h is not listed. The license holder, XXXX, is not listed (instead the STN number is listed). This does not conform to the regulation.

- c. The lot number or other lot identification – The lot number is located on the left hand side of the label. This conforms to the regulation.
 - d. The expiration date – The expiration date is located below the lot number. This conforms to the regulation.
 - e. The recommended individual dose, for multiple dose containers – This is for intravenous infusion (to be diluted) and for single use only. The statement “5 mL single use vial” is located at the center of the label. This conforms to the regulation. This is confusing text and could lead to a medication error (refer to DMETS review dated 4/18/06). A statement “for single use only” can be added to conform to the regulation as well.
 - f. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on center of the label. This conforms to the regulation.
 - g. If a Medication Guide is required under part 208 of the 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 – A Medication Guide is not required under 208.1 as this will not be used on an outpatient basis without direct supervision by a health professional. Therefore, this package label does not need to conform to the regulation.
2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This section does not apply.
 3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – The container does not bear a full label and will be enclosed in a package (carton). Please see comments under items 1 (a) - (g) above. Currently the vial label expresses the name (both proper and common), the lot number, and individual dose. It is missing the name of the manufacturer (as listed on the 356h), the address of

the manufacturer, and the license number. This does not conform to the regulation.

4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a partial label. Please see comments under items 1 - 3 above.
 5. Visual inspection. When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – A 5 mL vial will be used for containing the drug. The label length is approximately 2 5/8". There is a gap between the edges of the vial label and the gap runs the entire length of the vial to permit visual inspection of the contents. This conforms to the regulation.
- B. 21 CFR 610.61 Package label – This is a container label. Therefore, this does not need to conform to the regulation.
- C. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulations including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This is under one of the four categories of a "specified" biological product: Therapeutic DNA plasmid products; Therapeutic synthetic peptide product of 40 or fewer amino acids, Monoclonal antibody products for in vivo use; and Therapeutic recombinant DNA-derived products. Therefore the label does not need to conform to this regulation.
- D. 21 CFR 610.63 Divided manufacturing responsibility to be shown – This only has one manufacturer, Shire Human Genetic Therapies, Inc.. The final drug fill is performed by _____ under contract; however, Shire fits the requirements as the only manufacturer. Therefore, the label does not need to conform to this regulation.
- E. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. – The distributor is Shire Human Genetic Therapies, Inc. which is also the manufacturer. The manufacturer is not listed correctly, the address and license numbers are missing and do not conform with 21 CFR 610.60. As Shire is listed and is the distributor it is not an issue. Therefore, the label conforms with the regulation.
- F. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.

G. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter.
– The barcode is located on the right of the label. This conforms with the regulation.

H. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located above in the center of the label under “Rx Only”. It is noted as NDC 58092-700-01. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

I. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary name, Elaprase, and the established name, Idursulfase. Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.

J. 21 CFR 201.10 Drugs; statement of ingredients – The proprietary name is used in a larger size text when compared to the established name. The proprietary name, Elaprase, is size 15.23 pt font. The established name, Idursulfase, is size 7.69 pt font. Idursulfase is used in type at least half as large as the most prominent presentation of Elaprase. This conforms to the regulation. It is recommended that as the proprietary name is bolded, the established name should be bolded to avoid prominence of the proprietary name.

K. 21 CFR 201.25 Bar code label requirements – The bar code is located on the right of the label with sufficient white space surrounding to ensure for proper scanning. This conforms to the regulation.

L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only,” an identifying lot number, storage conditions, and reference to the package insert. Photostability studies are not complete for Idursulfase. Please refer to the chemistry, manufacturing, and controls reviews dated 7/18/06. An additional statement, “Protect from Light,” will need to be added to the label in order to conform with the regulation.

II. Carton

A. 21 CFR 610.60 Container Label – This is a package label. Therefore, this does not need to conform to the regulation.

B. 21 CFR 610.61 Package Label

a. The proper name of the product – The proper name, Idursulfase, is displayed on all four sides of the carton. In addition the proprietary name, Elaprase, is displayed prominently on the on all four sides of the carton above Idursulfase of the carton. This conforms to the regulation.

- b. The name, address, and license number of manufacturer – Shire Human Genetic Therapies, Inc. is the manufacturer. The correct address (as per the 356h) is not listed. Currently the logo (Shire Human Genetic Therapies) is listed. An addition of the word Inc or the full name of the manufacturer in a separate place will solve the issue. The license number is listed incorrectly. Instead of the STN number listed, the license placeholder, XXXX, should be listed. This does not conform to the regulation.
- c. The lot number or other lot identification – The lot number is listed on the bottom flap of the carton. This conforms to the regulation.
- d. The expiration date – The expiration date is listed below the lot number on the bottom flap of the carton. This conforms to the regulation.
- e. The preservative used and its concentration, of if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” – There are no preservatives used in the drug. The statement “Contains No Preservatives” is displayed on the side flap of the carton. This conforms to the regulation.
- f. The number of containers, if more than one – There is only one package container per drug. Each package contains one vial of drug. This conforms to the regulation. As a recommendation, the sponsor can place the language “contains one vial” on the carton if needed.
- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – It is listed as 2 mg/mL – 3 mL fill and 5 mL Single Use Vial on the front and back of the carton. This conforms to the regulation. The way the amount of product is expressed can be confusing and lead to medication errors (please refer to DMETS review dated 4/18/06). It is recommended that the product is expressed as 6 mg/3 mL (2 mg/mL) to avoid confusion.
- h. The recommended storage temperature – The statement “Store at 2-8C (36-46F)” is on the side of the carton under the NDC number. Please refer to the chemistry, manufacturing, and controls review dated 7/18/06 regarding appropriate storage temperature. This conforms to the regulation.
- i. The words “Shake Well”, “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product; - The statements “Do Not Freeze” and “Do not Shake” are located on the side of the carton. This conforms to the regulation.

- j. The recommended individual dose if the enclosed container(s) is a multiple-dose container; - This is for one-time use only. Therefore, this does not apply.
- k. The route of administration recommended, or reference to such directions in an enclosed circular; - The statement "Sterile for IV infusion only" is located on the front and back of the carton. In addition, the statement "See package insert for dosage information" is located on the side of the carton in the center. This conforms to the regulation. It is recommended that the statement "See package insert for dosage information" is revised to "See package insert for dosage and administration" so that the individual administering has access to all directions regarding aseptic technique.
- l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information; - Photostability studies are not complete for Idursulfase. Please refer to the chemistry, manufacturing, and controls reviews. An additional statement, "Protect from Light," will need to be added to the label in order to conform with the regulation.
- m. The type and calculated amount of antibiotics added during manufacture; - There are no antibiotics added during manufacture. Please refer to chemistry, manufacturing, and controls reviews. Therefore, this regulation does not apply.
- n. The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information. It is recommended that the inactive ingredients are listed or as another option, the statement "See package insert for dosage, administration, and ingredients" can be made.
- o. The adjuvant, if present; - There are no substances that modify the effect of the drug, thereby enhancing the pharmacological effect. Please refer to the chemistry, manufacturing, and control reviews for all substances in manufacture. Please refer to the clinical pharmacology review dated 5/19/06 for the pharmacological effect of the drug. This conforms to the regulation.
- p. The source of the product when a factor in safe administration; - The source is not an issue for this product (refer to the chemistry, manufacturing, and control reviews dated 7/18/06). This conforms to the regulation. Directions for aseptic technique and administration are contained in the package insert. It is recommended that statement "See package insert for dosage" is amended to "See package insert for dosage and administration."
- q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed

circular containing appropriate information; - The statement "See package insert for dosage information" is located on the side of the carton. This conforms to the regulation.

- r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency." The statement "No U.S. Standard of Potency" must be added to the carton. This does not conform to the regulation.
- s. The statement: "Rx only" for prescription biologicals. – The statement "Rx Only" is located on the front and back of the carton. This conforms to the regulation.

C. 21 CFR 610.62 Proper name; package label; legible type *[Note: Per 21 CFR 601.2(c)(1), certain regulations including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]* – This is under one of the four categories of a "specified" biological product: Therapeutic DNA plasmid products; Therapeutic synthetic peptide product of 40 or fewer amino acids, Monoclonal antibody products for in vivo use; and Therapeutic recombinant DNA-derived products. Therefore the label does not need to conform to this regulation.

D. 21 CFR 610.63 Divided manufacturing responsibility to be shown – This only has one manufacturer, Shire Human Genetic Therapies, Inc. Therefore, the label does not need to conform to this regulation.

E. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. – The distributor is Shire Human Genetic Therapies, Inc. which is also the manufacturer. The manufacturer is not listed correctly, the address and license numbers are missing and do not conform with 21 CFR 610.60. As Shire is listed and is the distributor it is not an issue. Therefore, the label conforms with the regulation.

F. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.

G. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter. – The barcode is located on the side of the label. There is sufficient surrounding white space to allow for scanning. This conforms to the regulation.

21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located above in the center of the label under “Rx Only”. It is noted as NDC 58092-700-01. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.

- I. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary name, Elaprase, and the established name, Idursulfase. Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.
- J. 21 CFR 201.10 Drugs; statement of ingredients – The proprietary name is used in a larger size text when compared to the established name. The proprietary name, Elaprase, is size 15.23 pt font. The established name, Idursulfase, is size 7.69 pt font. Idursulfase is used in type at least half as large as the most prominent presentation of Elaprase. This conforms to the regulation. It is recommended that as the proprietary name is bolded, the established name should be bolded to avoid prominence of the proprietary name.
- K. 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.
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only,” an identifying lot number, storage conditions, and reference to the package insert. Photostability studies are not complete for Idursulfase. Please refer to the chemistry, manufacturing, and controls reviews. An additional statement, “Protect from Light,” will need to be added to the label in order to conform with the regulation.

Conclusions from April 26, 2006 labeling

The proposed carton and vial labeling are acceptable only upon the following changes:

- The addition of the statement “Protect from Light” must be listed on carton label. The photostability studies are not complete. Please refer to chemistry, manufacturing, and controls reviews. This will conform to 21 CFR 610.61 and 21 CFR 201.100.
- The correct manufacturer (as per the 356h), Shire Human Genetic Therapies, Inc., must be listed along with the full address on both the carton and vial labels. In addition, as Shire is the only manufacturer, remove Manufactured for Shire Human Genetic Therapies, Inc. That language is only used if there is a different manufacturer from distributor or if there is joint manufacturing. This will conform to 21 CFR 610.60 and 21 CFR 610.61.
- The correct license place holder, US License XXXX, must be listed on both the carton and vial

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labels. This will conform to 21 CFR 610.60 and 21 CFR 610.61.

-The addition of the statement "No U.S. Standard of Potency" must be listed on the carton label. This will conform to 21 CFR 610.61.

The following is a list of suggestions for changes to the proposed carton and vial labels. Note that with the use of some of these suggestions, current required portions of the label may be altered or deleted (as long as 21 CFR 610.60, 21 CFR 610.61, 21 CFR 610.62, 21 CFR 610.63, 21 CFR 610.64, 21 CFR 610.65, and 21 CFR 610.67 are met):

-It is suggested to display the quantity of Idursulfase as 6 mg/3 mL (2 mg/mL) on both the carton and vial labels, to avoid medication errors. Please refer to the DMETS review.

-It is suggested to display the contents of all ingredients on the carton label. Or refer to the package insert for ingredient information.

-It is suggested that in the current carton label, the statement "Sterile for IV infusion only" is amended to "Sterile for Intravenous Infusion Only."

-As this solution will be diluted prior to use, it is suggested to add to the carton, the statement "Must be Diluted Prior to Use" or "Concentrated Solution For Intravenous Infusion Only." This may help prevent possible overdosage.

-It is suggested to add the statement "Single Use Only" to the carton and vial labels.

-It is suggested to bold the proper name, Idursulfase, on both the carton and vial labels, as the proprietary name, Elaprase, is bolded. This will avoid the look of prominence of the proprietary name.

-It is suggested to add the statement "Contains one vial" to the carton label.

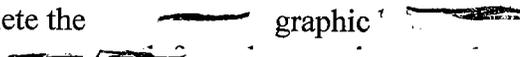
-If space is an issue on the carton and vial, please note that the NDC number can be moved directly under the barcode as a portion of the barcode. This will still allow for accurate scanning but will also free up additional space on the proposed labels.

-If space is an issue on the carton label, consider only placing the name, dosage, logo, and required statements on the front of the carton. Currently the front and back are identical. When displayed on a shelf in a pharmacy you only see the front. Other required or helpful information can be placed on the back of the carton.

DMETS comments relayed to the sponsor

A. GENERAL COMMENTS

1. In addition to increasing the font size and prominence of the proprietary name, ensure that the established name appears with at least equal prominence as the proprietary name in accordance with 21 CFR 610.62(b). Additionally, increase the prominence (i.e., font size) of the product strength commensurate with the proprietary and established name, delete the preposition “for” from the established name, and enclose the established name in parentheses.

2. Delete the  graphic.

Additionally, DMETS suggests that the total drug content and the product strength should be presented directly under the established name utilizing two different lines and within a box or border with the same color background. DMETS suggests the total drug content be the primary expression of strength followed immediately by the mg per mL concentration. Revise all labels and labeling to read:

(Idursulfase Injection)

Elaprase

6 mg/3 mL (2 mg/mL)

Expressing the total drug content and product strength in this manner may help prevent practitioners from misinterpreting the total drug content of a drug product. Medication errors can occur when a user or practitioner reads the product strength (e.g., 2 mg/mL), but fails to read or calculate the total drug content.

3. Relocate the net quantity (3 mL Vial) so it appears away from the product strength, preferably at the bottom of the principal display panel in a smaller font. This should aid in decreasing the risk of confusion between the size of the vial and the product strength.
4. Include the statement, “Must Be Diluted Prior to Intravenous Administration” on the principal display panel. Additionally, increase the prominence of these statements by bolding and/or using a red font color.
5. Add the statement “Discard any unused portion” to the statement “Single Use Vial”.
6. Revise to include the statement “Rx Only” on the principal display panel.
7. Include a “Usual Dosage” statement.

8. Decrease the prominence of the manufacturer name as it appears more prominent than the product strength and the proprietary and established name.

B. CONTAINER LABEL

See General Comments A1 to A5, A7, and A8.

C. CARTON LABELING

1. See General Comments A1 to A7.
2. Revise the statement "Must Be Diluted Prior to Intravenous Administration". Additionally, DMETS does not recommend the use of abbreviations in order to prevent medication errors due to misinterpretation (e.g., IV being misinterpreted as the Roman numeral 4).

Second set of DMETS comments relayed to sponsor:

A. CONTAINER LABEL

1. In addition to increasing the font size and prominence of the proprietary name, ensure that the established name appears with at least equal prominence as the proprietary name in accordance with 21 CFR 610.62(b). Additionally, increase the prominence (i.e., font size) of the product strength commensurate with the proprietary and established name.
2. Revise to include the net quantity (3 mL Vial). It should appear away from the product strength, preferably at the bottom of the principal display panel in a smaller font. This should aid in decreasing the risk of confusion between the size of the vial and the product strength.
3. Include the statement, "Must Be Diluted Prior to Intravenous Administration" on the principal display panel. This should help prevent medication errors where the drug is administered undiluted. Additionally, increase the prominence of this statement by bolding and/or using a red font color.
4. Revise the statement "Single Use Only" to read "Single Use Vial". Additionally, add the statement "Discard any unused portion" to the statement "Single Use Vial".

5. Include a "Usual Dosage" statement (e.g., "Usual Dosage: See package insert.").
6. Decrease the prominence of the manufacturer name as it appears more prominent than the product strength and the proprietary and established name.
7. The last letter of the proprietary name is presented in _____
_____. Revise so that _____ s

B. CARTON LABELING

1. See Container Label Comments A1 through A7.
2. Revise the statement "_____" to read "Must Be Diluted Prior to Intravenous Administration".
 - e. Additionally, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g., IV). Thus, we request that the Divisions not approve or use abbreviations in their labels and labeling as they can be misinterpreted (e.g., the abbreviation "IV" which can be misinterpreted as the Roman numeral 4) and contribute to error.
3. Revise so that the "Rx Only" statement _____

Review of July 17, 2006 submission of Carton and Vial Draft Labels

A. CONTAINER LABELING

- a. The manufacturer has been revised to state: Shire Human Genetic Therapies, Inc. Also the full manufacturer address is listed. This conforms to 21 CFR 610.60 and 21 CFR 610.61.
- b. The U.S. License placeholder is listed as: XXXX. This conforms to 21 CFR 610.60 and 21 CFR 610.61.
- c. The statement "Protect from Light" was added to conform to the photostability studies (refer to CMC review).
- d. The quantity of Idursulfase is now displayed as 6 mg/3 mL (2 mg/mL) to aid in the avoidance of medication errors (refer to DMETS review).
- e. A reference is made to the package insert for dosage AND administration to aid in the avoidance of medication errors.
- f. The product strength prominence is increased to match the established name. The new product strength prominence is 7.5pt. This will aid in the avoidance of medication errors.

- g. The Shire logo and proprietary name are now of the same prominence at 14pt font. With the increase in the proprietary name to 14pt font, the established name has been increased to 7.5pt font to conform to the regulations.
- h. The "Rx Only" statement is no longer _____ so that attention is now focused on important labeling statements such as product strength and proprietary and established name.

B. CARTON LABELING

- a. The manufacturer has been revised to state: Shire Human Genetic Therapies, Inc. Also the full manufacturer address is listed. This conforms to 21 CFR 610.60 and 21 CFR 610.61.
- b. The U.S. License placeholder is listed as: XXXX. This conforms to 21 CFR 610.60 and 21 CFR 610.61.
- c. The statement "Protect from Light" was added to conform to the photostability studies (refer to CMC review).
- d. The statement "No US Standard of Potency" was added to conform to the regulations.
- e. The quantity of Idursulfase is now displayed as 6 mg/3 mL (2 mg/mL) to aid in the avoidance of medication errors (refer to DMETS review).
- f. A reference is made to the package insert for dosage AND administration AND ingredient information.
- g. The product strength prominence is increased to match the established name. The new product strength prominence is 9pt font. This will aid in the avoidance of medication errors.
- h. The Shire logo and proprietary name are now of the same prominence at 17pt font. With the increase in the proprietary name to 14pt font, the established name has been increased to 9pt font to conform to the regulations.
- i. The "Rx Only" statement is no longer _____ so that attention is now focused on important labeling statements such as product strength and proprietary and established name.
- j. The statement "Must be diluted prior to administration prior to intravenous administration" is added to aid against medication errors (no abbreviations).

Conclusions from July 17, 2006 Vial and Carton Draft Labeling

The vial label conforms to the minimum requirements for a partial container per 21 CFR 610.60 (c). The regulation calls for a minimum of a name (proper or common), lot number, name of the manufacturer, and recommended individual dose for multiple containers. In addition, Shire has added other items to this label to aid against medication errors. Shire chooses not to use the DMETS suggestion of _____

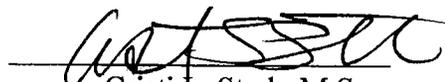
Shire also chose not to place a "usual dosage" statement on the container as there is already a reference to the package insert.

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The carton label conforms to the requirements under 21 CFR 610.60 for a package label. These requirements call for a proper name, name, address, and license of manufacturer, lot number, expiration date, preservative statement, number of containers, amount of product in container, recommended storage temperature, the words "Do Not Freeze", "Shake Well", and similar statements as indicated by the character of the product, recommended individual dose, route of administration, known sensitizing substances, antibiotics, inactive ingredients, adjuvant, source of product, identity of microorganism, and potency. Shire chooses not to use the DMETS suggestion of
/

Overall both the vial and carton labels conform to the regulations, including the position, prominence, and legible type of the proper name, and the barcode label requirements. Shire has also added suggestions from both the Division of Gastroenterology and the Division of Medication Errors and Technical Support. Both the vial and carton draft labeling are acceptable for approval.

 7/21/06
Cristi L. Stark, M.S.
Regulatory Project Manager

Supervisory Comment/Concurrence:

 7/21/06
Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff

PM LABELING REVIEW

B

3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

C

22 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: July 14, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to Shire

**APPEARS THIS WAY
ON ORIGINAL**

Stark, Cristi L

From: Lennihan, Jeannine [jlennihan@shire.com]
Sent: Friday, July 14, 2006 9:24 AM
To: Beaucage, Serge
Cc: Stark, Cristi L; Mehta, Nikhil; Wyant, Alyssa
Subject: BLA 125151: Quality information request and re-send of Final PMC
Attachments: Postmarketing Commitments _Final_.pdf; 0018_cover.pdf; 0018_response-07jun06.pdf; 0018_response-06jun06.pdf; emfalert.txt

14 July 2006

RE: Elaprase (idursulfase)
Quality Information

Dear Serge,

As requested in your phone conversation with Mr. Nikhil Mehta today, attached is a copy of the body of submission Serial 0018 to BLA 125151. I have also attached the Serial 0018 cover letter, that contains a summary of the FDA Quality questions contained in the two FDA faxes received 06 and 07 June 2006.

In addition, I am re-sending the PMC (previously sent on 11 July 2006 via email) to facilitate your review. These PMC will be filed to the BLA by Monday.

Sincerely,

Jeannine Lennihan Firestone
Regulatory Affairs, Project Manager
Shire
700 Main Street, Cambridge, MA 02139
Phone: 1-617-349-0573
Fax: 1-617-613-4009
www.shire.com

7/17/2006

sent on 7/14/06

Dear Nik,

As promised, below is an abridged version of the PMCs that will be included in the approval letter. Should you have any revisions, please let me know at your earliest convenience.

Best wishes
Serge

Approval Letter-Ready PMCs
Elaprase (idursulfase) BLA 125151
Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70

1. 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.
2. To develop and implement an improved enzyme potency assay which measures _____ 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.
3. 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 will be performed. Results from this study will be submitted by January 31, 2007.
4. An action limit for the appearance of any ne... _____ will be added to the _____ assay. The revised drug product specification will be submitted by January 31, 2007.
5. An _____ will be added to the drug product release specifications. The revised specifications will be submitted by September 30, 2006.
6. 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.
7. 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.
8. 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.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: July 13, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

**APPEARS THIS WAY
ON ORIGINAL**

10 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: July 13, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to Shire

**APPEARS THIS WAY
ON ORIGINAL**

E

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Stark, Cristi L

From: Wyant, Alyssa [asonntag@shire.com]
Sent: Tuesday, July 11, 2006 6:03 PM
To: Stark, Cristi L
Subject: Shire HGT's responses to FDA's draft Clinical and Nonclinical PMCs
Attachments: Shire Response to 30June2006 FDA Draft Clin-Nonclin PMCs 11July2006.doc; Shire Response to 30June2006 FDA Draft Clin-Nonclin PMCs 11July2006.pdf; emfalert.txt

RE: ELAPRASE BLA (STN 125151)

Dear Cristi,

Please find attached our responses to FDA's draft Clinical and Nonclinical PMCs, Version 2, dated 30 June 2006 (Word and PDF versions). We look forward to finalizing these commitments with you in the near future. Please contact either me or Nik Mehta with any questions about this information.

Kind regards,
Alyssa

Alyssa Wyant
Senior Regulatory Project Manager
Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139
Phone: 617 349 0593
Fax: 617 613 4009
Email: awyant@tktx.com
www.shire.com

7/17/2006

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: July 11, 2006
From: Shire Human Genetic Therapies, Inc.
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to FDA

**APPEARS THIS WAY
ON ORIGINAL**

Stark, Cristi L

From: Lennihan, Jeannine [jlennihan@shire.com]
Sent: Tuesday, July 11, 2006 12:34 PM
To: Beaucage, Serge
Cc: Stark, Cristi L
Subject: BLA 125151: Quality, Post Market Commitments
Attachments: Postmarketing Commitments _Final_.pdf; emfalert.txt

12 July 2006

Re: Elaprase (idursulfase)
Post Market Commitments

Dear Serge,

Thank you for your Fax, received 10 July 2006, containing suggested changes to the Post Market Commitments (PMC). We have revised the PMC as per your comments. Appended to this email is a copy of the amended PMC. As always, do not hesitate to contact me if you have any questions, or require any more information.

Sincerely,

Jeannine Lennihan Firestone
Regulatory Affairs, Project Manager
Shire
700 Main Street, Cambridge, MA 02139
Phone: 1-617-349-0573
Fax: 1-617-613-4009
www.shire.com

7/17/2006

2 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research**

To: Brian Harvey, M.D., Ph.D.
Director, Division of Gastroenterology Products
HFD-180

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420
Linda Kim-Jung 6/30/06
Denise Toyer 6/30/06

From: Todd D. Bridges, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420
T.D. Bridges 6/30/06

Date: June 28, 2006

Subject: ODS Review 06-0004-1; Elaprase (Idursulfase Injection) 6 mg/3 mL (2 mg/mL); BLA 125151/0

This memorandum is in response to a May 19, 2006 request from your Division for a re-review of the proprietary name, Elaprase. The proposed proprietary name was found acceptable by DMETS in OSE Review 06-0004 dated April 18, 2006. DMETS also reviewed the label and labeling during that review. Subsequently, the sponsor submitted an amendment to the application. This re-review of the name will rule out any objections based upon approvals of other proprietary or established names since the signature date of our initial review (OSE Review 06-0004). Revised container label and carton labeling were submitted for review and comment.

Since the initial review of Elaprase, DMETS has not identified any additional names with the potential for sound-alike and/or look-alike confusion with Elaprase.

In the review of the container label and carton labeling of Elaprase, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. In addition to increasing the font size and prominence of the proprietary name, ensure that the established name appears with at least equal prominence as the proprietary name in accordance with 21 CFR 610.62(b). Additionally, increase the prominence (i.e., font size) of the product strength commensurate with the proprietary and established name.
2. Revise to include the net quantity (3 mL Vial). It should appear away from the product strength, preferably at the bottom of the principal display panel in a smaller font. This should aid in decreasing the risk of confusion between the size of the vial and the product strength.
3. Include the statement, "Must Be Diluted Prior to Intravenous Administration" on the principal display panel. This should help prevent medication errors where the drug is administered undiluted. Additionally, increase the prominence of this statement by bolding and/or using a red font color.

4. Revise the statement "Single Use Only" to read "Single Use Vial". Additionally, add the statement "Discard any unused portion" to the statement "Single Use Vial".
5. Include a "Usual Dosage" statement (e.g., "Usual Dosage: See package insert.").
6. Decrease the prominence of the manufacturer name as it appears more prominent than the product strength and the proprietary and established name.
7. The _____
the proprietary name. Revise so that _____

B. CARTON LABELING

1. See Container Label Comments A1 through A7.
2. Revise the statement _____ to read "Must Be Diluted Prior to Intravenous Administration".
_____. Additionally, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g., IV). Thus, we request that the Divisions not approve or use abbreviations in their labels and labeling as they can be misinterpreted (e.g., the abbreviation "IV" which can be misinterpreted as the Roman numeral 4) and contribute to error.
3. Revise so that the "Rx Only" statement _____

In summary, DMETS has no objections to the use of the proprietary name, Elaprase. We recommend implementation of the above label and labeling comments in addition to the insert labeling comments forwarded in OSE Review 06-0004. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Elaprase acceptable from a promotional perspective. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: June 30, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to Shire

**APPEARS THIS WAY
ON ORIGINAL**

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: June 30, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

**APPEARS THIS WAY
ON ORIGINAL**

9 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: June 23, 2006
From: Shire Human Genetic Therapies, Inc.
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to FDA

**APPEARS THIS WAY
ON ORIGINAL**

Stark, Cristi L

From: Lennihan, Jeannine [jlennihan@shire.com]
Sent: Friday, June 23, 2006 11:29 AM
To: Stark, Cristi L
Cc: Beaucage, Serge
Subject: BLA 125151: Responses to Quality questions
Attachments: FDA Quality Questions TOC.4.pdf; FDA 07Jun06 A1.pdf; FDA 07Jun06 A3.pdf; Postmarketing Commitments.pdf; emfalert.txt

23 June 2006

RE: Elaprase (idursulfase)
Quality Information

Dear Cristi,

Attached is a partial response to the Quality questions received via fax on 06 June 2006 and 07 June 2006. This email completes the company's response to both faxes. A TOC detailing the receipt of responses for each question is included to facilitate your review. Please forward to CMC team.

Included is the updated CMC PMC. Please note that a PMC in reference to a completed response to FDA Question 07June06 Action Item 4 sent on 19 June 06, has been updated in this list as well. The attached TOC also captures this information.

As always, if you have any questions, please do not hesitate to contact me.

Sincerely,

Jeannine Lennihan Firestone
Regulatory Affairs, Project Manager
Shire
700 Main Street, Cambridge, MA 02139
Phone: 1-617-349-0573
Fax: 1-617-613-4009
www.shire.com

7/17/2006

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_____ § 552(b)(5) Deliberative Process

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_____ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: June 22, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

**APPEARS THIS WAY
ON ORIGINAL**

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: June 15, 2006
From: Shire Human Genetic Therapies, Inc.
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to FDA

**APPEARS THIS WAY
ON ORIGINAL**

Stark, Cristi L

From: Lennihan, Jeannine [jlennihan@Shire.com]
Sent: Thursday, June 15, 2006 8:33 AM
To: Stark, Cristi L
Cc: Beaucage, Serge
Subject: BLA 125151: Elaprase
Attachments: FDA 06Jun06 1 and 2 .pdf; FDA 06Jun06 3.pdf; FDA 06Jun06 3(2).pdf; FDA 06Jun06 6.pdf; FDA 07Jun06 A2.pdf; FDA 07Jun06 C2.pdf; FDA 07Jun06 C5.pdf; FDA 07Jun06 C4.pdf; Postmarketing Commitments.pdf; FDA Quality Questions TOC.pdf; emfalert.txt

15 June 2006

RE: Elaprase (idursulfase)
Quality Information

Dear Cristi,

Attached is a partial response to the Quality questions received via fax on 06 June 2006 and 07 June 2006. A TOC detailing the current status of these questions is included. Additionally, please find attached the Quality postmarketing commitments as discussed in the 07 June 2006 teleconference.

Please forward these responses to Mr. Gibbes Johnson, Mr. Barry Cherney, and Mr. Harold Dickensheets (I have cc'd Mr. Beaucage on this email as well, as I have direct secure email in place). Could you please confirm that you have received this email and associated attachments?

Attachments:

Postmarketing Commitments
FDA Quality Questions TOC
FDA 06Jun06 Question 1 and 2
FDA 06Jun06 Question 3
FDA 06Jun06 Question 3(2)
FDA 06Jun06 Question 6
FDA 07Jun06 Question A2
FDA 07Jun06 Question C2
FDA 07Jun06 Question C4
FDA 07Jun06 Question C5

If you have any additional questions, or have any problems opening these attachments, please do not hesitate to call me.

Sincerely,

Jeannine Lennihan Firestone
Regulatory Affairs, Project Manager
Shire
700 Main Street, Cambridge, MA 02139
Phone: 1-617-349-0573
Fax: 1-617-613-4009
www.shire.com

7/17/2006

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: June 6, 2006
From: Shire Human Genetic Therapies, Inc.
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to FDA

**APPEARS THIS WAY
ON ORIGINAL**

Stark, Cristi L

From: Wyant, Alyssa [asonntag@tktx.com]
Sent: Tuesday, June 06, 2006 11:25 AM
To: Stark, Cristi L
Subject: Responses to Clinical PMCs re: ELAPRASE BLA
Attachments: Response to Proposed Clinical Commitments 06June2006.pdf; emfinfo.txt

RE: ELAPRASE BLA (STN 125151)

Dear Cristi,

Attached please find Shire HGT's responses to FDA's proposed Clinical post-marketing commitments.

Please contact either me or Nik Mehta if you have any questions about this information or would like to schedule a teleconference to review our responses. Please also confirm your receipt of this email.

Kind regards,

Alyssa

Alyssa Wyant
Senior Regulatory Project Manager
Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139
Phone: 617 349 0593
Fax: 617 613 4009
Email: awyant@tktx.com
www.shire.com

7/17/2006

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✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 26, 2006
From: Shire Human Genetic Therapies, Inc.
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to FDA

**APPEARS THIS WAY
ON ORIGINAL**

Stark, Cristi L

From: Wyant, Alyssa [asonntag@tktx.com]
Sent: Friday, May 26, 2006 5:29 PM
To: Stark, Cristi L
Subject: Response to Pharmacology/Toxicology PMCs 3 and 4
Attachments: Response to PharmTox PMCs 3 and 4.pdf; emfinfo.txt

RE: ELAPRASE BLA 125151/0

Dear Cristi,

Per our discussions at the 18 May 2006 teleconference regarding the Pharmacology/Toxicology post-marketing commitments (PMCs), we have prepared the attached summary document with justifications for not conducting the Segment II or Segment III reproductive toxicology studies (Pharm/Tox PMCs 3 and 4). Please distribute this document to the appropriate agency review team members for their consideration.

In addition, we would appreciate an update on when we should expect to receive the CMC PMCs, as we are interested in having discussions with the agency on this topic as soon as possible.

Please contact either me or Nik Mehta if you have any questions about this information.

Kind regards,

Alyssa Wyant
Senior Regulatory Project Manager
Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139
Phone: 617 349 0593
Fax: 617 613 4009
Email: awyant@tktx.com
www.shire.com

7/17/2006

Response to Pharmacology/Toxicology PMC Items 3 and 4:

Heparan sulfate glycosaminoglycans (HS-GAG) destined for processing are routed through the endocytic vacuolar network to the lysosome for degradation by a process involving iduronate-2-sulfatase (I2S). I2S participates in a multi-enzyme sequential process operating at acid pH to degrade HS-GAG oligomers. This enables egress of the resulting monosaccharides and sulfate from the lysosome for use in cellular metabolism. Normally, HS-GAG concentrations in plasma, urine and tissues are controlled at multiple levels including, HS-GAG synthesis rate, the rate of HS-GAG entering the lysosome and the rate of circulating HS-GAG clearance by the kidney. As long as sufficient amounts of I2S and the other acid hydrolases are present in the lysosome, HS-GAG levels will be at steady-state. The only way I2S can affect HS-GAG levels, however, is by abnormally low levels of the enzyme in the lysosome. Low levels of I2S in Hunter syndrome lysosomes block the ability of the next enzyme in the HS-GAG degradation sequence to function due to lack of substrate (product of the I2S reaction) for that enzyme. Consequently, HS-GAG fragments accumulate behind the block both inside and outside the cell. However, once a threshold level of I2S is achieved by enzyme replacement therapy (ERT) with idursulfase, lysosomal degradation of HS-GAG can proceed by accommodating the rate of HS-GAG entering the lysosomal compartment. It follows that due to the sequential lysosome-restricted process of HS-GAG degradation, excess I2S delivered by ERT above normal levels will have no effect on HS-GAG concentrations. Moreover, because I2S enzyme activity requires the acidic pH of the lysosome and therefore does not function outside the lysosome, it cannot directly affect circulating levels of HS-GAG on its own. It requires coordination with a multi-step and multi-enzyme lysosomal process to completely degrade HS-GAG. Excess I2S in the lysosome will have no effect on steady-state levels of HS-GAG. It is therefore not possible to deplete levels of HS-GAG below normal by administration of I2S.

This is borne out by experimental evidence in studies with I2S-deficient mice indicating that super-physiologic levels of I2S only lower HS-GAG down to normal levels and never below normal. Administration of idursulfase at doses as high as 1.0 mg/kg weekly over 24 weeks resulted in reductions in HS-GAG to as much as normal levels, but not below normal (Shire HGT R&D report # 720-110-03-436). Published evidence also supports this conclusion where continuous exposure to I2S levels 30- to 70-fold above normal for as long as 7 months could not reduce GAG levels below normal controls (Cardone et al. 2006)ⁱ. These results are consistent with the biological role of I2S and its restricted function within the lysosome, where I2S only exists to participate in the elimination of HS-GAG destined for degradation. Consequently, in the context of toxicological testing in normal animals, administration of exogenous I2S cannot affect tissue or circulating levels of HS-GAG.

Regarding the request by the Agency to perform Segment II and Segment III reproductive toxicology studies, a concern was raised regarding possible effects of I2S on circulating or tissue levels of HS-GAG that may be associated with the biological properties of HS-GAG. HS-GAG can be involved in diverse events such as pattern formation during development, growth factor signalling and anticoagulant responses. Modulation of such responses might lead to effects on reproductive capacity, embryo-fetal development and/or other toxic thrombotic events. If it were possible to deplete HS-GAG by administration of idursulfase this would be a potential toxicological concern. However, as described in preceding sections, due to the specific requirement for I2S activation within the acidic environment of the lysosome, reductions in

circulating or tissue HS-GAG below normal, steady-state levels cannot occur via I2S-mediated mechanisms. Nonetheless, even if I2S were to exhibit residual enzymatic activity outside of the lysosome, structural changes to HS-GAG would be limited to removal of a single terminal 2-*O*-sulfate residue. Binding of HS-GAG to antithrombin is mediated primarily through an essential pentasaccharide sequence comprised of 3-*O*-sulfate residues. Removal of a single 2-*O*-sulfate group from the end of HS-GAG oligomers would have no effect on anticoagulant properties of HS-GAG. Excess circulating I2S, therefore, will not affect tissue or circulating levels of HS-GAG. In addition, excess I2S in the lysosome will also not affect HS-GAG levels because I2S is one enzyme in a multi-enzyme catabolic process and, apart from enzyme deficiency, cannot unilaterally affect HS-GAG levels.

The overt lack of toxicity of idursulfase when administered systemically is further supported by findings in chronic dosing as well as male rat fertility studies. In the case of chronic dosing studies, there were no toxicological effects attributable to weekly administration of idursulfase for a 6-month period at doses up to 12.5 mg/kg/week. Of particular note was the finding that no changes in hematology or coagulation parameters were observed that were attributable to idursulfase administration. In the case of male rat fertility studies, there were no idursulfase-related effects on fertility, pregnancy status, or number and type of implantations at doses up to 5 mg/kg/dose. In addition, acute dosing studies in rats and monkeys, at concentrations up to 20 mg/kg, demonstrated no idursulfase-associated toxicological findings.

Based on the lack of toxicologic findings and the preceding discussion regarding the mechanism of action of I2S with respect to HS-GAG degradation, it is unlikely that reproductively associated toxicologic events will occur in association with intravenous idursulfase administration. Consequently, the Sponsor requests that the proposed PMCs for Segment II and III studies for idursulfase be waived.

ⁱ Cardone M, Polito VA, Pepe S, Mann L, D'Azzo A, Auricchio A, Ballabio A, Cosma MP. Correction of Hunter syndrome in the MPS II mouse model by AAV2/8-mediated gene delivery. *Hum Mol Genet.* 2006 Apr 1;15(7):1225-36.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: 5/16/06

To: Nik Mehta	From: Cristi Stark
Company: Shire	Division of Gastroenterology Products
Fax number: (617)613-4444	Fax number: (301) 796-9905
Phone number:	Phone number: (301) 796-2120

Subject: major amendment confirmation letter

Total no. of pages including cover: 2

Comments: attached is a major amendment confirmation letter
Your action is now due on August 24, 2006.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2120. Thank you.



Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125151/0

MAY 16 2006

Shire Human Genetic Therapies, Inc.
Attention: Suzanne L. Bruhn, Ph.D.
Vice President, Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Bruhn:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Idursulfase.

We received your May 12, 2006, amendment to this application on May 15, 2006, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to August 24, 2006, to provide time for a full review of the amendment.

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

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

A handwritten signature in black ink that reads "Brian E. Harvey, M.D., Ph.D.".

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 16, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

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 § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 11, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to Shire

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 § 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 11, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

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✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 10, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

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✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 9, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Post Marketing Commitments sent to Shire

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✓ § 552(b)(4) Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 5, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

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ON ORIGINAL**

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✓ § 552(b)(4) Draft Labeling

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 4/3/06

TO: Cristi Stark, Regulatory Project Manager
Joanna Ku, M.D., Clinical Reviewer
Division of Gastroenterology Products, HFD-180

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

BLA: 125151/0

APPLICANT: Transkaryotic Therapies(TKT)/Shire

DRUG: idursulfase

THERAPEUTIC CLASSIFICATION: Standard Review IS

INDICATION: treatment of iduronate-2-sulfatase deficiency (Mucopolysaccharidosis II, MPS II, Hunter Syndrome)

CONSULTATION REQUEST DATE: January 13, 2006

DIVISION ACTION GOAL DATE: April 6, 2006

PDUFA DATE: May 25, 2006

I. BACKGROUND:

Mucopolysaccharidosis, also known as Hunter Syndrome, is a rare inborn error of metabolism in which the enzyme iduronate sulfatase is deficient. This leads to an abnormal accumulation glucosaminoglycans (GAGs) or mucopolysaccharides within tissues of the body, and affects all organ systems. Thickening of the tongue and trachea can cause breathing and swallowing difficulties while disease induced COPD and valvular heart disease cause problems with exercise tolerance and lack of endurance. Accumulation of GAGs in the bones and joints causes skeletal deformity and problems with mobility. The deposition of mucopolysaccharides also leads to liver and spleen enlargement. With the early onset form of the disease accumulation in the central nervous system leads to mental retardation. There is no cure for this syndrome.

Treatment is palliative and supportive and focuses on the management of clinical symptoms. An enzyme treatment for a related enzyme deficiency was approved in 2005.

The primary objective of this clinical trial is to determine the efficacy and safety of enzyme replacement therapy with idursulfase. The primary efficacy endpoint is composite of three clinical measurements. The components are forced vital capacity (FVC) as a measure of respiratory function, joint range of motion (JROM), and the 6 minute walk test (6 MWT) as a measure of functional capacity.

The investigators were chosen for various reasons. Dr. Muenzer at UNC is the second highest enrollee

According to the review division, Dr. Eng at Baylor had an unusual pattern of "discarding" patients, i.e. 50% of patients were enrolled but not selected to be randomized (6 out of 12 patients were enrolled but not randomized to enter into the study).

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
Dr. Christine Eng site 048	Houston, TX	TKT024	2/27-3/1/06	3/21/06	NAI
Dr. Joseph Muenzer site 013	Chapel Hill, NC	TKT024	2/27-3/6/06	3/21/06	NAI
Dr. Roberto Giugliani site 020	Porto Alegre, Brazil	TKT024	3/28/06	pending	NAI (pending review)

*If international site, please insert column for country.

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.

A. Protocol: #TKT024 "A Phase II/III, 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"

1. Christine Eng, M.D., Houston, TX Site 048: The data were acceptable.
 - a. There were six subjects enrolled at Dr. Eng's site. Her site was chosen for inspection because she enrolled twelve subjects, but randomized only six. The inspection took place February 27-March 1, 2006. All six records were audited. Dr. Eng stated that five of the 12 subjects she enrolled were not randomized because they could not perform pulmonary function tests, and the family of the sixth subject withdrew consent.
 - b. There were no limitations to the inspection.
 - c. There were no discrepancies between the source documents, case report forms (CRFs), and data listings supplied by the sponsor. No 483 was issued.
 - d. The data are acceptable for consideration in the IND review decision.

2. Joseph Muenzer, M.D., Chapel Hill, NC Site 013: The data were acceptable.
 - a. There were ten subjects randomized at Dr. Muenzer's site. His site was chosen for inspection because of high enrollment. The inspection took place February 27 to March 6, 2006. All subject records were audited.
 - b. There were no limitations to the inspection.
 - c. There were no discrepancies between the source documents and the data listings supplied by the sponsor. No 483 was issued.
 - d. The data were acceptable for consideration in the BLA review decision.
3. Roberto Giugliani, M.D., Porto Alegre, Brazil, Site 020: The data were acceptable.
 - a. There were twenty one subjects enrolled at Dr. Giugliani's site. His site was chosen for inspection because of high enrollment. The inspection took place March 28-April 3, 2006. 17 of 21 subject records were reviewed.
 - b. There were no limitations to the inspection.
 - c. There were no discrepancies between the source documents and the data listings supplied by the sponsor. No 483 was issued.
 - d. Based on preliminary inspection information, the data were acceptable for consideration in the BLA review decision. If conclusions change upon receipt and review of the full EIR the review division will be notified.

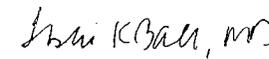
III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The studies appear to have been well conducted at all the sites. There were no Form FDA 483s issued. No follow up other than routine surveillance is recommended. Observations noted for Dr. Giugliani's site are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.


Dianne D. Tesch
Consumer Safety Officer

CONCURRENCE:

Supervisory comments


Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: May 2, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

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Brony, Michael

From: Brony, Michael
Sent: Tuesday, May 02, 2006 9:26 AM
To: Stark, Cristi L
Cc: Brony, Michael
Subject: RE: DDMAC consult:STN 125151/0:Elaprase

Hi Cristi,

Please find below a copy of DDMAC's comments:

Date: May 2, 2006

From: Michael Brony, Division of Drug Marketing, Advertising, and Communications (DDMAC)

To: Cristi Stark, Division of Gastrointestinal and Coagulation Drug Products

Re: 125151/0 Elaprase (idursulfase) Solution for intravenous infusion label review

On page 5 of the draft label, lines 120-121, states: “

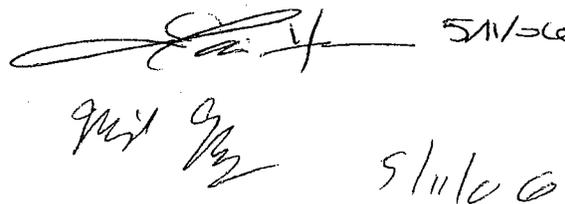
DDMAC recommends deleting the part of the sentence that states, “
This minimizes the risks associated Elaprase therapy.

Additionally, we have no comments on the carton or vial carton.

I will get you the signed copy from Elaine when she comes back from the conference.

Thanks

Michael



Handwritten signature and initials, including "5/11/06" and "5/11/06".

-----Original Message-----

From: Stark, Cristi L
Sent: Wednesday, April 26, 2006 10:42 AM
To: Brony, Michael
Subject: DDMAC consult:STN 125151/0:Elaprase

Michael,

We are taking a final action on May 19, 2006. So I need these asap. We have already sent some labeling to the sponsor. Attached is the current PI and the current carton and vial. Please note that DDMAC and DMETS did find the tradename ELAPRASE acceptable two weeks ago.

<< File: Elaprase draft PI labeling 4_24_06.doc >> << File: carton-container.pdf >> << File: vial.pdf >>

Thanks,
Cristi

From: Brony, Michael

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

Date: April 21, 2006
From: Cristi L. Stark, CDER/ODEIII/DGP, HFD-180
To: BLA 125151/0 file
Shire Human Genetic Therapies, Inc.
Elaprase (Idursulfase)
Subject: Package Insert Labeling sent to Shire

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CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; WO 22, MAIL STOP 4447)

DATE RECEIVED: January 4, 2006	DESIRED COMPLETION DATE: April 23, 2006	ODS CONSULT #: 06-0004
DATE OF DOCUMENT: November 23, 2005	PDUFA DATE: May 25, 2006	

TO: Brian Harvey, M.D., Ph.D.
 Director, Division of Gastroenterology Products
 HFD-180

THROUGH: Linda Y. Kim-Jung, Pharm.D., Team Leader *wyk 4/18/06*
 Denise Toyer, Pharm.D., Deputy Director *Carol Helquist for 4/18/06*
 Carol Holquist, R.Ph., Director *Carol Helquist 4/18/06*
 Division of Medication Errors and Technical Support

FROM: Todd D. Bridges, R.Ph., Safety Evaluator *T.D. Bridges 4/18/06*
 Division of Medication Errors and Technical Support

PRODUCT NAME: Elaprase™ (Idursulfase Injection) 6 mg/3 mL ? mg/mL)	SPONSOR: Transkaryotic Therapies, Inc.
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BLA#: 125151/0

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Elaprase™. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to BLA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS has concerns with the potential for dosage calculation errors and recommends the implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with use of this product.
3. DDMAC finds the proprietary name, Elaprase™, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 18, 2006

BLA #: 125151/0

NAME OF DRUG: **Elaprase™**
(Idursulfase Injection)
6 mg/3 mL
(2 mg/mL)

BLA SPONSOR: Transkaryotic Therapies, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastroenterology (HFD-180), for assessment of the proprietary name, Elaprase™, regarding potential name confusion with other proprietary or established drug names. Container label, carton and insert labeling were provided for review and comment. Additionally, the sponsor submitted a risk management plan. This plan was the subject of internal meetings between members of the review division and the Office of Drug Safety. DMETS reviewed the risk management plan from a medication error safety perspective and a coordinated response will be sent from the Office of Drug Safety.

PRODUCT INFORMATION

Elaprase™ (Idursulfase) is a purified form of the lysosomal enzyme, iduronate-2-sulfatase (I2S). Elaprase™ is indicated for the treatment of patients with Hunter Syndrome. The recommended dose and dosing interval will be 0.5 mg/kg once-weekly as an intravenous infusion. Elaprase™, which will be supplied in 5 mL single-use glass vials containing 3 mL (6 mg) of Idursulfase in a concentrated solution for intravenous infusion, should be stored in a refrigerator at 2°C – 8°C (36°F – 46°F). The total volume of Elaprase™ to be administered to a patient should be diluted in 100 mL of 0.9% Sodium Chloride Injection, USP. Distribution of this product will occur through a limited number of specialty pharmacies and wholesalers. Sites of care that will administer Elaprase™ infusions will access the product from one of these vendors. Elaprase™ will not be distributed directly to patients.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to Azimar to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. The SAEGIS^{vi} Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Elaprase. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name, Elaprase, acceptable from a promotional perspective.
2. The Expert Panel identified one proprietary name and two established names that were thought to have the potential for confusion with Elaprase. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

ⁱ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, Missouri.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA)

^v www location <http://www.uspto.gov/tmdb/index.html>.

^{vi} Data provided by Thomson & Thomson's SAEGIS™ Online service, available at www.thomson-thomson.com

Table 1: Potential Look-Alike Names Identified for Elaprase

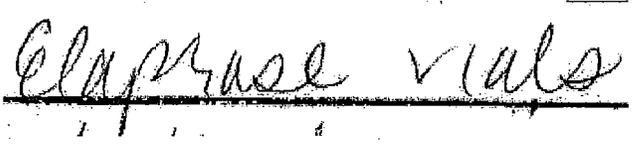
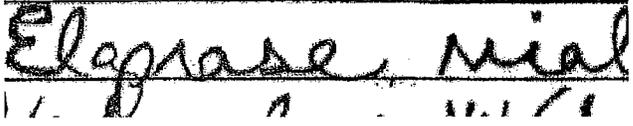
Product Name	Established Name, Dosage Form(s)	Usual Adult Dose*	Other
Elaprase	Idarubicin Injection, 2 mg/mL	12 mg/kg weekly intravenously OR 12 mg/kg every other week intravenously.	N/A
Dapsone	Dapsone Tablets: 25 mg, 100 mg.	Dermatitis herpetiformis: 50 mg to 300 mg daily.	LA
Enpresse	Levonorgestrel/Ethinyl Estradiol Tablets, USP: 0.05 mg/0.03 mg, 0.075 mg/0.04 mg, 0.125 mg/0.03 mg.	One tablet daily.	LA
Iloprost	Iloprost Solution for inhalation: 20 mcg.	The first inhaled dose should be 2.5 mcg (as delivered at the mouthpiece). If this dose is well tolerated, increase dosing to 5 mcg and maintain that dose. Take Iloprost 6 to 9 times daily (no more than every 2 hours) during waking hours.	LA

*Frequently used, not all-inclusive.
**LA (look-alike).

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Elaprase with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten pharmacy requisition orders or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two pharmacy requisition orders were written, each consisting of a combination of marketed and unapproved drug products and an order for Elaprase (see page 5). These orders were optically scanned and one order was delivered to a random sample of the participating health professionals via e-mail. In addition, one of the requisition orders was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal requisition orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN REQUISITION	VERBAL REQUISITION
Requisition Sample #1: 	Elaprase 2 vials
Requisition Sample #2: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A (page 11) for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

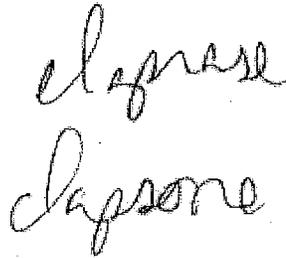
In reviewing the proprietary name, Elaprase, the primary concerns identified related to look-alike confusion with Dapsone, Enpresse, and Iloprost. Additionally, DMETS is concerned with the potential for dosage calculation errors (i.e., errors in calculating the volume of solution to be withdrawn from the vial based on the patient's weight).

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Elaprase.

1. Look-Alike/Sound Alike Assessment

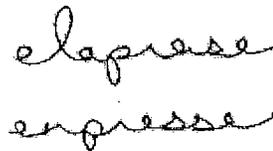
- a. Dapsone was identified as having look-alike similarities to the proposed name, Elaprase. Dapsone is indicated for the treatment of dermatitis herpetiformis (DH) and all forms of leprosy. Dapsone is available as 25 mg and 100 mg tablets. The usual dose is 50 mg to 300 mg once daily. The letter "d" of Dapsone, when scripted in lower-case, may look similar to the first two letters of Elaprase (see page 6). Additionally, both names contain the letters "-ap-" in similar positions and the endings of each name ("-sone" vs. "-rase") can look-alike when scripted. However, Dapsone is supplied in two strengths (25 mg and 100 mg) and thus, a prescription for Dapsone will have the strength indicated which will help to differentiate the two drug names. Additionally, the dosage of Elaprase varies with patient weight while the usual dosage of Dapsone is generally invariant. Thus, the patient specific dosage of Elaprase indicated on a prescription may lessen any confusion stemming from the look-alike similarities between Dapsone and Elaprase.

Although the dose of these products could overlap (e.g., the dose of Elaprase for a patient weighing 100 kg is 50 mg), these products differ with regard to dosing frequency (once daily vs. once weekly), route of administration (orally vs. intravenously), and quantity to dispense (e.g., #60 vs. 6 vials). The dosing frequency, route of administration, and ordered quantity indicated on a prescription may lessen any confusion stemming from look-alike similarities involving this name pair. Furthermore, distribution of Elaprase will occur through a limited number of specialty pharmacies and wholesalers. Sites of care that will administer Elaprase infusions will access the product from one of these vendors. Even though these names have orthographic similarities, DMETS believes that the product differences described above will minimize the risk of confusion and error between these two medications:

The image shows two lines of handwritten text in cursive. The top line is 'elaprase' and the bottom line is 'elaprase'. The two words are nearly identical in appearance, illustrating the orthographic similarity mentioned in the text.

- b. Enpresse may look similar to Elaprase when scripted. Enpresse is a triphasic combination oral contraceptive containing the progestational compound, levonorgestrel and the estrogenic compound, ethinyl estradiol. Enpresse is indicated for prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

The look-alike similarity stems from the fact both names begin with the letter “e” and end with the letters “se” (see below). Additionally, both names contain the letter combination “pr” in similar positions. However, the upstroke of the letter “l” in Elaprase may help to distinguish the name from Enpresse if scripted prominently. Unlike Enpresse, medication orders for Elaprase are likely to be written with specific patient dosing based upon weight. This individualized dosing on an order may help to distinguish the two names. Furthermore, distribution of Elaprase will occur through a limited number of specialty pharmacies and wholesalers. Sites of care that will administer Elaprase infusions will access the product from one of these vendors. Elaprase will not be distributed directly to patients which may aid in decreasing the risk of confusion between this name pair. Moreover, these products differ with regard to dosing frequency (once daily vs. once weekly), and route of administration (orally vs. intravenously). The dosing frequency, route of administration, and ordered quantity indicated on a prescription may lessen any confusion stemming from look-alike similarities involving this name pair. In conclusion, DMETS believes that the limited distribution of Elaprase combined with the differentiating product characteristics between Enpresse and Elaprase will help to decrease the risk for medication errors.

The image shows two lines of handwritten text in cursive. The top line is 'elaprase' and the bottom line is 'enpresse'. The two words are nearly identical in appearance, illustrating the orthographic similarity mentioned in the text.

- c. Iloprost was found to have look-alike potential with Elaprase. Iloprost, currently marketed under the proprietary name Ventavis, is indicated for pulmonary arterial hypertension and is administered six to nine times daily (no more than every 2 hours) during waking hours. Iloprost is supplied as a 20 mcg/2 mL solution for inhalation in 2 mL single-use vials. The letters “I” and “o” of Iloprost may look similar to the letters “e” and “a” of Elaprase, respectively, when scripted in cursive (see below). Additionally, within both names there are the same four letters (“l”, “p”, “r”, and “s”) located at the same positions (second, fourth, fifth, and seventh). However, dosing for Elaprase is based on patient weight while the standard dosing for Iloprost is unvarying (i.e., 6 to 9 times daily) and thus, the individualized dosing on an order for Elaprase may help to differentiate these two products. Additionally, distribution of Elaprase will occur through a limited number of specialty pharmacies and wholesalers. Sites of care that will administer Elaprase infusions will access the product from one of these vendors. Elaprase will not be distributed directly to patients which may aid in decreasing the risk of confusion between this name pair. Furthermore, these products differ with regard to dosing frequency (six to nine times daily vs. once weekly route of administration (inhaled vs. intravenously), and quantity to dispense (e.g., #100 or 1 box vs. 6 vials). Moreover, the likelihood that a prescriber will include “...via nebulizer” in the directions for use for Iloprost may help to distinguish this name pair on a medication order. Therefore, orthographic differences combined with the individualized dosing and limited distribution of Elaprase will help minimize the potential for confusion between the two drug products.

elaprase
iloprost

2. Concerns with Dose Calculation

The sponsor reports that 5.2% of patients treated with Elaprase received an incorrect dose. The sponsor states that the errors were attributed to the difficulty in product preparation with respect to calculation of the volume of solution to be withdrawn from the vials based on the patient’s weight. If the vials are commercially labeled in a similar manner as those used in the clinical trials, we envision the occurrence of similar errors. These calculation errors may be more magnified in real world setting, especially when practitioners are busy, distracted, and tired. To this end, DMETS believes it would be prudent for the sponsor to

Furthermore, DMETS recommends an education campaign to accompany the launch of this product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the Elaprase container labels, carton labeling and package insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. In addition to increasing the font size and prominence of the proprietary name, ensure that the established name appears with at least equal prominence as the proprietary name in accordance with 21 CFR 610.62(b). Additionally, increase the prominence (i.e., font size) of the product strength commensurate with the proprietary and established name, delete the preposition “for” from the established name, and enclose the established name in parentheses.

2. Delete the

—
—
Additionally, DMETS suggests that the total drug content and the product strength should be presented directly under the established name utilizing two different lines and within a box or border with the same color background. DMETS suggests the total drug content be the primary expression of strength followed immediately by the mg per mL concentration. Revise all labels and labeling to read:

(Idursulfase Injection)

Elaprase

6 mg/3 mL (2 mg/mL)

Expressing the total drug content and product strength in this manner may help prevent practitioners from misinterpreting the total drug content of a drug product. Medication errors can occur when a user or practitioner reads the product strength (e.g., 2 mg/mL), but fails to read or calculate the total drug content.

3. Relocate the net quantity (3 mL Vial) so it appears away from the product strength, preferably at the bottom of the principal display panel in a smaller font. This should aid in decreasing the risk of confusion between the size of the vial and the product strength.
4. Include the statement, “Must Be Diluted Prior to Intravenous Administration” on the principal display panel. Additionally, increase the prominence of these statements by bolding and/or using a red font color.
5. Add the statement “Discard any unused portion” to the statement “Single Use Vial”.
6. Revise to include the statement “Rx Only” on the principal display panel.
7. Include a “Usual Dosage” statement.

8. Decrease the prominence of the manufacturer name as it appears more prominent than the product strength and the proprietary and established name.

B. CONTAINER LABEL

See General Comments A1 to A5, A7, and A8.

C. CARTON LABELING

1. See General Comments A1 to A7.
2. Revise the statement "Sterile for IV infusion only" to read "Must Be Diluted Prior to Intravenous Administration". The word "Sterile" in the statement is unnecessary because this product is given parenterally and presumed to be sterile. Additionally, DMETS does not recommend the use of abbreviations in order to prevent medication errors due to misinterpretation (e.g., IV being misinterpreted as the Roman numeral 4).

D. PACKAGE INSERT LABELING

1. Delete the use of trailing zeroes throughout the insert labeling. The use of terminal zeroes may result in error as decimals are often overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list.
2. The statement _____
_____ To help reduce the potential for inadvertent administration of the concentrated solution, revise the statement to read "Must Be Diluted Prior to Intravenous Administration".

3. CONTRAINDICATIONS

4. PRECAUTIONS

The information found in the Information for Patients subheading should be repeated at the end of the insert labeling in accordance with 21 CFR.57(f)(2).

5. DOSAGE AND ADMINISTRATION

- a. Relocate the statement "Elaprase is a concentrated solution for intravenous infusion and must be diluted in 100 mL of 0.9% Sodium Chloride Injection, USP." so that it appears —
— under this section heading.

- b. Preparation and Administration Instructions: Use Aseptic Techniques

DMETS believes fewer steps in calculation of the dose may help to reduce the potential for calculation errors such as those made during the pivotal clinical trial. Additionally, as currently presented, the steps to calculate the dose are only valid for a 3 mL vial, which does not take into account the possibility of other package sizes being introduced into the marketplace at a later date.

To this end, we recommend Step 1 be revised to read as follows.

- c. In consideration of the calculation errors made during the pivotal clinical trial, DMETS recommends that the sponsor —
—

6. STORAGE

Relocate information pertaining to the stability of diluted Elaprase to — n the
DOSAGE AND ADMINISTRATION section.

7. HOW SUPPLIED

Since the extractable volume of Elaprase is only 3 mL, references to the —
should be deleted. This will prevent confusion and medication errors resulting from practitioners thinking the vial contains 5 mL instead of 3 mL.

Appendix A: Prescription Study Results for Elaprase

<u>Requisition #1</u>	<u>Requisition #2</u>	<u>Voice</u>
Elaphase	Elaphase	Alapace
Elaprase	Elaphase	Alaprace
Elaprase	Elaphase	Aloprace
Elaprase	Elaprase	Elaprace
Elaprase	Elaprase	Elaprace
elaprase	Elaprase	Elaprase
Elaprase	Elaprase	Elaprase
Elaprase	Elaprase	Elaprase
Elaprase	Elaprase	Elaprice
Elaprase	Elaprase	eleprase
Elaprase	Elaprase	eliprase
Elaprase	Elaprase	Eliprase
Elaprase	Elaprase	eloprice
Elaprase	Elaprase	
Elaprase		
Elaprase		
Eleprase		
Eleprase		

STN 125151/0 Clin/Pre-Clin Midcycle Itinerary:

Location: White Oak Conference Room 5201

Date: February 15, 2006

Time: 2:00-3:30pm

Schedule:

2:00-2:05pm: Introduction, upcoming dates, and purpose (*C. Stark*)

2:05-2:10pm: Background on disease and study (*J. Ku*)

2:10-2:15pm: Product update/review issues (details will be discussed at product/facilities Midcycle on 3/9/06) (*G. Johnson & S. Beaucage*)

2:15-2:25pm: Pharm/tox review (*R. Honchel*)

2:25-2:40pm: Clin Pharm review (*H. Zhao*)

2:40-3:20pm: Clinical review (*J. Ku*)

3:20-3:30pm: Questions, wrap up, action items (*C. Stark*)

Upcoming dates of interest (note that labeling meetings may shift to team meetings and additional meetings may be added in May):

- Product/Facilities Midcycle – March 9, 2006
- Team Meeting – March 22, 2006
- Labeling Meeting – April 5, 2006
- Labeling Meeting – April 11, 2006
- Labeling Meeting – April 18, 2006
- (Internal Goal Date – April 13, 2006)
- Labeling Meeting – April 25, 2006
- Labeling Meeting – May 1, 2006
- First Action Due – May 25, 2006

✓

53 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



Our STN: BL 125151/0

FEB 3 2006

Transkaryotic Therapies, Inc.
Attention: Suzanne L. Bruhn, Ph.D.
Vice President, Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Bruhn:

Please refer to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated January 19, 2006. While conducting our filing review we identified the following review issues:

1. In regard to release and stability testing of Idursulfase (I2S) drug substance and product:
 - a. An upper percentage limit for the _____ should be established.
 - b. Each peak group of the _____ assay should be reported as a range of percent values.
 - c. The acceptance criteria for _____ must be amended to include a limit on the presence of _____
 - e. _____ per mole of I2S must be routinely monitored as part of drug substance release testing.
 - f. The potency assay for I2S should be designed and performed appropriately so that _____
 - g. In measurements of enzyme potency justify the use of the heparin sulfate disaccharide substrate containing _____ instead of a _____
 - h. We have the following comments regarding the heparin disaccharide enzyme activity potency validation report:

[Redacted]

i. The methodology used in the [Redacted] assay is not rigorous. A

[Redacted]

Thus, the use of this assay methodology in release testing is not appropriate or of significant value.

j. A potency assay which [Redacted]

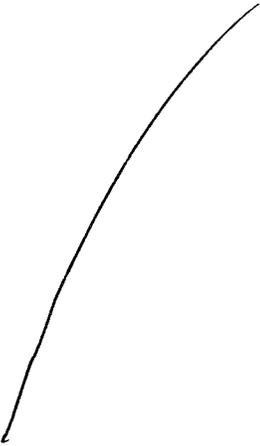
This assay must be validated and used in drug substance and product release and stability testing.

k.

l. Provide data comparing the abilities of [Redacted] to detect

m. Provide a legible copy of the drug product [Redacted] method validation report "qctr-03-031-sds-page-" [Redacted] as the figures are not clear.

2. In regard to the comparability of I2S manufactured by the Phase II/III and commercial processes:

- a. Provide Figures 3.2.S.2.6.2-18 through 3.2.S.2.6.2-31 each as a set of two profiles stacked above each other (one for Lot DP04-003 and the other for Lot D303-025) for a better assessment of the presence/absence of peaks and evaluation of their relative intensities.
 - b. The data, plots and results of a comparison of _____, commercial qualification lots and a minimum of _____ lots of Phase II/III clinical materials must be provided for the following assays:
 - i. Determination of the _____ for the heparin disaccharide substrate.
 - ii. Determination of IC_{50} using the _____ assay.
3. In regard to comparability of the stability profiles of I2S manufactured by the Phase II/III and commercial processes:
- a. In addition to the tables of comparative test results already provided, please present these test results in the form of _____, etc...as appropriate when comparing the thermal stress stability profiles (at both 40°C @ _____ and 25°C @ _____ of I2S drug product through _____)
 - b. Comparability with respect to _____
- 
4. Develop and provide validation data for a neutralizing assay that can detect the presence of antibodies that inhibit the entry of I2S into cells. Test and provide data from patient samples that are positive in the screening assay with this inhibition-of-entry neutralization assay.

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

this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

While conducting our filing review, we have determined that the following information is necessary to take a complete action on your supplement:

1. Describe how patients were identified and initially screened to be considered for enrollment in Study TKT024.
2. Provide a list of patients who were granted exemptions to the inclusion/exclusion criteria in Study TKT024 and provide the reasons for the exemptions.
3. In the report for Study TKT024, on page 4000 of volume 13, the letter addressed to TKT024 Investigators seems to be missing page(s), as only the first and last pages were included. Provide the missing interval pages.
4. In the report for Study TKT024, on page 289 of volume 1, the last paragraph states that patient 024-012-0008, who died of respiratory failure secondary to pulmonary infection, had a history of “severe pulmonary involvement with recurring respiratory tract infections.” Clarify why the patient’s Baseline CRF had no documentation of such prior infections. The immediate cause of death was cardiac arrest; the Baseline CRF states the patient had class II congestive heart failure while the SAE CRF states that the patient did not have any cardiac history. Clarify the cardiac history of the patient.
5. Provide the baseline laboratory hematology data for patient 024-020-0003.
6. Patient 024-059-0002 died during participation in Study TKT024EXT. Provide the CRF’s for this patient.
7. Patient 018-013-0006 died during participation in Study TKT018. Provide the CRF’s for this patient, including all available information about his death.

If any of the information requested above has already been submitted, please identify the specific location in your submission where it can be found.

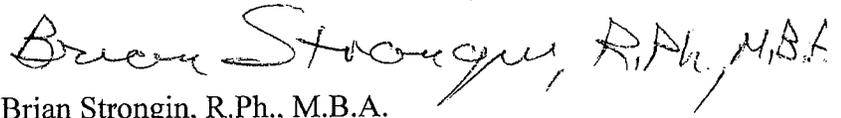
Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

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

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

A handwritten signature in black ink that reads "Brian Strongin, R.Ph., M.B.A." The signature is written in a cursive style with a large initial 'B' and 'S'.

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

CONCURRENCE PAGE

RPM - Communication Screen Data Check

Letter Type: Deficiencies Identified (DI)

RPM – Milestone Screen Data Check

Confirm “Deficiencies Identified” Entry and Close Date

cc: C. Stark
J. Ku
J. Hyde
B. Harvey
J. Beitz
A. Rajpal
H. Zhao
S. Beaucage
G. Johnson
B. Cherney
A. Rosenberg
S. Kozlowski
R. Honchel
J. Choudary
HFD-005/Mike Jones
HFD-40/Office of Medical Policy/R. Temple if application or clinical issues
HFD-123/OBP Director/Keith Webber if application or product issues
HFD-320/DMPQ Director if application or facility issues
HFD-328/Mike Smedley if application or facility issues
Division BLA file (hard copy)
HFD-020/ Immediate Office (hard copy)

History: CLStark:2.1.2006;2.2.2006;2.3.2006



Our STN: BL 125151/0

JAN 19 2006

Transkaryotic Therapies, Inc.
Attention: Suzanne L. Bruhn, Ph.D.
Vice President, Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Bruhn:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated November 23, 2005, for Idursulfase to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The user fee goal date is May 25, 2006. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before February 5, 2006.

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

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

Juliana DeBeauvoir for Brian Strongin

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

CONCURRENCE PAGE

RPM – Communication Screen Data Check

Letter Type: Filing Notification (FL) *Note – If 74-day letter will NOT be sent, include one of the following letter types in the communication screen:

- Deficiencies (DI) [*If Deficiencies are identified in letter*]; or,
- No Deficiencies Identified (NDI) [*If Filing review did not identify substantive deficiencies*]

RPM – Milestone Screen Data Check

Confirm “Filing Action” Close Date
 If applicable – Confirm “Deficiencies Identified” Close Date

USE IF FILING OR FILING WITH NO DEFICIENCIES IDENTIFIED

cc: C. Stark
 Division BLA file (hard copy)

USE IF FILING WITH DEFICIENCIES IDENTIFIED

cc: HFX-XXX/Review team (incl. RPM), division director(s) & team leaders
 HFD-005/Mike Jones
 HFD-40/Office of Medical Policy/R. Temple if application or clinical issues
 HFD-123/OBP Director/Keith Webber if application or product issues
 HFD-320/DMPQ Director if application or facility issues
 HFD-328/Mike Smedley if application or facility issues
 Division BLA file (hard copy)
 HFD-020/ Immediate Office (hard copy)

History: CLStark:1.18.2006

File Name: N:\Stark\TKT\STN 125151_0\STN 125151_0 filing ltr.doc

Office	Name/Signature	Date
DGP		1/18/06
CDER/ODM/III/DGP	J. Dubéau for B. Strangin	1/19/06

Memorandum

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

CONVERSATION RECORD

Date: January 3, 2006

CDER Representatives:

Carolyn Renshaw, Facility/CMC Reviewer, CDER/OC/DMPQ/TRFB, HFD-328 *CR*

Organization Representatives:

Suzanne L. Bruhn, Ph.D., Vice President, Global Regulatory Affairs
Robert Corcoran, Vice President, Quality
David Pizzi, Director, Regulatory Affairs

1/5/06

Organization: Transkaryotic Therapies, Inc. (TKT)

Telephone Number: 617-503-0394

Subject: STN 125151/0, Idursulfase
Pre-license inspection planning discussion

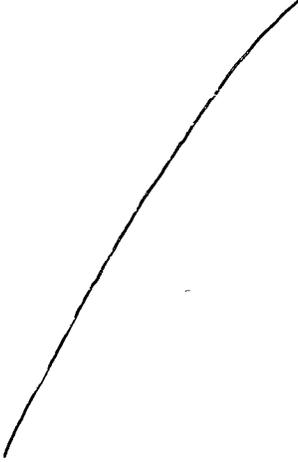
To: Administrative File, STN125151/0

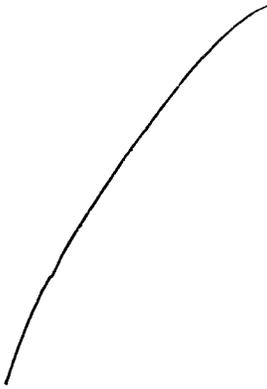
Conversation Summary:

I contacted TKT to elicit information regarding the drug substance production and testing facilities for idursulfase, BLA STN 12515.0. The following issues were discussed (FDA questions in regular font, TKT responses in italic):

- Please provide an idursulfase production schedule for late February to the beginning of April 2006.
 - *We will submit this in an amendment as well as a fax.*
- Since this is a multi-product facility, please describe the other products produced in the same areas and equipment as idursulfase
 - *Three products are produced at the drug substance facilities:*
 - *Idursulfase (subject of BLA)*

/

- 
- *Is it possible for the inspectors to observe the production of the other products as representative of idursulfase production if idursulfase is not in production during the PLI?*

- 
- Please describe the distance between the three TKT facilities. You list the same FEI number for each.
 - *TK3 (DS manufacture), TK8 (headquarters and testing), and TK9 (warehouse for raw materials and DS storage) are within 5-20 minutes drive of each other.*
 - *Management is the same for all three facilities.*
 - Please describe your inspection history for these sites.
 - *No FDA GMP/pre-approval inspection has occurred at these sites.*
- 

- Please explain your relationship with Shire.
 - *TKT is a wholly owned subsidiary of Shire.*
 - *Shire acquired TKT in July 2005.*
 - *No Shire products are produced at the TKT facilities.*
 -

- Regarding Table 2.3.S.2-1 “Contract Testing Laboratories”, please explain if _____ are used for testing of product intended for the US market. Our inspection information database lacks information on these sites.
 - *Both sites have been and will be used for _____ of idursulfase intended for US market.*
 - *These sites were previously named _____ which may explain the lack of information in your database.*
 - *TKT performed vendor qualification for these sites and ensured the assays were validated.*

- Please include the registration numbers for these sites in the amendment so we can perform another compliance check using the name “ _____” and the registration numbers.

- Please explain if _____ will be used for product intended for distribution in the US.

The conversation concluded.

cc: HFD-180, Stark, C., OND/ODE3/DGP (e-copy and archival)
HFD-328, Uratani (e-copy)
HFD-328, Renshaw
HFD-328, Hughes (e-copy)
HFD-122, Beaucage (e-copy)
HFD-122, Cherney (e-copy)
HFD-328, TFRB Blue Files (STN 125151.0)
HFD-328, TFRB Facility Files, TKT, FEI 1000513202, Cambridge, MA

Archived File: S:\archive\BLA\125151.0.tel.01-03-06.doc



DEC 12 2005

Transkaryotic Therapies, Inc.
Attention: Suzanne L. Bruhn, Ph.D.
Vice President, Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Bruhn:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): BL 125151/0

Name of Biological Product: Idursulfase

Indication: — treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II)

Date of Application: November 23, 2005

Date of Receipt: November 23, 2005

User Fee Goal Date: May 25, 2006

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
<http://www.fda.gov/oc/datacouncil/spl.html>.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. 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

If you have any questions, please contact the Regulatory Project Manager, Cristi Stark, at (301) 796-1007.

Sincerely,

A handwritten signature in black ink, appearing to read 'Cristi Stark', written in a cursive style.

Cristi L. Stark, M.S.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



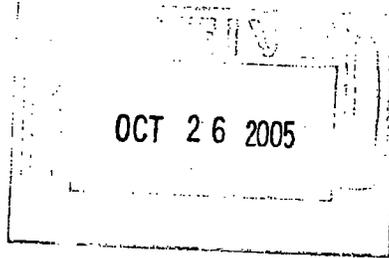
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our Reference: BB-IND —

Transkaryotic Therapies, Inc.
Attention: Suzanne Bruhn, Ph.D.
Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139



OCT 26 2005

Dear Dr. Bruhn:

Please refer to your **Investigational New Drug Application (IND)** for "Iduronate-2-Sulfatase (human, recombinant, human fibroblast cells, Transkaryotic Therapies)" and to the meeting held on September 27, 2005, between representatives of your firm and this agency. As requested in your letter of July 6, 2005, a copy of our memorandum of that meeting (or telephone conversation) is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact me at (301) 796-1007.

Sincerely yours,

Cristi L. Stark, M.S.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: OCT 26 2005
From: *Cristi Stark, DGP, ODEIII*
To: IND —
Subject: Type B Meeting Summary

Meeting Date: September 27, 2005

Time: 12:00-1:30pm

Location: White Oak Conference Room 1311

Meeting Requestor/Sponsor: Transkaryotic Therapies

Product: Iduronate-2-Sulfatase (human, recombinant, human fibroblast cells, Transkaryotic Therapies)

Proposed Use: Treatment of Mucopolysaccharidosis II (Hunter syndrome, MPS II)

Type of meeting: pre-BLA

Meeting Purpose: To discuss the content and format of the BLA.

FDA Attendees: John Hyde, Anne Pariser, Brian Harvey, Serge Beaucage, Gibbes Johnson, Brian Strongin, Stella Grosser, Anil Rajpal, Jasti Choudary, Cristi Stark, Marc Walton, Tanya Clayton

Sponsor Attendees: Paul Martha, Joseph Muenzer, Bill Ciambone, Marc Wiles, Alyssa Wyant, Marcio Voloch, Peter O'Brien, Robert Mensah, David Pizzi, Howard Yuwen, Suzanne Bruhn

Note: *FDA provided TKT with draft responses to questions via fax on September 26, 2005. The following minutes include those responses along with additional comments from the meeting discussions.*

Page 2, IND - preBLA

Sponsor questions and FDA response:

Clinical:

1. *Are the clinical data adequate and sufficient to support a BLA with the proposed indication(s) and dose for the intended population?*

On review of data contained in the pre-BLA package, the following are noted:

- a) The mildly affected MPS II patients are not well represented in the patient population in the TKT024 pivotal study; this may be insufficient to support a broad indication.
- b) TKT024EXT study clinical outcomes for at least the first six months would be of interest and should be included in the BLA submission. This is particularly true for patients in the placebo group transitioning to active treatment.

Discussion at meeting: TKT stated that there are clinical data at four and eight months. FDA clarified that the request for this information was not a requirement, but the data might be very helpful in support of efficacy.

- c) The six-minute walk test (6MWT) efficacy endpoint is highly dependent on patient effort. As inadvertent unblinding to treatment due to infusion reactions (IRs) is likely to occur with the infusion of any protein, please be sure to include analyses of IRs that examine the correlation between IRs and response to treatment. Depending on the pattern of IRs, appropriate analyses could include any or all of the following: analyses of response to treatment separately for the subgroups with and without IRs, or in subgroups with early (e.g., first 4 to 6 weeks) vs. late IRs; analyses of treatment response stratified by, or otherwise adjusted for, frequency of IRs; comparison of rates of improvement before and after the initial IR. We would be interested in similar analyses of IRs and response in the TKT024EXT study for the placebo group after crossing over to active treatment. In addition to the classic reactions, you should try to identify unblinding IRs by looking for adverse events that occur on the day of infusion.

Discussion at meeting: TKT stated that they will describe all efforts to avoid unblinding in the BLA.

2. *Does the FDA agree that assessment of changes in absolute forced vital capacity (FVC) volumes are a useful aid in determining the clinical benefit of idursulfase therapy in Study TKT024?*

No. The magnitude of the absolute changes in FVC is of unclear clinical significance. As FVC depends on height and age, it must be interpreted relative to growth over the length of the study and as a percent of predicted. Absolute changes in FVC are also not directly

Page 3, IND — preBLA

related to clinical benefit. The results of FVC will be interpreted along with the results of the 6MWT, and other secondary and exploratory endpoints (e.g., patient-reported outcome data).

Discussion at meeting: TKT noted that the primary analysis would use percent predicted.

3. *TKT intends to provide the safety update to the BLA approximately 4 months following the original BLA submission. The safety update will include interim safety data from the ongoing studies TKT018 and TKT024EXT. Is this an acceptable timeline for the safety update, assuming that the BLA will have Priority Review status?*

This is acceptable only if the 4-month safety update is limited to timely updates from the two ongoing extension studies (TKT018 and TKT024EXT), and not a substitute for providing complete, detailed safety data in the original BLA submission (see answer to #4 below).

4. *TKT intends to submit safety synopses instead of full study reports for the ongoing studies TKT018 and TKT024EXT. Therefore, we will not include blank CRF's or patient CRF's for deaths, SAEs, or withdrawals due to AEs. Is this approach acceptable?*

No, this is not acceptable. The total patient exposure in the clinical development program is only 108 patients, so all safety data are relevant. Safety data that are as detailed and complete as possible would be expected, including detailed information on SAEs, deaths and AEs leading to withdrawal. In addition, the safety cutoff dates of April 2005 for TKT018 and TKT024EXT are too early. The safety cutoff date should not be more than six months prior to the BLA submission date (listed as November-December 2005 in pre-BLA package).

Discussion at meeting: TKT will submit all case report forms (CRFs) and serious adverse events (SAEs) in the BLA.

5. *TKT does not intend to include SAS programs and macros with the electronic datasets in the original BLA submission. Is this acceptable to FDA?*

No. Please include all SAS programs at the time of submission.

Nonclinical:

6. *Is the nonclinical package adequate to support a BLA filing?*

The package appears adequate.

Page 4, IND — preBLA

CMC:

7. *TKT believes that sufficient information has been collected from analytical and nonclinical studies to demonstrate the comparability of the material tested in Phase II/III trial and that intended for commercial use. Does FDA concur?*

On the basis of the information provided in the pre-BLA briefing package, the comparability analysis of Idursulfase manufactured by the Phase II/III and Commercial scale processes has the following deficiencies:

- (a) A side-by-side comparison of — commercial qualification lots and a minimum of — lots of Phase II/III clinical materials should be performed to demonstrate comparability of the two manufacturing processes. Please provide qualitative and quantitative results.
- (b) Side-by-side comparability of the materials produced by the two manufacturing processes should be demonstrated through degradation of the I2S lots under forced conditions. Stress stability tests may include ...
- (c) With the exception of the — which is used in the enzyme activity assay, has little structural relation to GAGS which are the physiological target for I2S.

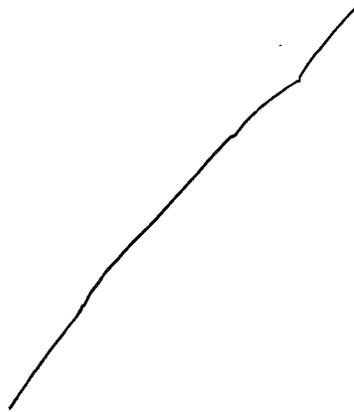
Discussion at meeting: TKT stated they now plan to use — as a substrate.

- (d) The methodology used in — assay is not rigorous.

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(e) All comparability data submitted using cell lines, including the — assay, should include clearly labeled raw data values prior to any calculations or subtractions of background, etc...

(f) The side-by-side comparability study should include the following tests:



In addition, all CMC comparability data submitted in the BLA should be consolidated into one section.

The results of the PK study in cynomolgus monkeys appear to demonstrate the comparability of the Phase II/III and commercial scale materials. However, we require individual animal data to make a determination of comparability. Please provide the following in the BLA submission: (1) individual concentration versus time data; (2) individual PK parameter values; and (3) summary statistics of PK parameter values for each of the materials.

With regard to clinical PK data, the meeting package provides graphs only of the mean concentration versus time profiles for patients receiving the commercial scale material and for patients receiving the Phase II/III scale material. Please also provide the following in the BLA submission: (1) individual concentration versus time data; (2) individual PK parameter values; (3) summary statistics of PK parameter values for each of the materials; and (4) a PK comparability analysis by calculation of the point estimate and 90% confidence interval of the ratio of log-transformed means of AUC for the test and reference products.

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8. *Will the data presented in the BLA be sufficient to support a 24-month Drug Product shelf-life claim?*

The proposed stability program for the Drug product can be improved through the use of the following stability-indicating tests:

- (a) —
(b) Improved potency assays (see discussion above and Additional CMC recommendations below)
(c) —

9. *Detailed narrative descriptions of analytical test methods will be provided in the BLA. An example is provided in Appendix 3. Please confirm that the format and contents of the narrative description is acceptable.*

Given that SOPs of the test methods will be included in the validation section of these methods (see question 10) there is no need for separate narrative descriptions of the test methods.

10. *Should FDA require the submission of actual copies of analytical test method SOPs, the SOPs will be provided in the methods validation package. Does FDA agree?*

SOPs for non-compendial analytical test methods should be included in the validation section of the test methods in the BLA. The suitability of compendial analytical test methods for drug substance and/or drug product must be demonstrated in the BLA.

11. *According to the FDA Draft Guidance to Industry "Analytical Procedures and Method Validation (issued August 2000) [1], it states that a separate methods validation package need not be submitted for BLAs. Please confirm.*

This is correct.

Regulatory:

12. *Idursulfase is intended to treat Hunter syndrome, a serious and life-threatening condition, and has demonstrated the potential to address unmet medical needs for such condition. TKT intends to request Priority Review of the BLA for this product which has been developed under Fast Track and Orphan Product programs. Does FDA concur that this standard has been met?*

Filing priority will be determined at the time of the filing decision.

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13. *TKT proposes to submit the original BLA per ICH CTD guidelines in a hybrid electronic format. Is the submission format as proposed acceptable?*

Yes.

Discussion at meeting: FDA added that they would like TKT to be sure the SAE tabulations included hyperlinks to the corresponding CRFs.

14. *Does the FDA review division expect any paper copies of the original BLA to be submitted?*

That depends on how the BLA is being submitted. If the official submission is electronic, then no additional paper reviewer aids are required.

Discussion at meeting: TKT stated the submission will be all electronic. FDA stated that then the only paper needed would be for signature pages.

Additional Comments/Recommendations:

1. If you and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

You should anticipate that a long-term Registry to follow MPS II patients would be a post-marketing commitment, provided the BLA is approved. You should begin formulating the design and implementation of a Registry in anticipation of this PMC requirement.

2. If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

RiskMAPs

2.5.5 Overview of Safety with appropriate cross references to section 2.7.4 Summary of Clinical Safety and any other relevant sections of the Common Technical Document for the BLA application.

Pharmacovigilance plans

2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include

Page 8, IND preBLA

proposed RiskMAPs in the BLA Clinical Data Section (21 CFR 601.25(b)(3)) and clearly label and index them.

Discussion at meeting: TKT stated the pharmacovigilance plans included postmarketing reports and a registry, and that these would be described in Module 5. There are no plans for a RiskMAP.

3. For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm> >

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

TKT has no plans to submit a RiskMAP; however they will provide a Pharmacovigilance plan and have a Global Registry.

4. If there is any information on product medication errors from the premarketing clinical experience, Office of Drug Safety requests that this information be submitted with the BLA application.

Discussion at meeting: TKT stated that they do not have medication errors.

5. You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available. The proposed proprietary name of _____ was found unacceptable. You need to submit a new proposed proprietary name.

Discussion at meeting: TKT replied that they will submit a new proposed trade name in the BLA submission.

6. Additional CMC recommendations:

With Regard to Release and Stability Testing of Drug Substance and Product:

- (a) For reasons discussed above, the potency assays using _____ and the _____ assay are of limited utility and are not optimal for control in the manufacture of an approved therapeutic enzyme. You should develop and

Page 9, IND — preBLA

implement an enzyme activity potency assay —
— You should evaluate the feasibility of using a —
— The — assay should be replaced with an assay which

(b) You should add a potency assay to the drug product stability program which —

In regard to Drug Substance Lot release tests:

- —
- Addition of an — est to complement the — assay is recommended.
- Inclusion of an action limit for — , in the — release test is required.

In regard to Drug Product Lot release tests:

- A method that would detect product-related impurities and/or substances such as — is required.

In regard to the Drug Substance Stability Program:

- — s recommended as a stability indicating test.

In regard to the Drug Product Stability Program:

- Stability Tests on Drug Product Diluted in Infusion Bags are required.

Action Items:

- Teleconference to reach agreement on CMC issues/details.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

STN # 125151/0

Date: January 26, 2006

From: Brian E. Harvey, M.D., Ph.D., Division Director

Subject: Designation of Review Schedule for original BLA review

Sponsor: Transkaryotic Therapies, Incorporated

Product: Idursulfase

Clinical Indication: — treatment of patients with Hunter syndrome
(Mucopolysaccharidosis II, MPS II)

Standard (10 month)

Priority (6 month)

Signature

Brian E. Harvey

Date

1/26/06

RECORD OF MEETING

<u>IND</u>	<u>Number</u>	<u>Office</u>	<u>Meeting Date</u>	<u>Date of Memo</u>	<u>Date of Last Revision</u>
IND	—	OTRR	01-JUL-1999	07-SEP-2005	07-SEP-2005

Title: Iduronate-2-Sulfatase (human, recombinant, human fibroblast cells, Transkaryotic Therapies)

Sponsor: Transkaryotic Therapies Inc

Sponsor Participants: KURT GUNTER
KEN LOVEDAY
JOSEPH MUENZER
THOMAS SCHUETZ
SANDRA SELDEN
DOUGLAS TRECO

FDA Participants: EARL DYE
BLAIR FRASER
MARTIN GREEN
MELVIN LESSING
JOHN MCCORMICK
ELLIS UNGER
MARC WALTON
KAREN WINESTOCK

Purpose: PRE-IND (PI)

Summary:

FROM: Karen D. Winestock
Consumer Safety Officer
OTRR/DARP/AAB

SUBJECT: Pre-IND Teleconference Meeting Minutes for Iduronate-2 Sulfatase
Transkaryotic Therapies, Incorporated
1:00 - 2:00
WOC I DARP Conference Room

TO: Clinical Trials Minutes File

Additional FDA Attendee: Sally Hausman

INTRODUCTION:

Thomas Shuetz of Transkaryotic Therapies gave an overview of the draft Phase 1/2 clinical protocol design, endpoints, and clinical development plan. The sponsor intends to evaluate enzyme safety and obtain information on dose ranging for a latter pivotal study.

RECORD OF MEETING

<u>IND</u>	<u>Number</u>	<u>Office</u>	<u>Meeting Date</u>	<u>Date of Memo</u>	<u>Date of Last Revision</u>
IND		OTRR	01-JUL-1999	07-SEP-2005	07-SEP-2005

Their goal is to obtain long-term efficacy data from this initial study then proceed with a maintenance trial to expand the safety database. Data from this initial trial would allow the sponsor to glean potential efficacy endpoints. Lastly, the sponsor wanted to change the study's length to a 3 to 6 month study pending further study data.

PRECLINICAL DISCUSSION ISSUES:

Martin Green informed the sponsor that CBER preferred that this study only be done on monkeys instead of monkeys and rodents and that staggered multiple dosing was not necessary at this time. He informed the sponsor that dosing be initiated at the same time on 4 monkeys/dose/group and that a 13-week interim kill be performed on half of the monkeys, then proceed with the study for 6 months, then sacrifice the remaining monkeys. Secondly, trough levels should be done before dosing and monkeys should be bled on the first and last day and the sponsor should make sure the monkeys were not bled out. The sponsor also needed to do biodistribution studies to see if the biologic is active in monkeys. CBER also informed the sponsor that some of the data from these studies needed to be submitted with the IND application.

Transkaryotic Therapies asked CBER why rodent dosing should not be performed since the ICH recommends using two species of animals and that traditional toxicology information usually looks at two species in order to compare effects. Secondly, the sponsor informed CBER that they wanted to use rats to generate more dosing data.

CBER informed the sponsor that for biologics relevant animals needed to be used and that acute study information was not needed.

The sponsor agreed to do PK bleeding on day 1, at an interim time, before the last dose, and then sometime after the last dose had been given. This information would be included in the toxicity studies.

CLINICAL DISCUSSION ISSUES:

*Assuming that the nonclinical toxicology studies support the dose range of the proposed Phase 1/2 study, are the increments between doses and the time interval between dose groups (dose group stagger) appropriate?

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IND		OTRR	01-JUL-1999	07-SEP-2005	07-SEP-2005

Ellis Unger informed the sponsor that based on toxicity studies a single dosing regime should be initiated first and he asked why the sponsor wanted to do multiple dosing. Martin Green also questioned the sponsor regarding their ability to adequately assess dosing effects using their proposed repeat dosing regime and whether the uptake seen in monkeys would be the same in humans. The sponsor informed CBER that they envisioned their product — and that multiple doses would allow them to better evaluate safety of the product and that in order to obtain proper dosing information, patients would require multiple doses.

Transkaryotic Therapies informed CBER that they assumed the uptake in monkeys and humans would be the same but they were not certain. They felt that a definitive answer to this question would require performing a longer than 6-month study and given the limited patient database this question could not be properly addressed. In response to the dosing regime, the sponsor agreed to do a single dose study with observation for a while then proceed with a multiple dose study.

Transkaryotic Therapies asked CBER if there were any safety issues.

Marc Walton asked the sponsor about potential immune responses, specifically, if there were any safety risks that might result in patients whom endogenous enzyme is absent.

The sponsor informed CBER that the disease is caused by multiple mutations, but that all patients have at least a small amount of this enzyme present. Thus, the sponsor believes a single dose is unlikely to generate adverse events. Marc Walton pointed out that the sponsor had no real evidence that this was the case, and that this premise was somewhat speculative.

The sponsor asked what would be the minimum interval for single dosing before they could go to multiple dosing? Marc Walton informed the sponsor that all decisions regarding the dosing regime would be based on the preclinical information and the study's design.

*Are the inclusion/exclusion criteria in the proposed Phase 1/2

RECORD OF MEETING

<u>IND Number</u>	<u>Office</u>	<u>Meeting Date</u>	<u>Date of Memo</u>	<u>Date of Last Revision</u>
IND	OTRR	01-JUL-1999	07-SEP-2005	07-SEP-2005

study appropriate?

* Is it appropriate to _____

Ellis Unger asked the sponsor if _____

_____ Ellis Unger also questioned why there was an exclusion of patients with an I.Q. below 70. The sponsor informed CBER that the disease is a continuum and that the distinction between "mild" and "severe" is artificial. The exclusionary factor of I.Q. < 70 was used to facilitate subject cooperation. CBER informed the sponsor that if they wanted to use the I.Q. of 70 as an exclusionary factor, the features investigators must distinguish needed to be listed. However, CBER felt it would be better to do a study that focused on the entire spectrum of the disease state and that the sponsor should not enroll patients who would cripple the study. The sponsor informed CBER that the I.Q. criteria would be removed but, that they might do a subset study using patients with pared down capabilities.

*We believe that change in urine GAG levels is an appropriate primary endpoint for this Phase 1/2 study, and if a significant decrease were observed, would support a licensure application. Please comment.

Marc Walton informed the sponsor that it was too early to discuss a primary endpoint for accelerated approval and that the sponsor should first propose surrogate endpoints and show why they are likely to predict clinical benefit. CBER informed the sponsor that this data should be assembled and discussed during the IND stage. The sponsor informed CBER that the BMT data would be summarized in tabular form and literature on urine GAG and metabolism changes would also be submitted.

*It is our belief that a placebo control arm would not be appropriate in a pivotal study in patients with Hunter Disease. Please comment.

CBER acknowledged that performance of a placebo-controlled study could be difficult, due to parental pressures for the active enzyme. CBER explained that if the sponsor wanted to do an

RECORD OF MEETING

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IND		OTRR	01-JUL-1999	07-SEP-2005	07-SEP-2005

uncontrolled trial, they would have to show a clinical benefit that would not be seen during the natural progression of the disease, i.e., unequivocal alteration of the natural history of the disease. John McCormick informed the sponsor that they must know the rate of downhill progression for the parameter(s) to be assessed. The sponsor expressed understanding on this point.

CBER asked the sponsor what the target date of submission would be. The sponsor informed CBER that before this meeting the date was December 1999.

DECISIONS/CONCLUSIONS REACHED:

Nonclinical

1. A 6-month monkey study will be performed with 3-month interim data submitted with IND application. Data will be collected from interim bleeds at the beginning, middle, and end of the study.
2. Biodistribution studies will be performed and the data submitted.
3. QA and QC toxicology data signatures would not have to be submitted with the IND, but must be submitted within 120 days of the IND submission.
All other information data sects and summary studies needed to be submitted with the IND.
4. Toxicity data would be submitted on a disc.

Clinical

1. A single dose study would be performed followed by a multiple dose study.
2. In Phase 1/2 protocol inclusion/exclusion criteria for cooperative patients must be explained.
3. I.Q. criteria will be replaced with more specific clinical conditions.
4. Sponsor will look at changes in urinary GAG.

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5. Sponsor will propose surrogate endpoints and support their proposal with data that show the likelihood of predicting clinical benefit.

6. Sponsor will provide data on natural history of the disorder and provide information about the rate of change of clinical parameters to be assessed.

The meeting was adjourned.

Signature: _____ Mail Code: _____

Forward the signed original of this form to DCC for filing
in the IND



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference: BB-IND

JAN 08 2003

Transkaryotic Therapies, Incorporated
Attention: Neil Kirby, Ph.D.
Vice President, Global Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Kirby:

Please refer to your **Investigational New Drug Application (IND)** for "Iduronate-2-Sulfatase (human, recombinant, human fibroblast cells, Transkaryotic Therapies)" and to the meeting held on December 10, 2002, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

A handwritten signature in cursive script that reads "Katherine Needleman".

Katherine Needleman, M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: JAN 08 2003
From: Katherine Needleman, M.S., DARP, TPPB, HFM 588 KN
To: Transkaryotic Therapies Inc (TKT)
Subject: IND - End of Phase 2 Meeting Summary

Meeting Date: December 10, 2002

Time: 3:00 – 4:30 p.m. EST

Location: WOC-1, Conference Room 2

Meeting Requestor/Sponsor: Transkaryotic Therapies Inc (TKT)

Product: Iduronate-2-Sulfatase (human, recombinant, human fibroblast cells, Transkaryotic Therapies)

Proposed Use: Enzyme replacement therapy for mucopolysaccharidosis II (MPS II, Hunter Syndrome)

Type of meeting: End of Phase 2

Meeting Purpose: To provide preclinical and clinical comments based on the briefing document provided for review and questions presented by TKT.

Sponsor questions and FDA response, in order of discussion:

1. *Does the FDA agree that the primary endpoint is clinically relevant in MPS II?*

- No. The liver/spleen component of the composite, unlike the other components, is not readily interpretable with respect to clinical meaningfulness. The other components of the composite are generally more clinically interpretable because they assess functional outcomes. The use of a composite primary endpoint is reasonable as long as the components of that composite are interpretable assessments of clinical benefit. FDA has the following specific concerns about the proposed primary endpoint:
 - As noted, the combined liver/spleen volume component is of unclear clinical meaningfulness. While TKT indicates that liver and spleen size may have some correlates with clinical chemistry changes, the cited small changes in liver function tests and rise of platelets (all values still within the normal range) are not

a meaningful benefit to patients. Therefore, this component is not an appropriate element of a clinical endpoint.

- For other endpoints, such as relative change from baseline to week 52 in percent predicted FVC and 6 minute walk test, the absolute changes are more readily interpretable, and FDA recommends using the absolute changes in these assessments for the primary statistical analysis. However, the relative change in these endpoints as a sensitivity analysis to help understand the effects of this product would be appropriate.
- Regarding the joint range of motion as a component of the primary endpoint, TKT has proposed specific criteria for each joint to determine grading of outcome. It is important that these criteria establish a clinically meaningful change, not simply a reproducible assessment. TKT has not provided justification for these criteria. Please evaluate and submit the data supporting the proposed criteria as establishing a clinically meaningful change, and ensure that each joint's criteria satisfies this principle.

2. *If statistical significance ($p < 0.05$) were reached with the primary endpoint, would the FDA consider the finding to be sufficient to support approval of a BLA?*

- Not with the endpoint as currently proposed; see question 1. The data has to be indicative of clinically meaningful benefit in the components of this composite primary endpoint and the safety profile has to be balanced against the potential benefits to be realized with the use of this product.

3. *Does the FDA believe that the rank sum method is a valid method for measuring the statistical difference between the DRX006A treated group and placebo groups?*

- Yes. The rank sum method is reasonable for the primary statistical analysis of efficacy. However, the separate and parallel analyses of each component of this endpoint are important to comprehensively exploring the study results.

4. *Does the FDA believe that the sample size is sufficient to demonstrate safety in this rare disease?*

- In general, FDA considers the safety database of all subjects exposed to the product. However, the most relevant safety data frequently comes from controlled studies. A balance between the demonstrated benefits and the safety findings/risks will be an important consideration in assessing the sufficiency of the overall safety database, and it is impossible to determine a "requisite" sample size for safety until we acquire more data from the proposed studies. Safety signals observed during the trial could mandate a need for expansion of the sample size for safety assessments. Based upon the available data, the proposed sample size for a safety database may be reasonable. However, it is impossible to concur on this number at the present time.

5. *Accelerated approval regulations provide for marketing of a product on the basis of endpoints other than standard clinical efficacy endpoints. TKT would like to discuss the use of unvalidated surrogates for efficacy in the development and registration of DRX006A in the treatment of MPS II.*

- FDA will consider the use of surrogates in the design of clinical studies. There are multiple issues related to the use of surrogate endpoints as major study outcomes. Some of the concerns include the following: TKT would need to establish that any unvalidated surrogates are reasonably likely to predict the clinical benefits expected in MPS II, by submitting sufficient data to support the adequacy of the surrogate as a predictor of clinical benefit. In addition, studies designed to be confirmatory of the surrogates (ie., studies utilizing clinical endpoints) need to be planned and reviewed with FDA on a timely basis in order to ensure that they can be successfully conducted. In general, it is wise to initiate the confirmatory studies prior to the accelerated approval of this product. TKT should take into consideration the ability to complete any proposed confirmatory studies, and how marketing of the product might impact this ability. One approach would be for TKT to design separate studies, one (or more) to investigate the product's effect on the surrogate and another study or set of assessing clinical endpoints (the confirmatory studies). An alternative approach might involve the performance of a single major clinical study in which a surrogate endpoint is assessed at an interim analysis and the study continued in a manner that allows end-of-study clinical endpoints to be assessed. Hence, the same study would provide the results of surrogate outcomes but continue in sufficient duration such that the study agent's treatment effects could be conclusively assessed using clinical endpoints. The latter design might lessen concerns about unavailability of such rare subjects for multiple trials. The sponsor may wish to consider other study design options.

6. *Do the nonclinical studies (see Attachment 1) support initiation of the Phase III clinical trial?*

- In general, no. This conclusion is based in large part, upon the manufacturing changes and the need for more comprehensive data from the summarized animal studies. Please submit the data from the following studies that were cited as ongoing/planned in the original submission, and which are mentioned briefly in Attachment 1:
 - Studies in knock out (KO) mice evaluating the efficacy of DRX006A as related to dosing frequency.
 - The relationship of urinary GAG levels to tissue GAGs.
 - Studies in the KO mouse to look at the systemic and tissue distribution profile of DRX006A.

- Use of KO mouse to assess the potential for immunogenicity in relation to activity.
- There are notable CMC changes that are occurring with the product. TKT needs to perform some bridging studies in the KO mice to assess the overall safety/activity comparability of the Phase 3 material with the Phase 2 material. The studies should include both products and be designed to assess the parameters listed above (immunogenicity, systemic/tissue distribution, activity, toxicity, etc).
- Before giving the new iteration of the product to humans, the animal comparability/safety data must be submitted for review.
- Before initiating a major clinical study using the new iteration of the product, the sponsor should obtain human pharmacokinetic (PK) studies. One approach would be to obtain these data from the on-going uncontrolled clinical study. The sponsor is encouraged to contact FDA pharmacologists (Dr. Green and others) to discuss these issues.
- Mercedes Serabian is available at (301) 827-5095 to discuss these and any additional preclinical issues that may be required.

Additional Comments/Recommendations:

Clinical Comments:

- The proposed subject population for the study is broad, covering a large spectrum of disease severity and predominant organ involvement. This approach may be useful in obtaining a broader clinical experience with the study agent, and FDA encourages studies that include as broad of a clinical population as feasible. However, the broadness also may severely limit the ability of the study to demonstrate efficacy. Specifically, the inclusion of subjects with minimal or no impairment applicable to the primary efficacy outcome limits the ability of the study agent to affect a clinical benefit in these subjects. Additionally, the broad range of impairment leads to the possibility of imbalance in randomization in the nature of involvement and/or severity between groups. While this broad approach may be appropriate to study some effects of DRX006A in MPS II, specific and differential effects in subsets of this population might be missed and efficacy may be difficult to readily demonstrate. In order to improve the study, FDA recommends stratifying the eligible subjects by certain criteria relevant to ascertainment of efficacy, such as severity at baseline.
- Data from Phase 1 and preclinical studies do not provide sufficient information to identify the optimal dose and dosing regimen for a Phase 3 trial. Nor is there presently adequate information to form solid estimates on the nature, degree, and frequency of clinical benefit that can be expected. FDA recommends very strongly that TKT conduct

additional (Phase 2) dose ranging studies to provide better information regarding product activity with balanced toxicity and intolerance effects. In addition, FDA recommends that these studies extend to durations sufficient to observe meaningful changes in endpoints that will allow for a better design of a Phase 3 (confirmatory) study. A well-designed Phase 2 study will better ensure successful ultimate clinical development of the product.

- FDA notes that it is conceivable a dose ranging study might provide sufficient data to support a license supplement. However, the design of such a study involves many considerations and the sponsor should submit the protocol for such a study in a manner that allows a comprehensive FDA review and the opportunity for alteration of the study design, if necessary.

Chemistry, Manufacturing, and Controls Comments:

- In addition to the immunological assays discussed during the December 9, 2002 teleconference, FDA has an additional immunogenicity issue. Please review the data for infusion reactions that may have taken place during the initial trials. If such infusion reactions are noted, FDA recommends developing assays to monitor the potential development of allergic reactions (e.g. RAST assays).

FDA Attendees: Bradley Glasscock, Katherine Needleman, Yuan Who Chen, Ilan Irony, Dwaine Rieves, Marc Walton, Mercedes Serabian, Ghanshyam Gupta, Janet Whitley

Sponsor Attendees: Neil Kirby, Thomas Schuetz, Suzanne Bruhn, Stephen Schmitz, Robert Mensah, Alan Kimura, Joseph Muenzer (University of North Carolina)