CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-575

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022575 SUPPL # HFD # 180

Trade Name VPRIV

Generic Name velglucerase alfa

Applicant Name Shire HGT

Approval Date, If Known 2/26/10

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

Investigation #2 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: R. Wesley Ishihara
Title: Chief, Project Management Staff
Date:

Name of Office/Division Director signing form: Donna Griebel, M.D.
Title: Director, Division of Gastroenterology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/26/2010

JULIE G BEITZ
02/26/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 022575 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:Division of Gastroenterology Products PDUFA Goal Date: 2/26/10 Stamp Date: 8/31/2009

Proprietary Name: VPRIV

Established/Generic Name: velaglucerase alfa

Dosage Form: Lyophilized powder for reconstitution with Sterile Water for injection

Applicant/Sponsor: Shire HGT

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For long-term enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/17/2010

700 Main Street
Cambridge, MA 02139
Tel 617.349 0200
Fax 617 613 4004
www.shire.com

Shire
Human Genetic Therapies

Debarment Certification Statement

This certifies that Shire Human Genetic 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 Federal Food, Drug, and Cosmetic Act in connection with this application.

Nikhil Mehta, PhD
Vice President, Global Regulatory Affairs

June 18, 2009.
Date

PMC 1600-01

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to utilize an antibody screening assay cut point based on a mean + 1.645 standard deviation for assay values from treatment naïve Gaucher patients. Shire will utilize the same methodology to calculate the anti-imiglucerase ECL cut point.

PMR/PMC Schedule Milestones:

Protocol Submission Date:	NA
Study Initiation Date:	NA
Study Completion Date:	NA
Final Study Report Submission Date:	05/31/2010
Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Prelimary re-analysis by the sponsor indicates that a lowered cutpoint does not change patient immunogenicity profiles sufficiently to suggest a serious safety concern. Therefore, this commitment is appropriates as a PMC since it will involve a laboratory study that will take several months to complete, and it does not address a safety concern that would justify delaying approval of a product for which there is a drug shortage.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

PMC 1600-01

4. If not required by regulation, characterize the review issue leading to this **PMC**

b(4)

In their original NDA submission, the sponsor utilized ~~~ as a cutpoint for defining patient serum samples as positive for anti-velaglucerase and anti-imiglucerase antibodies. Based on the data for assay validation, this criterion results in very high confidence (99.95%) that samples judged to be negative are truly negative, and conversely, a very low (0.05%) confidence that a given sample judged to be positive is in fact negative. The sponsor has found that using a mean + 1.645 SD of healthy normal human serum samples as suggested in (Mire-Sluis, et. al., 2004) results in an unacceptably high (20%) level of positive values for sera from treatment-naïve Gaucher patients. Therefore, it is reasonable to establish a cutpoint based on mean+ 1.645 SD for assay values from treatment-naïve Gaucher patients, with the expectation that this will yield an ~ 5% false positive rate.

5. What type of study or clinical trial is required or agreed upon (describe)?

This study will contain the following elements

1. Evaluation of the mean +1.645 standard deviations of data sets for treatment naïve anti-velaglucerase and anti-imiglucerase screening assay values as cutpoints for positive sera. In order to account for individual assay variation, it may be necessary to develop "floating" cutpoints that rely on appropriate assay controls to normalize the read-outs from individual assays to the read-outs obtained during the original assessment of pre-treatment Gaucher sera.

2. Implementation of revised cutpoints for anti-velaglucerase and anti-imiglucerase positive sera based on the above studies.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

PMC 1600-01

Agreed upon:

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

- ☒ Other

  Laboratory study to develop screening assay cutpoints based on assay values for pre-treatment Gaucher serum samples.

6. Is the PMR/PMC clear and feasible?

   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

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

PMC 1600-02

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to revise the cut point for the confirmatory anti-velaglucerase and anti-imiglucerase assay to a level that is less than or equal to the cut point of the screening assay.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	05/31/2010
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The sponsor has determined that 14 out of the 15 patient serum samples found to be positive with a preliminary revision of the cutpoint for the screening assay were also positive with the existing confirmatory assay cutpoint. This indicates that the existing confirmatory assay cutpoint may be close to a value necessary to confirm positive immune reactions. Therefore, this commitment is appropriate as a PMC since it will involve a laboratory study that will take several months to complete, and it does not address a safety concern that would justify delaying approval of a product for which there is a drug shortage.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

PMC 1600-02

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

PMC 1600-02

4. If not required by regulation, characterize the review issue leading to this **PMC**

For the confirmatory assay (RadioImmunoPrecipitation, or RIP), the positive cut point is currently set at the LOD value, [redacted]. The sponsor has been asked, (PMC 1) to analyze pre-treatment Gaucher Serum samples to revise the cutpoint of the screening assay [redacted] in the original NDA submission). This re-evaluation will result in a lower cutpoint for the screening assay. Therefore, the cutpoint of the confirmatory assay will need to be revised to be less than or equal to the cuptoint for the revised screening assay.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Contingent upon re-evaluation of the anti-velaglucerase an danti-imiglucerase screening assay to produce a lowered cuptoint, the cutpoint of the confirmatory assay will need to be revised to be consistent with the screening assay. This may require re-validation of the confirmatory assay for higher sensitivity.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness

PMC 1600-02

☐ Nonclinical study, not safety-related (specify)

☒ Other
Laboratory study to revise the cutpoint for the confirmatory anti-velaglucerase and anti-imiglucerase assay

6. Is the PMR/PMC clear and feasible?

☒ Are the schedule milestones and objectives clear?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-03

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to re-assess the IgE cut point for the current ECL methodology using a chemically synthesized hybrid control. Shire commits to support assay validation using patient baseline values.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	05/31/2010
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Hypersensitivity reactions, which are likely to involve an IgE response, were very limited in number during the sponsor's clinical trials. Therefore, this commitment is appropriate as a PMC since it will involve a laboratory study that will take several months to complete, and accurate measurement of IgE responses does not address a safety concern that would justify delaying approval of a product for which there is a drug shortage.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

A high degree of linearity was demonstrated for the response of this assay to [redacted] aIgG-human IgE control antibody over the range 0.156 -10 µg / ml. However, the calibration range is much greater than the expected [redacted] range for an IgE response. The sponsor has established an assay cutpoint that is 10-fold the mean background of pre-immune serum assay values. The sponsor states that the naïve patient sera values varied widely in providing a rationale for this cutpoint. In order to establish a new, lower cutpoint, the sponsor will need to re-validate their IgE assay over a lower range appropriate to that expected for IgE responses. The sponsor will also need to assess Gaucher patient baseline serum samples using the revised cutpoint.

b(4)

PMC 1600-03

5. What type of study or clinical trial is required or agreed upon (describe)?

This study will contain the following elements:

a. Validation of the anti-velaglucerase and anti-imiglucerase IgE assay in the range consistent with expected IgE responses.

b. Assessment of Gaucher patient baseline serum samples using the revised cutpoint.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other

Laboratory study to validate the IgE assay in the expected range of IgE responses, and assess Gaucher patient baseline serum samples using the revised cutpoint.

PMC 1600-03

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-04

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to develop an assay to measure the ability of patient antibodies to block the uptake of velaglucerase and imiglucerase into target cells.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	11/30/2010
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

During the sponsor's clinical trials, there was no clear loss of efficacy that would suggest the presence of neutralizing antibodies. Therefore, this commitment is appropriate as a PMC since it involves a laboratory study that will take nine months to complete, and it does not address a efficacy concern that would justify delaying approval of a product for which there is a drug shortage.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Enzyme Replacement Therapies (ERT) require that ERT products are active within target cells for which the deficiency of a given enzyme is deleterious. Thus uptake of enzyme replacement products into appropriate target cells is a critical aspect of their mechanism of action. For this reason an assay for antibody neutralization of cell uptake is an important part of profiling patient immune responses, and will need to be developed by the sponsor.

PMC 1600-04

5. What type of study or clinical trial is required or agreed upon (describe)?

The study will consist of the following elements.

a. Design and development of an uptake neutralization assay.

b. Validation of the assay

c. Implementation of the assay for evaluation of patient neutralizing responses

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other

Laboratory study to develop an assay to measure the ability of patient antibodies to block the uptake of velaglucerase and imiglucerase into target cells.

PMC 1600-04

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-05

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: To reanalyze all archived pharmacokinetic (PK) samples for Study TKT032 (using adequate in-process quality controls and standard curves) and recalculate velaglucerase alfa PK parameters

PMR/PMC Schedule Milestones:

Protocol Submission Date:	_____
Study Initiation Date:	_____
Study Completion Date:	05/31/2010
Final Study Report Submission Date:	06/30/2010
Other: _____	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Considering the supply shortage of the currently marketed imiglucerase and the demonstrated clinical efficacy and safety of velaglucerase alfa, a definitive PK characterization can be deferred post approval as described in 21 CFR §320.22 (e). Thus, the post marketing commitment (PMC) study is recommended.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

It has been concluded that the in-process velaglucerase alfa assay performance, in the definitive PK trial, was insufficient since duplicates rather than 3-5 replicates of quantity control (QC) samples were included in patient PK sample assays. As such, the PK parameters characterized by the sponsor and submitted in the current NDA cannot be considered accurate and reliable for labeling purposes.

PMC 1600-05

5. What type of study or clinical trial is required or agreed upon (describe)?

The agency recommends the sponsor reanalyze all archived pharmacokinetic (PK) samples for Study TKT032 using adequate in-process quality controls and standard curves (see VII. C. Application to Routine Drug Analysis in Bioanalytical Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf.). Using these new assay results, prepare a new PK report that would adequately characterize velaglucerase alfa PK.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other
Reanalyzing the archived PK samples for study TKT032 and recalculating velaglucerase alfa PK parameters using new assay results.

PMC 1600-05

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-06

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: To conduct a prospective PK study in patients with Type 1 Gaucher disease in the case that the sponsor fails to adequately characterize velaglucerase alfa PK using the archived PK samples (PMC #1600-05)

PMR/PMC Schedule Milestones:

Protocol Submission Date:	12/31/2010
Study Initiation Date:	_____
Study Completion Date:	03/31/2013
Final Study Report Submission Date:	09/30/2013
Other: _____	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Considering the supply shortage of the currently marketed imiglucerase and the demonstrated clinical efficacy and safety of velaglucerase alfa, a definitive PK characterization can be deferred post approval as described in 21 CFR §320.22 (e). Thus, the post marketing commitment (PMC) study is recommended.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

It has been concluded that the in-process velaglucerase alfa assay performance, in the definitive PK trial, was insufficient since duplicates rather than 3-5 replicates of quantity control (QC) samples were included in patient PK sample assays. As such, the PK parameters characterized by the sponsor and submitted in the current NDA cannot be considered accurate and reliable for labeling purposes and require that a new study be performed in the case that the sponsor fails to adequately characterize velaglucerase alfa PK using the archived PK samples (see PMC #1600-05).

PMC 1600-06

5. What type of study or clinical trial is required or agreed upon (describe)?

We recommend that the sponsor conduct a new PK study as a PMC with an appropriately validated assay to characterize the pharmacokinetics of velaglucerase alfa in the proposed patient population. The number of evaluable patients should be sufficient and the patients' age should cover the full range of the proposed age groups including pediatric population. The limit of quantitation of the assay method should be sensitive enough to characterize the distribution and elimination phases.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☒ Other

A prospective PK study in patients with Type 1 Gaucher disease in the case that the sponsor fails to adequately characterize velaglucerase alfa PK using the archived PK samples (see PMC #1600-05).

PMC 1600-06

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-07

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to develop and implement a kinetic assay with a physiologically relevant substrate for drug substance and drug product release and stability testing. Results and specifications will be included in the final report.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	12/31/2011
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire already has an assay in place to measure enzyme activity. The enzyme activity assay requested in this PMC is expected to be more sensitive because it will mimic the natural substrate/enzyme interactions. Implementation of this assay will require lengthy development studies. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes that the benefit of approval outweighed the risk associated with a less sensitive assay and therefore decided the assay could be developed as a Post marketing Commitment.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

PMC 1600-07

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

The enzymatic activity assay used in the release and stability program for drug substance and drug product measures enzyme activity using a surrogate substrate at saturating concentration. Based on the data submitted in the NDA, the enzyme activity assay that measures the kinetic parameters Km and kcat using a physiologically relevant substrate is more sensitive than the enzyme assay that uses the surrogate substrate to changes in the product induced by a variety of stress conditions. Therefore, the enzyme assay based on the surrogate substrate may not be adequately sensitive to monitor subtle but significant changes in product quality.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should develop and implement an assay that measures the kinetic enzymatic parameters Km and kcat using a physiologically relevant substrate, and use this assay for drug substance and drug product release and stability testing.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

PMC 1600-07

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-08

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to develop and implement a quantitative method that measures total carbohydrate content. Results and specifications will be included in the final report.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	02/28/2011
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire currently has a qualitative method in place for glycan profiling. While this assay could detect major changes in glycan content, a quantitative method that measures moles of carbohydrate per mole of protein is a much more sensitive method to ensure that carbohydrate content of the product is consistent. Implementation of this assay will require lengthy development studies. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes that the benefit of approval outweighed the risk associated with a less sensitive assay and therefore decided that the assay could be developed as a Post marketing Commitment.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Shire monitors glycan content of velaglucerase using High Performance Anion Exchange-Pulsed Amperometric Detection. The method assesses the relative distribution of the major glycan species present in velaglucerase but does not monitor the total amount of carbohydrates linked to velaglucerase. Thus, some lots could have a much lower glycan content relative to the amount of API present but would not be evaluated. Since the total amont of these sugars relative to protein and not to each other is a critical parameter for assuring product efficacy, we believe actual glycan content should be specified in addition to the percentage of the glycans present.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should develop and implement an assay that quantitatively measures the total carbohydrate per mole of protein, and include the new assay in the drug substance release specifications.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

PMC 1600-08

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-09

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to replace the non-quantitative SDS-PAGE Silver stain method with a quantitative SDS-PAGE Coomassie test for release of drug substance and drug product. Results and specifications will be included in the final report.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	02/28/2011
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire is currently using an SDS-PAGE with Silver staining procedure to evaluate impurities that can be distinguished by molecular weight. This procedure is very sensitive but not quantitative. The SDS-PAGE with Coomassie staining procedure is sufficiently sensitive and allows for quantitative measurements of these impurities, therefore providing a more consistent way of assessing product quality. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes that the benefit of approval outweighed the minor risk associated with a lack of a quantitative measure of these impurities and therefore decided the assay could be developed as a Post marketing Commitment.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

PMC 1600-09

4. If not required by regulation, characterize the review issue leading to this **PMC**

Shire currently uses SDS-PAGE Silver stain to monitor purity of drug substance and drug product at release, but switches to SDS-PAGE Coomassie stain for stability testing. We believe it is important to have quantitative assays to measure product purity at release and over the product's shelf life. While very sensitive, SDS-PAGE Silver stain is not a quantitative method while the SDS-PAGE Coomassie stainign method is quantitative and has sufficient sensitivity to monitor relevant product and process related substances (covalent aggregates, truncated API and host cell protein impurities). Therefore, Shire should apply the SDS-PAGE Coomassie staining method to drug substance and drug product release.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should replace the non-quantitative SDS-PAGE Silver stain method with a quantitative SDS-PAGE Coomassie stain test. Results and specifications will be included in the final report.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

6. Is the PMR/PMC clear and feasible?

☒ Are the schedule milestones and objectives clear?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-10

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to demonstrating that [redacted] is well controlled to ensure no impact on product quality. The results will be included in the final report. b(4)

PMR/PMC Schedule Milestones:

Protocol Submission Date:	NA
Study Initiation Date:	NA
Study Completion Date:	NA
Final Study Report Submission Date:	02/28/2011
Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire decided not to include a quantitative measure of [redacted] content in the drug substance release specifications because they believe the process is well controlled and yields physiologically insignificant levels [redacted]. However, while the information provided supported this conclusion, it was not sufficient to ensure that the process will consistently deliver the appropriate level of impurity clearance particularly at the extremes of allowable operating parameters. Because of supplier issues, this assay can not currently be performed for release until a new assay is developed. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, and the fact that the process appears well controlled and is well within established operating parameters, the Division believes the risk to product quality is low and therefore providing additional information on process control could be developed as a Post marketing Commitment

b(4)

2. If required, characterize the **PMR.** Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

- **Which regulation?**
  - ☐ Accelerated approval
  - ☐ Animal efficacy confirmatory studies
  - ☐ Pediatric requirement
  - ☐ FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Shire monitored for process-related impurities at release and has provided a rationale for excluding based on the fact that the levels detected are much lower than the physiologically relevant levels. However, insufficient information has been provided to ensure that the process will consistently deliver the appropriate level of impurity clearance. We recommend that Shire provides data to show that the process, when performed according to the ranges of acceptable operating parameters established in the batch record instructions, will consistently yield a product with the expected impurity profile.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire will need to develop a new assay to measure and either use it as a release specification or provide clearance studies demonstrating that when run at the extremes of the established operating parameters, the process provides adequate clearance of this process related impurity.

b(4)

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

PMC 1600-10

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-11

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to demonstrate the clearance capability of the process to remove [redacted] through [redacted] spike studies. The results will be included in the final report.. b(4)

PMR/PMC Schedule Milestones:

Protocol Submission Date:	NA
Study Initiation Date:	NA
Study Completion Date:	NA
Final Study Report Submission Date:	11/30/2010
Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire measured levels [redacted] in drug substance and concluded that the amounts received by patients would be below physiological levels. However, the information provided was not sufficient to ensure that the process will deliver the appropriate level of impurity clearance when urn at the extremes of the established operating parameters. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, and that the process seems well controlled and is well within the established operating parameters the Division believes the risk to product quality is low and therefore the studies can be performed as a Post marketing Commitment.

b(4)

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Shire is monitoring for process-related impurities at release and has provided a rationale for excluding [redacted], based on the fact that the levels detected are much lower than the physiologically relevant levels. However, insufficient information has been provided to ensure that the process will consistently deliver the appropriate level of impurity clearance. We recommend that Shire provides data to show that the process, when performed according to the ranges of acceptable operating parameters established in the batch record instructions will consistently yield a product with the expected impurity profile.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

b(4)

Shire will provide clearance studies demonstrating that when run at the extremes of the established operating parameters, the process provides adaquete clearance

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

PMC 1600-11

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-12

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to re-evaluating drug substance and drug product release and stability specifications. Shire will submit the revised specifications and supporting data in the final report.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	12/31/2011
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Although the current release and stability protocols provide some assurance of product quality and stability, a more robust evaluation should be developed by Shire. The acceptance criteria for many assays are fairly wide. While the lots produced so far have shown acceptable results that are on line with the manufacturing history and clinical experience, there is a risk that maintaining the current acceptance criteria could potentially result in lots that are within specification but out of trend with lots used in the clinical trials. This practice is frequently used for new products to ensure product availability while information is obtained on process capability. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes to have the studies and assay developed as a Post marketing Commitment is a low risk.

2. If required, characterize the **PMR.** Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

PMC 1600-12

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Shire proposed acceptance criteria for the drug substance and drug product release and stability specifications based on a calculation of the tolerance intervals because only a limited number of lots have been manufactured, hence process capability is not well understood. The acceptance criteria proposed by Shire appear too wide and do not reflect manufacturing history or clinical experience.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should re-evaluate the release and stability control strategies and tighten acceptance criteria based on results of lots manufactured with the commercial process and characteristics of the lots used in the clinical trials.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

_____

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

_____

☐ Subpopulation (list type)

_____

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

PMC 1600-12

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-13

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to update the specifications for SEC, RP-HPLC, and glycan map, and to include acceptance criteria for the leading shoulder in SEC-HPLC, for peak ~~~ in RP-HPLC, and for peak ~~~ in the glycan map. b(4)

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	07/01/2010
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The acceptance criteria established by Shire for SEC-HPLC, RP-HPLC and glycan map do not include specific criteria for low levels peaks detected in the chromatograms. Since the risk to product quality is dependent on the nature of the attribute, DTP believes each peak should be specified rather then allowing for a limit on total impurities, as this provides better assurance of product quality. While the testing results presented so far demonstrate that the product is within manufacturing history and clinical experience, these low levels peaks should also be monitored to ensure the risk to product quality is controlled. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, there is an important benefit for approval. On the other hand, the Division believes the risk to product quality, by allowing these validation studies and specifications to be implemented in a post approval commitment, is low.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

PMC 1600-13

4. If not required by regulation, characterize the review issue leading to this **PMC**

For the SEC-HPLC assay, Shire set acceptance criteria for the main peak and the aggregate peak. However, Shire did not set an acceptance criterion for the leading shoulder. The leading shoulder represents an oxidized form of velaglucerase (oxidation of Cys126), which Shire has shown to have decreased enzyme activity and lower cellular uptake compared to the non-oxidized form. We believe the oxidation of Cys126 is a critical quality attribute that should be routinely monitored on release and stability. For the RP-HPLC assay, Shire set acceptance criteria for the main peak and peak —. However, Shire did not set acceptance criteria for peaks —. We believe that limits should be set that reflect the risk to product quality based on your existing knowledge regarding the specific attribute. Given Shire's lack of knowledge concerning these substances, individual peaks should be specified rather then establishing collective acceptance criteria that could allow for much greater amounts of these substances then what was observed in the clinical studies.
The glycan mapping acceptance criteria do not include an acceptance criterion for peak — consists of phosphorylated and capped glycan species, which we believe should be routinely monitored.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should update the specifications for SEC-HPLC, RP-HPLC and glycan map to include acceptance criteria for the leading shoulder (SEC-HPLC), Peak — (RP-HPLC) and Peak — (glycan map). This will involve some validation studies and risk analsis for establishing appropriate limits.

b(4)

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

PMC 1600-13

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

6. Is the PMR/PMC clear and feasible?

☒ Are the schedule milestones and objectives clear?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-14

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to update the peptide map specification using new acceptance criteria to reflect better control of impurities. Shire commits to adding the peptide map as a drug substance and drug product release and stability test with the new acceptance criteria.

PMR/PMC Schedule Milestones:

Protocol Submission Date:	NA
Study Initiation Date:	NA
Study Completion Date:	NA
Final Study Report Submission Date:	07/01/2010
Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire already has a peptide map assay in place to evaluate drug substance identity. This assay is multifunctional and is useful to assesss product purity as well. Shire is monitoring purity using SEC-HPLC and RP-HPLC, and this assay will provide additional assurance that the product quality characteristics are well controlled. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes that the benefit of approval outweighs the risk associated with a less robust evaluation/assurance of impurities and therefore decided that the specification could be developed as a Post Marketing Commitment

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

PMC 1600-14

4. If not required by regulation, characterize the review issue leading to this **PMC**

5. Shire is using peptide mapping solely to determine identity. Peptide mapping is a relevant assay to assess purity as well as identity, and the information gained through this assay should be incorporated in the release and stability programs for drug substance and drug product. While the applicant may be looking at this information this should be clearly documented in the specification.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should re-evaluate the current peptide map assay and use it in the determination of product purity. This will involve some validation studies and risk analysis for establishing appropriate limits.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness

PMC 1600-14

☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-15

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to include the cellular uptake bioassay for drug product release testing.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	04/01/2010
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire is already using the cellular uptake assay to monitor drug product stability. Incorporation of the assay in the drug product release testing will add an additional layer of control on drug product quality for routine release. Since glycan content is measured and is a critical attribute for ensuring receptor binding and uptake there is overlapping control for this biological property of the product. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes that the benefit of approval outweighs the risk associated with a less robust assurance of product potency and therefore decided that the specification could be developed as a Post Marketing Commitment

2. If required, characterize the **PMR.** Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

PMC 1600-15

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Shire is currently using the cellular uptake assay in drug product stability; however, the assay is not included in the dug product release testing. We believe cellular uptake is a critical quality attribute that should be monitored both at release and during stability.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire will include the cellular uptake assay in drug product release and involves no studies. The PMC will be implemented in a timely fashion.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

_____

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

_____

☐ Subpopulation (list type)

_____

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

PMC 1600-15

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-16

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to provide a report containing the sub-visible particulates [redacted] analyses, risk assessment and risk mitigation strategies.. b(4)

PMR/PMC Schedule Milestones:

Protocol Submission Date:	NA
Study Initiation Date:	NA
Study Completion Date:	NA
Final Study Report Submission Date:	09/30/2010
Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Immunogenicity is a concern for all protein products and can be triggered by aggregated products. Standard assays are in place to monitor for aggregation, such as Size Exclusion HPLC. Small aggregate can be detected by this method. Additionally, assays to monitor for particulates, based on USP methods, are also in place to monitor particles greater than 10 micrometer. However, protein particles below 10 micrometers are not routinely monitored. While the risk for immunogenicity is unknown, Shire should collect data on protein particulates [redacted] and develop a risk mitigation strategy. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes that the benefit of approval outweighs the risk associated with a theoretical risk associated with protein aggregates and therefore decided that the specification could be developed as a Post Marketing Commitment b(4)

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

- **Which regulation?**
  - ☐ Accelerated approval
  - ☐ Animal efficacy confirmatory studies
  - ☐ Pediatric requirement
  - ☐ FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

PMC 1600-16

4. If not required by regulation, characterize the review issue leading to this **PMC**

Large protein aggregates in therapeutic protein products may enhance immune responses to the active moiety. These product-related variants should be appropriately characterized and controlled. While USP method <788>, monitors particulates that are greater then 10 µm in size, particulates that are smaller then 10 µm are not evaluated by this test. Although there is a gap in current analytical technology for quantitation of sub-visible particulates between 0.1 and 2.0 µm, suitable techniques such as light obscuration can quantitate particles in the [redacted] range an should be employed in the assessment of product quality. We therefore believe Shire should evaluate the risk to product quality with regard to these particulates. b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should develop and implement an assay that quantifies protein particulates in the the [redacted] range at release and during real time and stressed conditions, and evaluate the risk to product quality in relationship to safety and efficacy. Shire should develop a risk assessment and a risk mitigation strategy if warranted. b(4)

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness

PMC 1600-16

☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

6. Is the PMR/PMC clear and feasible?

☒ Are the schedule milestones and objectives clear?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-17

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to include drug substance and drug product stress conditions in the annual stability program. The revised stability protocols will be included.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	04/01/2010
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The current annual stability protocol for drug substance and drug product provides for one lot of drug substance and drug product to be entered on stability at the approved storage conditions. However, the approved storage conditions (-65 to -85 °C and 2 to 8 °C, respectively) are not permissive for significant product degradation and therefore do not provide an adequate level of sensitivity to confirm that routine minor changes in operations or equipment do not have an impact on product quality. Because stress stability studies can detect subtle differences in product quality that may not be ready detectable by release tests or the proposed stability protocol, FDA requested the addition of a stress stability protocol that would be capable of detecting these differences in a timely manner. Considering that the stability protocol will be implemented during the next year and the fact the new protocol will be approved in a post approval supplement before implementation, there is no approval issue.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

PMC 1600-17

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

PMC 1600-17

4. If not required by regulation, characterize the review issue leading to this **PMC**

The annual stability program Shire has in place for drug substance and drug product provides for one lot of drug substance and one lot of drug product to be entered in the stability program at the proposed storage conditions. However, the purpose of the annual stability program is not to confirm stability at the intended storage conditions, but rather to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the stability profile of the product. Stability studies conducted under the recommended storage conditions (-65°C and 2-8°C for drug product) are not adequate to address this issue because little or no degradation is likely to occur under these conditions even when there is a problem with product stability. We believe accelerated and stressed stability studies should be incorporated in the annual stability program for drug substance and drug product.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should implement an annual stability program that includes accelerated and stressed conditions.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

PMC 1600-17

- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- ☐ Dose-response study performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

  _____

- ☐ Other

  _____

6. Is the PMR/PMC clear and feasible?

   - ☒ Are the schedule milestones and objectives clear?
   - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

PMC 1600-18

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Title: Shire commits to evaluate the impact of pH on the in-use stability of the drug product and to provide assurance that procedures are in place to control this risk to product quality.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	NA
	Study Initiation Date:	NA
	Study Completion Date:	NA
	Final Study Report Submission Date:	12/31/2010
	Other: _____	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Shire provided data assessing the stability of the drug product after dilution in saline solution. However, saline solutions are known to vary significantly in pH levels, yet the impact of different pH values may have on the stability of the diluted product was not addressed. The pH of the final container may vary between 5.7 and 6.3 so it is rather narrow and stress studies at pH 8.0 and 4.0 showed that approximately 50% of product potency is lost over 4 days so there is some risk associated with this issue. However, the product is formulated with a weak buffer and more importantly, significant amounts of protein contribute to the buffering capacity of the product and finally, the product can only be stored for 1 day in saline. So, although product quality can be impacted it would be expected to be much less then observed under the stress conditions evaluated. Considering that velaglucerase will alleviate the current drug shortage for imiglucerase, an orphan drug for the treatment of Gaucher's disease, the Division believes that the benefit of approval outweighs the risk associated with the potential impact to product quality by a slight shift in the pH and therefore decided that the study could be developed as a Post Marketing Commitment.

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**
     - ☐ Accelerated approval
     - ☐ Animal efficacy confirmatory studies
     - ☐ Pediatric requirement
     - ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Shire provided data assessing the stability of the drug product diluted in saline solution for infusion. However, Shire did not address the impact that saline solution of different pH may have on product quality. It is known the saline can vary by several pH can vary by several units so this parameter should be studied to ensure the product has sufficient buffering capacity when resuspended in saline.

5. What type of study or clinical trial is required or agreed upon (describe)?

Shire should perform a study to assess the impact of saline solution with different pH on product quality. This could involve simply a pH study if the value stays within the range known to have no impact to product quality but may involve a physicochemcal analysis of the product if the fromulation does not keep the solution within the appropriate range.

Required

- ☐ Pharmacoepidemiologic study (list risk to be evaluated)
- ☐ Registry studies
- ☐ Primary safety study or clinical trial (list risk to be evaluated)
- ☐ Subpopulation (list type)
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing studies
- ☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

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

PMC 1600-18

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
03/02/2010

JOHN E HYDE
03/02/2010

Ishihara, Richard

From: Ishihara, Richard
Sent: Thursday, February 25, 2010 12:04 PM
To: 'Wyant, Alyssa'
Cc: 'Yuwen, Howard'; 'Mehta, Nikhil'; Ishihara, Richard; 'Bayless, Lynn'
Subject: (NDA 022575) VPRIV PMCs and PI

Follow Up Flag: Follow up
Flag Status: Red

Attachments: 10-0225 VPRIV PI FDA revised.doc; 10-0225 VPRIV PMCs FDA proposed.doc

Dear Alyssa,

As discussed, I am providing additional edits to the PI. I will call you to discuss further. I am also providing you with updated PMC language with mostly minor edits and one correction. I will also discuss this with you when I call. These are the versions that I will need you to send to the application as "agreed to" versions of the PI and PMCs. Thanks.


10-0225 VPRIV PI FDA revised.d...


10-0225 VPRIV PMCs FDA propose..

Respectfully,

Wes Ishihara
LT, U.S. Public Health Service Commissioned Corps
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-0069 (office)
(240) 328-8926 (mobile)
(301) 796-9905 (fax)
richard.ishihara@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/25/2010

Ishihara, Richard

From: Ishihara, Richard
Sent: Wednesday, February 24, 2010 5:11 PM
To: 'Mehta, Nikhil'
Cc: 'Wyant, Alyssa'; 'Bayless, Lynn'; 'Yuwen, Howard'; Ishihara, Richard
Subject: (NDA 022575) VPRIV PI FDA Comments

Follow Up Flag: Follow up
Flag Status: Red

Attachments: 10-0224 VPRIV PI FDA revised clean.doc; 10-0224 VPRIV PI FDA revised redline.pdf

Dear Nik,

Attached you will find FDA revisions to the VPRIV PI.


10-0224 VPRIV PI FDA revised c...


10-0224 VPRIV PI FDA revised r...

Respectfully,

Wes Ishihara
LT, U.S. Public Health Service Commissioned Corps
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-0069 (office)
(240) 328-8926 (mobile)
(301) 796-9905 (fax)
richard.ishihara@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/25/2010

Ishihara, Richard

From: Ishihara, Richard
Sent: Wednesday, February 24, 2010 12:52 PM
To: 'Mehta, Nikhil'
Cc: 'Wyant, Alyssa'; 'Bayless, Lynn'; Ishihara, Richard
Subject: (NDA 022575) FDA Comments on VPRIV PMCs

Importance: High

Follow Up Flag: Follow up
Flag Status: Red

Attachments: 10-0224 VPRIV PMCs FDA proposed redline.pdf; 10-0224 VPRIV PMCs FDA proposed.doc

Dear Nik,

Attached you will find FDA comments on the VPRIV PMCs. We will use this for discussion during today's meeting.

10-0224 VPRIV PMCs FDA propose..

10-0224 VPRIV PMCs FDA propose..

Respectfully,

Wes Ishihara
LT, U.S. Public Health Service Commissioned Corps
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-0069 (office)
(240) 328-8926 (mobile)
(301) 796-9905 (fax)
richard.ishihara@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/25/2010

Ishihara, Richard

From: Ishihara, Richard
Sent: Monday, February 22, 2010 12:54 PM
To: 'Mehta, Nikhil'
Cc: 'Bayless, Lynn'; 'Yuwen, Howard'; 'Wyant, Alyssa'; Ishihara, Richard
Subject: RE: (NDA 022575) VPRIV PI - Section 14

Follow Up Flag: Follow up
Flag Status: Red

Attachments: 10-0222 VPRIV PI FDA revised Section 14.pdf

Dear Nik,

After further internal review, the team has the attached additional edits to Section 14.

10-0222 VPRIV PI
FDA revised S...

Respectfully,

Wes Ishihara

From: Ishihara, Richard
Sent: Friday, February 19, 2010 5:27 PM
To: 'Mehta, Nikhil'
Cc: 'Bayless, Lynn'; Yuwen, Howard; 'Wyant, Alyssa'; Ishihara, Richard
Subject: (NDA 022575) VPRIV PI - Section 14

Dear Nik,

Attached you will find revisions to Section 14 of the VPRIV PI that FDA would like Shire to consider. Most of the revisions are in line with the "Guidance for Industry - Clinical Studies Section of Labeling for Human Prescription Drug and Biologic Products - Content and Format" (link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075059.pdf). Please note that portions of this section are still under review and additional comments may be necessary.

<< File: 10-0219 VPRIV PI FDA Revised Sec 14 Only.doc >>

Respectfully,

Wes Ishihara
LT, U.S. Public Health Service Commissioned Corps
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-0069 (office)
(240) 328-8926 (mobile)
(301) 796-9905 (fax)
richard.ishihara@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/23/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022575

DISCIPLINE REVIEW LETTER

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

Dear Dr. Mehta:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VPRIV (velaglucerase alfa for injection).

Our review of the CMC section of your submission is complete, and we have identified the following deficiency:

You are proposing a qualification program for your drug substance reference standard that includes release testing and additional characterization assays. The acceptance criteria you have established for the qualification program are the same acceptance criteria you are using for release testing. Use of the release testing acceptance criteria would allow for product characteristics in a new reference standard to be out of trend with the desired or expected product characteristics. The reference standard chosen should be suitable for its intended purpose, which in many cases would translate to ensuring the quality characteristics that the product is expected to possess. This is particularly important when the results of an analytical method are expressed as a percentage of the reference standard. In such cases, the product attribute of a new standard must be highly similar to the previous standard in order to prevent a drift in that product characteristic over time. Your acceptance criteria in the established specifications are not suitable for this purpose.

We recommend that you revise your reference standard qualification program by tightening your acceptance criteria for attributes that are relevant to the intended purpose of the standard and by including additional characterization assays that are also relevant to the intended purpose of the standard. For a potency standard, such assays may include measurement of Km and kcat using a physiologically relevant substrate, mannose receptor binding, and any additional assays that are useful to characterize the physiochemical properties of this standard. Additionally, the qualification program should also include a stability protocol for your reference standard that is aligned with the above principles. Note that it may be necessary to have multiple standards, each specifically designed for its intended purpose. With these comments in mind, submit a revised reference standard qualification protocol and include a detailed description of how the reference

standard will be used and a justification for the proposed acceptance criteria for the standard. Alternatively, other regulatory pathways may be further discussed.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call me at (301) 796-0069.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/19/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022575

POSTMARKETING COMMITMENTS

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

Dear Dr. Mehta:

Please refer to your new drug application (NDA) dated and received on August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for VPRIV (velaglucerase alfa).

We have reviewed the chemistry, manufacturing, and controls (CMC), non-clinical, clinical pharmacology, and clinical sections of your submission and are providing you with our proposed postmarketing studies. We request that you review our proposal and submit a response to NDA 022575 by close of business February 23, 2010.

CMC

1. The enzymatic activity assay you are using in your release and stability program for drug substance and drug product measures enzyme activity using a surrogate substrate at saturating concentration. Based on the data you submitted in the NDA, the enzyme activity assay that measures the kinetic parameters Km and kcat using a physiologically relevant substrate is more sensitive than the enzyme assay that uses the surrogate substrate to measure changes in the product induced by a variety of stress conditions. Therefore, the enzyme assay based on the surrogate substrate may not be adequately sensitive to monitor subtle but significant changes in product quality. We recommend that you implement measurement of Km and kcat using a physiologically relevant substrate for drug substance and drug product release and stability. We suggest the following PMC language:

   To develop and implement a potency assay that measures the kinetic parameters Km and kcat using a physiologically relevant substrate in the drug substance and drug product release and stability protocols. The proposed specification and supporting data will be included in the final report.

   Final Report Submission: [*insert proposed date*]

2. You are monitoring glycan content of velaglucerase using High Performance Anion Exchange-Pulsed Amperometric Detection. The method assesses the relative distribution of the major glycan species present in velaglucerase. However, this method does not monitor the total amount of carbohydrates linked to velaglucerase which we believe is a critical parameter when assessing product quality as it relates to safety and efficacy. We recommend that a quantitative measurement of total carbohydrate/mole of protein be included in your drug substance release specifications. We suggest the following PMC language:

   To develop and implement an assay that quantifies the total carbohydrate/mole of enzyme for drug substance release. The proposed specification and supporting data will be included in the final report.

   Final Report Submission: [*insert proposed date*]

3. You are using SDS-PAGE Silver stain to monitor the purity of the drug substance and drug product at release, but switch to SDS-PAGE Coomassie for stability testing. We believe it is important to have quantitative assays to measure product purity at release and over the product's shelf life. While very sensitive, SDS-PAGE Silver stain is not a quantitative method. Additionally, although SDS-PAGE Coomassie can be a quantitative method, you are not applying this method quantitatively to your drug substance and drug product stability protocols. We recommend that a quantitative SDS-PAGE Coomassie be included in the drug substance and drug product release and stability protocol, to quantitatively monitor purity. We suggest the following PMC language:

   To implement a quantitative SDS-PAGE Coomassie assay for drug substance and drug product release and stability testing.

   Final Report Submission: [*insert proposed date*]

4. Your SOP for SDS-PAGE Silver stain, SDS-PAGE Coomassie and SDS-PAGE immunoblot specify that the analyst compares the samples to the reference standard and monitors for the appearance of new bands that may appear in the gel. However, no assay control is included in the SOP that would allow for assurance whether the impurities are expected or unexpected. We therefore recommend use of an appropriate reference standard control, which contains the expected degradation products of velaglucerase, in addition to the velaglucerase reference standard. We suggest the following PMC language:

   To update the SOP for SDS-PAGE Silver stain, SDS-PAGE Coomassie, and SDS-PAGE immunoblot to include an appropriate reference standard that contains degradation products of velaglucerase.

   Final Protocol Submission: [*insert proposed date*]

5. You are monitoring for process-related impurities at release and have provided a rationale for excluding [redacted] from release testing, based on the fact that the levels detected are much lower than the physiologically relevant levels. However, insufficient information has been provided to ensure that the process will consistently deliver the appropriate level [redacted] clearance. We recommend that methods that monitor for [redacted] be included in your release specifications for the drug substance, or that you provide data to show that the process, when performed according to the ranges of acceptable operating parameters established in the batch record instructions, will consistently yield a product with the expected impurity profile. b(4)

   We suggest the following PMC language:

   a. To establish a drug substance release specification for [redacted] content; and
   b. To establish a drug substance release specification for [redacted] content ; or
   c. To provide validation data supporting [redacted] clearance. b(4)

   Final Protocol Submission: [*insert proposed date*]
   Final Report Submission: [*insert proposed date*]

6. You have proposed acceptance criteria for your drug substance and drug product release and stability specifications based on a calculation of the tolerance intervals. The acceptance criteria you proposed appear too wide and do not reflect your manufacturing history or clinical experience. Additionally:

   a. In your SEC-HPLC assay you have set acceptance criteria for the main peak and the aggregate peak. However, you have not set an acceptance criterion for the leading shoulder. The leading shoulder represents an oxidized form of velaglucerase (oxidation of Cys126), which you have shown to have decreased enzyme activity and lower cellular uptake compared to the non-oxidized form. We believe the oxidation of Cys126 is a critical quality attribute that should be routinely monitored on release and stability.

   b. In your RP-HPLC assay, you have set acceptance criteria for the main peak and peak [redacted]. However, you have not set acceptance criteria for peaks [redacted]. We believe that limits should be set that reflect the risk to product quality based on your existing knowledge regarding the specific attribute. Given your lack of knowledge concerning these substances, individual peaks should be specified rather than establishing collective acceptance criteria that could allow for much greater amounts of these substances than were observed in your clinical studies. b(4)

   c. Your glycan mapping acceptance criteria do not include an acceptance criterion for peak [redacted]. Peak [redacted] consists of phosphorylated and capped glycan species, which we believe should be routinely monitored. b(4)

d. You are using peptide mapping solely to determine identity. Peptide mapping is a relevant assay to assess purity as well as identity, and the information gained through this assay should be incorporated in your release and stability programs.

e. You are currently using the cellular uptake assay in drug product stability; however, the assay is not included in your dug product release testing. We believe cellular uptake is a critical quality attribute that should be monitored both at release and during stability.

We recommend that you re-evaluate your release and stability control strategies, tighten acceptance criteria and establish acceptance criteria for the SEC-HPLC leading shoulder, the RP-HPLC peak — and the glycan mapping peak – We also recommend that peptide mapping should be used to monitor purity and the cellular uptake assay should be included in the release protocol for drug product. We suggest the following PMC language: b(4)

To re-evaluate the release and stability specifications for drug substance and drug product, and:

a. To tighten drug substance and drug product release and stability acceptance criteria to better reflect the product used in the clinical trials.

b. To establish an acceptance criterion for the SEC-HPLC leading shoulder in drug substance and drug product release and stability specifications.

c. To establish an acceptance criterion for the RP-HPLC peak — in drug substance and drug product release and stability specifications. b(4)

d. To establish an acceptance criterion for glycan mapping peak – in the drug substance release specification.

e. To include peptide mapping to monitor purity in drug substance and drug product release and stability specifications.

f. To include the cellular uptake assay in the drug product release specifications.

Final Report Submission: [*insert proposed date*]

7. Because large protein aggregates in therapeutic protein products may enhance immune responses to the active moiety, these product-related variants should be appropriately characterized and control. While USP method <788>, monitors particulates that are greater than 10 µm in size, particulates that are smaller then 10 µm are not evaluated by this test. Although there is a gap in current analytical technology for quantitation of sub-visible particulates between 0.1 and 2.0 µm, suitable techniques such as light obscuration can quantitate particles in the — range and should be employed in your assessment of product quality. We therefore believe you should evaluate the risk to b(4)

product quality with regard to these particulates. We suggest the following PMC language:

To characterize the types and amounts of sub-visible particulates ____ in the drug product at release and under real time and stressed stability conditions and to evaluate the risk to product quality as it may relate to safety and efficacy. The results of these studies, together with a summary of your risk assessment and any proposed risk mitigation strategy, will be included in the final report. b(4)

Final Report Submission: [*insert proposed date*]

8. Your annual stability program for drug substance and drug product provides for one lot of drug substance and one lot of drug product to be entered in the stability program at the proposed storage conditions. However, the purpose of the annual stability program is not to confirm stability at the intended storage conditions, but rather to demonstrate that routine changes such as rotation of operators or minor equipment changes do not have a significant impact on the stability profile of the product. Stability studies conducted under the recommended storage conditions (-65°C and 2-8°C for drug product) are not adequate to address this issue because little or no degradation is likely to occur under these conditions even when there is a problem with product stability. We believe accelerated and stressed stability studies should be incorporated in your annual stability program for drug substance and drug product. We propose the following PMC language:

   To revise the annual drug substance and drug product stability program to include accelerated and stressed conditions.

   Final Report Submission: [*insert proposed date*]

Immunogenicity

9. You have established ____ a cut point for defining patient serum samples as positive for anti-velaglucerase and anti-imiglucerase antibodies. Based on the data for assay validation, this criterion results in a very high confidence (99.95%) that samples judged to be negative are truly negative, and conversely, a very low (0.05%) confidence that a given sample judged to be positive is in fact negative. Based on your evaluation of normal human serum samples, you have found that using a mean $\pm$ 1.645 standard deviations (SD), as suggested in Mire-Sluis, et. al., 2004, results in an unacceptably high (20%) level of positive values for sera from treatment-naïve Gaucher patients. Therefore, it is reasonable to attempt to establish a cut point based on mean $\pm$ 1.645 SD for assay values from treatment-naïve Gaucher patients, with the expectation that this will yield a ~ 5% false positive rate. It may also be reasonable to link this cut point to the calibration curve and positive control values on individual assay plates used for analysis of patient sera. We propose the following PMC language: b(4)

To develop a cut point for the anti-velaglucerase and anti-imiglucerase antibody screening assay that yields a false positive rate in the range of 5% of pre-immune patient serum samples.

Final Report Submission: [*insert proposed date*]

10. For the RIP assay, the positive cut point is currently set at the Limit of Detection (LOD) value, that is, [redacted] You have been asked in PMC # 1 to re-evaluate the cut point of the screening assay [redacted] to yield a higher false positive rate. This re-evaluation will, in all likelihood, result in a lower cut point for the screening assay. Therefore, the cut point of the confirmatory assay will need to be revised to be less than or equal to the cut point for the revised screening assay. We propose the following PMC language: b(4)

    To revise the cut point for the confirmatory anti-velaglucerase and anti-imiglucerase screening assays so that it is consistent with a revised cut point in the antibody screening assay.

    Final Report Submission: [*insert proposed date*]

11. A high degree of linearity was demonstrated for the response of the confirmatory IgE assay over the range 0.156 -10 ug/ml using the [redacted] antibody crosslinked to human IgE. However, the calibration range is much greater than the expected [redacted] range for an IgE response. In order to establish a new, lower cut point, you will need to re-validate your IgE assay over a lower range appropriate to that expected for IgE responses. If adequate sensitivity cannot be demonstrated in a lower range, you will need to develop a new, more sensitive IgE assay. We propose the following PMC language: b(4)

    To develop an assay for detection of anti-velaglucerase and anti-imiglucerase IgE antibodies that has a sensitivity commensurate with the expected range of IgE responses.

    Final Report Submission: [*insert proposed date*]

12. Enzyme Replacement Therapies (ERT) require that ERT products are active within target cells for which the deficiency of a given enzyme is deleterious. Thus, uptake of enzyme replacement products into appropriate target cells is a critical aspect of their mechanism of action. For this reason, an assay for antibody neutralization of cell uptake is an important part of profiling patient immune responses, and will need to be developed. We propose the following PMC language:

    To develop an assay that will measure the ability of patient antibodies to block the uptake of velaglucerase and imiglucerase into target cells.

    Final Report Submission: [*insert proposed date*]

Clinical Pharmacology

13. Provided that you have retained the samples from Study TKT032, re-analyze all archived pharmacokinetic (PK) samples for Study TKT032 using adequate in-process quality controls and standard curves (see VII. C. Application to Routine Drug Analysis in Bioanalytical Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf). Using these new assay results, prepare a new PK report that would adequately characterize the PK of velaglucerase alfa.

    In case the available PK samples are not stable enough to be re-analyzed, or there are significant numbers of missing samples such that the PK for velaglucerase alfa can not be adequately characterized, conduct a prospective PK study in patients with Type 1 Gaucher disease. The study should include the following considerations:

    - Use of an accurate, precise, and validated analytical method (see the FDA Guidance document referred to in the link above);
    - Inclusion of a sufficient number of patients representing the entire age range of the intended patient population; and
    - Inclusion of a sufficient number of time points for PK sampling in order to fully characterize the profile (i.e., sampling until velaglucerase alfa concentrations are undetectable using an appropriately established LOQ based on assay performance).

Final Protocol Submission:	[*insert proposed date*]
Study Completion Date:	[*insert proposed date, if applicable*]
Final Report Submission:	[*insert proposed date*]

If you have any questions, call me at (301) 796-0069.

Sincerely yours,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/19/2010

Ishihara, Richard

From: Ishihara, Richard
Sent: Friday, February 19, 2010 5:27 PM
To: 'Mehta, Nikhil'
Cc: 'Bayless, Lynn'; Yuwen, Howard; 'Wyant, Alyssa'; Ishihara, Richard
Subject: (NDA 022575) VPRIV PI - Section 14

Attachments: 10-0219 VPRIV PI FDA Revised Sec 14 Only.doc

Dear Nik,

Attached you will find revisions to Section 14 of the VPRIV PI that FDA would like Shire to consider. Most of the revisions are in line with the "Guidance for Industry - Clinical Studies Section of Labeling for Human Prescription Drug and Biologic Products - Content and Format" (link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075059.pdf). Please note that portions of this section are still under review and additional comments may be necessary.

10-0219 VPRIV PI
FDA Revised S...

Respectfully,

Wes Ishihara
LT, U.S. Public Health Service Commissioned Corps
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-0069 (office)
(240) 328-8926 (mobile)
(301) 796-9905 (fax)
richard.ishihara@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/19/2010

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2010

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: by secure email	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 022575) VPRIV Container labels and Carton Labeling Comment

Total no. of pages including cover: 1

Comments:

You are requested to respond to the below comment regarding the container labels and carton labeling for VPRIV:

The light green text used for the 400 unit product strength is difficult to read because it provides poor contrast against the white background. Revise the color of the 400 unit strength text in order to increase the contrast and improve readability.

Document to be mailed: ☐ YES X NO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	TRIAGE-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/18/2010

Ishihara, Richard

From: Ishihara, Richard
Sent: Wednesday, February 17, 2010 3:01 PM
To: Yuwen, Howard
Cc: 'Wyant, Alyssa'; 'Bayless, Lynn'; Ishihara, Richard
Subject: (NDA 022575) FDA Revisions to the VPRIV Package Insert

Attachments: 10-0217 VPRIV PI FDA Revisions Redline.pdf; 10-0217 VPRIV PI FDA Revisions clean.doc

Dear Howard,

I am sending this email to you in lieu of Dr. Mehta, as we have secure email established. In addition, I have copied Alyssa and Lynn. Attached you will find additional FDA revisions to the VPRIV package insert that will be discussed during tomorrow's tcon. Please note that we have withheld Section 14 from the attached document as this section is still being worked on internally at FDA. Comments on Section 14 will be forthcoming. Please let me know if you have any questions.


10-0217 VPRIV PI FDA Revisions...


10-0217 VPRIV PI FDA Revisions...

Respectfully,

Wes Ishihara
LT, U.S. Public Health Service Commissioned Corps
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-0069 (office)
(240) 328-8926 (mobile)
(301) 796-9905 (fax)
richard.ishihara@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/17/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022575

LABELING COMMENTS

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

Dear Dr. Mehta:

Please refer to your new drug application (NDA) dated and received on August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for VPRIV (velaglucerase alfa for injection).

We also refer to your submissions dated October 1, 2009.

We have reviewed your proposed container labels and carton labeling for VPRIV and are providing you with our comments.

Container Labels

1. The established name does not have a prominence commensurate to that of the proprietary name. Revise the established name per 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

2. Add the dosage form (i.e., for injection) to the listed established name velaglucerase alfa. In addition the dosage form should be presented in the same size and font as the established name. The established name should read:

   velaglucerase alfa for injection

3. Revise the product strength to read: XXX units/vial.

4. Relocate the product strength from the bottom of the principle display panel so that it immediately follows the established name and dosage form. In addition, increase the font size of the product strength on the container labels for improved readability. Thus, the

presentation of the proprietary name, established name, dosage form and product strength will appear as follows

VPRIV
(velaglucerase alfa for injection)
XXX units/vial

5. The product strengths are not differentiated, thus making the labels appear identical. Revise the product strengths so that they are readily distinguishable from one another through the use of colors, borders, shading or some other means, and ensure that they do not overlap to help minimize the risk of errors.

6. Revise the statement [redacted] to read: "Single use vial. Discard unused portion".

7. Include the route of administration "For intravenous use only" on the 200 unit vial.

8. Delete or decrease the size of the circle graphics and the Shire logo to allow room to incorporate the changes above.

9. Add the lot identification number and the expiration date [21 CFR 201.17].

Carton Labeling

10. See Container Labels comments 1 thru 5.

11. Revise the statement [redacted] to read: "Single use vial. Discard unused portion". b(4)

12. Include the route of administration "For intravenous use only" on the principle display panel.

13. Decrease the size of the circle graphics and the Shire logo on the 200 unit carton labeling to allow room to incorporate the changes noted in comment 10 above.

14. On the side panel of the carton labeling, delete the phrase [redacted]. Revise the sentence to read: "Following reconstitution with XX mL Sterile Water for Injection, USP the resultant concentration is 100 units/mL". b(4)

15. The proprietary name and established name appear on the side panel without the product strength. Revise to include the product strength.

16. The following statements are BLA requirements that may be removed:

    a. Contains one vial

    b. Contains no preservative

c. No U.S. standard of potency

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. It is requested that you promptly submit revised container labels and carton labeling consistent with the above comments.

If you have any questions, call me at (301) 796-0069.

Sincerely yours,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/10/2010

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 3, 2010

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-9400	**Fax number:** (301) 796-9905
Phone number: 781-482-2958	**Phone number:** (301) 796-0069

Subject: (NDA 22575) Information Request

Total no. of pages including cover: 2

Comments:
Please see the attached.

Document to be mailed: ☐ YES X NO

1. Provide information on Patient 034-048-0001 (Study TKT 034), who experienced a hypersensitivity episode on transition from imiglucerase to velaglucerase, and withdrew from the study. Clarify whether this patient continued treatment with imiglucerase, and whether there were any further adverse events.

2. For validation of the anti-velaglucerase and anti-imiglucerase screening assays, the acceptance criterion for limit of detection (LOD) is given as:

   LOD = [3.3 x (SD of y intercepts)]/slope of calibration curve.

   However, the below formula appears to have been used during validation to arrive at a 5 ng/ml LOD.

   LOD = [3.3 x (SD of y intercepts) + mean of y intercepts] / slope of calibration curve

   Your clarification is requested.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
02/04/2010

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 27, 2010

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-2958	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 22575) VPRIV Clinical IR

Total no. of pages including cover: 2

Comments:
Please see the attached.

Document to be mailed: ☐ YES X NO

We are evaluating Trial 034 to obtain information that may be helpful in providing appropriate dosing instruction for patients previously treated on a stable dose of imiglucerase. For Trial 034, submit:

1. A spreadsheet (e.g. Excel file) and graphical representation of hemoglobin concentrations across study visits for each individual patient. The patients should be separated by the dosage received. Specifically, create a graphic for each of the 15 U/kg, 30 U/kg, 45 U/kg, and 60 U/kg cohorts depicting each individual patient's laboratory information across study visits.

2. Create a graphic for each of the treatment cohorts showing only the mean hemoglobin concentration for the patients in that cohort. Repeat this for the platelet data as well as data for spleen and liver volumes, if available. The spreadsheet should contain treatment dose, individual patient identifier information, age, and laboratory values (i.e., hemoglobin, platelet, spleen volume, and liver volume) by study week.

Verify for Trial 034, that no patients required dosing adjustments over the study period (i.e., no patients required an increase in their velaglucerase dose as their clinical parameters had not returned to baseline within three months).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
01/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022575

LABELING COMMENTS

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

Dear Dr. Mehta:

Please refer to your new drug application (NDA) dated and received on August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for VPRIV (velaglucerase alfa).

We also refer to your submissions dated August 31 and November 20, 2009.

We have reviewed your proposed package insert for VPRIV and are providing you with our comments to facilitate labeling negotiations (see Attachment 1). We request that you review our proposed revisions and submit a response to NDA 022575 within a week of this letter.

If you have any questions, call me at (301) 796-0069.

Sincerely yours,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment: (1) VPRIV Package Insert with FDA Comments (redline)
(2) VPRIV Package Insert with FDA Comments (clean)
(3) Table: Adverse Reactions Occurring More Commonly in Children than Adults

34 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative Documents Section-_____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
01/29/2010

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 22, 2010

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-2958	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 22575) VPRIV (velaglucerase alfa) Information Request

Total no. of pages including cover: 2

Comments:
Please see the attached.

Document to be mailed: ☐ YES X NO

1. The production depyrogenation cycle [redacted]. The validation report 08-1501-REQ uses [redacted] for the [redacted] study and [redacted] for the [redacted]. These validation temperatures do not support the production cycle temperature. Justify this discrepancy.

b(4)

2. For biological indicators, provide the incoming acceptance criteria for the D-value and spore population.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
01/22/2010

Ishihara, Richard

From: Ishihara, Richard
Sent: Tuesday, January 19, 2010 4:50 PM
To: Yuwen, Howard
Cc: Ishihara, Richard
Subject: (NDA 22575) VPRIV; AE Coding to Support Labeling Discussions

Follow Up Flag: Follow up
Flag Status: Yellow

Attachments: velaglucerase pooled 32-34-39.JMP

Dear Howard,

I am forward this to you in lieu of Dr. Mehta because I don't think I have secure email established with Dr. Mehta. Attached you will find our Clinical Reviewer's AE dataset to support future labeling discussions. We are providing this to you in advance of the labeling discussion in hopes to make labeling negotiations more efficient. Please let me know if you have any questions.

velaglucerase
pooled 32-34-39....

Respectfully,

Wes Ishihara
LT, U.S. Public Health Service Commissioned Corps
Division of Gastroenterology Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-0069 (office)
(301) 796-9905 (fax)
richard.ishihara@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
01/19/2010

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2010

To: Nikhil Mehta	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-2958	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 22575) VPRIV (velaglucerase alfa) Request for Information.

Total no. of pages including cover: 2

Comments:
Please see the attached.

Document to be mailed: ☐ YES X NO

You are requested to respond to the following items:

1. Provide information on the source [redacted]

2. Provide the specifications [redacted]

3. In reference to your December 18, 2009, response to our Information Request, dated December 11, 2009, you provided that there was an aborted [redacted] on May 22, 2009, due to a critical failure [redacted] (fire/facility evacuation). The qualification data submitted in your December 18, 2009, response [redacted] predates this failure [redacted] Annual Performance Qualification Summary Report dated 19-March-2009) and is therefore invalid. Provide the revalidation report [redacted] performed after the completion of repairs. b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
01/07/2010

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2009

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-2958	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 022575) VPRIV (velaglucerase alfa) Information Request

Total no. of pages including cover: 4

Comments:
Please see attached.

Document to be mailed: ☐ YES X NO

Chemistry, Manufacturing, and Controls

1. Your purification process does not include two robust, orthogonal viral inactivation and removal steps, as recommended by ICH Q5A. Justify why the ICH guidelines were not followed and provide the theoretical dose equivalent and a risk assessment for the potential viral contamination of the drug product.

2. Based on the data you provided, it appears that IEX-HPLC and glycan mapping profiles of velaglucerase secreted by the cells at the beginning of the [redacted] are different from profiles of velaglucerase secreted at later stages. Provide justification for these differences.

3. We noted that lots manufactured with the AF2 process are within specification but out of trend with the lots manufactured with the AF1 process in regard to IEX-HPLC and glycan mapping, potentially due to the implementation of the acceptance criterion for pooling of the unpurified bulk [redacted]. Justify:

   a. The rationale used to establish the unpurified bulk pooling acceptance criterion.

   b. Why the AF1 and AF2 differences noted would not affect clinical performance of velaglucerase.

4. Your annual drug substance and drug product post-approval stability program should include accelerated and stressed stability conditions.

5. Provide justification for the high content [redacted] in the EP08-004 pooled clarified harvest used to conduct the [redacted] spike studies for validation of [redacted] removal. Describe which controls are in place in your manufacturing process to prevent high levels of host [redacted] in cell culture. b(4)

6. Your process characterization studies show that at the minimum cell culture viability tested in the production [redacted] (i.e., 30 percent viable cells), there is an increase in host cell protein (HCP) content and a decrease in enzyme specific activity. Justify why you have selected greater than 30 percent cell viability as the acceptance criterion for the cell viability performance parameter.

7. Table 3.2.S.2.5.1-11 summarizes host cell-derived impurity concentrations across the mercaptoethylpyridine (MEP) chromatography. While the DNA amount decreases from the load to the elution samples, the HCP content increases. Provide an explanation for the HCP results and describe how the $\log_{10}$ reduction was calculated in this case.

8. You have not submitted the results of studies conducted to address the impact of leachable and extractable materials from bags used to store the unprocessed bulk, the unpurified bulk, and the drug substance container closure system. Justify why these studies are not needed.

9. You have not provided the results of studies conducted to support the hold time of the unprocessed bulk ——— . Justify why these studies are not needed. b(4)

Immunogenicity

10. Your cut-points for anti-velaglucerase and anti-imiglucerase screening assays create a 99.9% expectation that values above the cut-point are positive and, conversely, a vanishingly small expectation that values below the cut-point are actually positive.

    a. Supply adequate justification for this approach. Alternatively, you may adopt a more conservative approach that allows for approximately 5 percent false positives in the screening assays.

    b. In order to assist our review of these assay cut-points, provide in MS Excel format:
        i. Raw data for the 51 normal human serum (NHS) samples used in the background analysis and the associated calibration curves.
        ii. Raw data and the associated calibration curves for patient serum samples.

11. For your Radio Immuno Precipitation (RIP) IgG confirmatory assay, the mean for 59 baseline serum samples from Gaucher patients is approximately 4 times lower than your assay cut-point. Provide the raw data for these baseline serum samples in MS Excel format, as this may provide the basis for a more appropriate cut-point.

12. For your anti-velaglucerase IgE confirmatory assay, provide the background values for Gaucher treatment-naïve samples in MS Excel format, as these may provide the basis for a cut-point.

13. We recommended that you develop an assay for antibody neutralization of cell uptake, as this is a critical aspect of the in vivo function of your product.

Clinical

14. In your amendment dated December 15, 2009, you responded to the clinical items of our information request dated December 11, 2009. In this amendment, you provided a document that contrasts the updated safety information from what was originally submitted to the NDA; however, this response did not address our request in a manner that will facilitate an efficient review. Provide a separate document with clear notation regarding which adverse events reports have changed in frequency during the 3-month safety update, as well as a brief statement of whether the updated safety information changes the overall safety profile of velaglucerase alfa.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
12/23/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022575

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, Massachusetts 02139

ATTENTION: Howard Yuwen, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Yuwen:

Please refer to your Drug Application (NDA) dated August 31, 2009, received August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velaglucerase Alfa for Injection, 200 units/vial and 400 units/vial.

We also refer to your September 22, 2009, correspondence, received September 23, 2009, requesting review of your proposed proprietary name, Vpriv. We have completed our review of the proposed proprietary name, Vpriv, and have concluded that it is acceptable.

The proposed proprietary name, Vpriv, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 22, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nitin M.Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Richard W. Ishihara, at (301) 796-0069.

Sincerely,
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

CAROL A HOLQUIST
12/16/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 11, 2009

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-2958	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 22575) VPRIV (velaglucerase alfa) Information Request

Total no. of pages including cover: 2

Comments:
Please see the attached.

Document to be mailed: ☐ YES X NO

Chemistry, Manufacturing, and Controls

1. Provide the most recent qualification data and reports for the following equipment identified in batch records submitted to the NDA (Section 3.2.R):

b(4)

2. Provide the data and report conducted in 2009 for that includes simulation of lyophilization.

3. Provide the floor plans for the manufacturing facility that includes, but is not limited to air classifications, personnel flow, and materials flow.

b(4)

Clinical

4. Your submitted 3-momth safety update, dated December 1, 2009, included a revised version of the document submitted in the original NDA submission, dated August 31, 2009. Provide a separate document that contrasts the updated safety information from the information that was originally submitted as part of the NDA submission.

5. Further clarification is needed to clearly identify which velaglucerase alfa clinical trial material was used for each study. Verify and complete the following table:

Study	**Velaglucerase alfa supply**	**Corresponding Drug Product Lot #'s**
TKT025	material	
TKT025 EXT	AF1	
TKT032	AF1	
TKT034	AF2	
HGT-GCB-039	AF1	
HGT-GCB-044	AF2	

b(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
12/11/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2009

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-2958	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 022575) VPRIV (velaglucerase alfa) clinical information request

Total no. of pages including cover: 2

Comments:
See attached.

Document to be mailed: ☐ YES X NO

1. **For the following three patients, provide all available aPTT results in an electronic dataset (.xpt):**

    a. TKT034 site 154 patients 0001 and 0002

    b. HGT-GCB039 site 180 patient 0001

2. **Regarding trial TKT032:**

    a. Patient 032-152-0005 had a significant CK elevation (p. 122, Section 8.4.2.1 of the Clinical Study Report). Provide an explanation for an event leading to CK elevation. The report states the lab abnormality was unrelated to treatment but does not state the cause.

    b. Provide your definition of clinically significant abnormal lab values. Clarify whether there is a specific value cut-off for each lab test or whether this is investigator determined.

    c. On p. 123 (Section 8.4.2.2), there is a patient for whom the laboratory value "total protein" was found to be significantly elevated. Provide the actual elevated lab value, your assessment on whether this elevation is considered clinically significant, provide the outcome, and indicate whether there was normalization at the end of the study.

    d. On p. 123 (Section 8.4.2.2) for hematological parameters, detail the specific lab value shifts from normal to abnormal and specify the criteria used to define normal versus abnormal. Also, describe any normalization that was observed after the abnormal value was obtained.

    e. On page 127 (Section 8.5.2), assess whether any of the abnormal physical exam findings were clinically significant. If exam findings are considered clinical significant, provide additional details.

3. **In the Clinical Summary of Safety Report (2.7.4)**

    Explain why under sections 2.7.4.4.1, 2.7.4.4.2, and 2.7.4.4.3 it is stated "Not applicable". Verify that there were no abnormalities considered clinically significant in each of these parameters (vital signs, physical exam finding, and ECG findings).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
11/19/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: OSE			Wes Ishihara, ODEIII/DGP, 301-796-0069	
DATE 11/17/09	IND NO.	NDA NO. 22575	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 8/31/09
NAME OF DRUG VPRIV (velaglucerase alfa)	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG Inborn Errors of Metabolism	DESIRED COMPLETION DATE 1/5/09

NAME OF FIRM: Shire Human Genetic Therapies, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- X REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- X SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

VPRIV (velaglucerase alfa) is currently under review (NDA 22575) and is a competitor to the currently marketed product, Cerezyme (imiglucerase alfa; NDA 020367). A review of any significant adverse events associated with Cerezyme is needed to support the review of VPRIV. Specifically, the review team seeks to understanding the following:

1. VPRIV and Cerezyme have only one amino acid difference in their chemical structure. We would like to evaluate the reported adverse events for Cerezyme to understand any potential safety signal that we should be vigilant for in the post marketing period should VPRIV be approved.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
11/17/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: 11/13/09

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 781-482-2958	**Fax number:** (301) 796-9905
Phone number: 781-482-9400	**Phone number:** (301) 796-0069

Subject: (NDA 022575) Document preparation for VPRIV (velaglucerase alfa)

Total no. of pages including cover: 2

Comments:

Regarding the pre-approval inspection for VPRIV, please identify the best site for FDA to initially meet with Shire's management on Monday, November 16, 2009.

Also in support of the pre-approval inspection for VPRIV, ensure that the following documents are readily available:

- Index of all written procedures, policies, methods (SOPs local and corporate, same for policies if that is a separate category; QC methods)
- Master Validation Plan (including schedule for annual/ periodic re-validations)
- Schedules for next week (production, laboratory, cell banking facility)
- Organizational chart with enough detail to identify the principal individuals at all sites in MA and the reporting structure. Detailed information regarding the quality system (quality unit) organization would be helpful (organization, duties, site-specific responsibilities)
- Identification of all operations at each of the firm's sites in MA.
- List of all marketed batches of Elaprase from January 2008 to present
- List of all approved vendors/ suppliers/ contract laboratories/ contract manufacturers
- Large, readable detailed facility diagrams, equipment trains, lists of equipment with designation as to whether dedicated or multi-product use.
- Qualification program of process critical materials: [redacted] b(4)
- Qualification programs of QC assays critical materials: 1) Anti-Host Cell protein antibody; 2) Cell line, detection and capture anti-GCB antibodies used in the cellular uptake assay; and 3) Anti-GBC antibody used in Western Blot.

Document to be mailed:	☐ YES	X NO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
11/13/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022575

FILING COMMUNICATION

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

Dear Dr. Mehta:

Please refer to your new drug application (NDA) dated and received on August 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for VPRIV (velaglucerase alfa).

We also refer to your submissions dated July 30, September 17, 22, and 28, and October 1, 9, 12, and 23, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is February 28, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 31, 2010.

During our filing review of your application, we identified potential review issues and request the following information:

Chemistry, Manufacturing, and Controls

1. In regard to your drug substance characterization studies, provide the following information and clarifications:

a. The lot(s) of drug substance that were used.

b(4)

l. Identification of all the bands separated by IEF and any summary data to support the assignments.

m. The results of studies demonstrating removal of media components from drug substance, or alternatively, a risk assessment evaluating the risk to product quality and patient safety posed by these process-related impurities. In addition, a description of the other non-protein components in the hydrolysate media components.

n. Reports of studies performed to assess removal of impurities

or specify where in the NDA the reports are provided. b(4)

2. In order to assess the comparability of drug substances manufactured by the AF1 and AF2 processes, generate and/or provide the following information:

a. Additional forced degradation studies, where velaglucerase is subjected to a variety of stressed conditions that cause incremental degradation and allow for an evaluation of the kinetics of degradation. A variety of analytical and functional assays, including, but not limited to, kinetic parameters measurements using the physiologically relevant and the surrogate substrate, RP-HPLC, SEC-HPLC, SDS-PAGE, etc., should be used in these studies.

b. For all available AF1 lots used in the pivotal clinical trial and all AF2 lots manufactured to date:

i. The results of IEX-HPLC analyses, where the percentage area for all peaks identified is calculated. The results should be reported in graphic form, comparing, for each peak, the results obtained with the AF1 and AF2 processes.

ii. The results of glycan map analyses, where the percent area for the peaks in and for the peak is calculated. The results should be reported in graphic form, comparing, for each peak, the results obtained with the AF1 and AF2 processes. b(4)

c. In your comparability study:

i. Full scale RP-HPLC, IEX-HPLC and SEC-HPLC chromatograms with legible axis scales.

ii. Full scale legible mass spectra profiles.

iii. Enzyme kinetic studies performed on the AF1 and AF2 drug substances using both the physiologically relevant substrate and the surrogate substrate.

iv. Mannose receptor binding assay and cell uptake assay performed on the AF1 and AF2 drug substances.

3. In regard to your assay validations, provide the following information and clarifications:

    a. The method used to calculate peak areas for your RP-HPLC and SEC-HPLC assays.

    b. An explanation of how the RP-HPLC column temperature is maintained.

    c. Results of studies conducted to assess the robustness of your RP-HPLC assay. System robustness should be tested to ensure its capacity to remain unaffected by small variations in method parameters. Parameters to be tested should include: temperature, flow rate, mobile phase composition, and different columns.

    d. It is not clear if the SEC-HPLC assay was conducted under temperature-controlled environment. The temperature shift would affect the retention time, the distribution of monomer (main), aggregate, and shoulder peaks. The effect of temperature shifts on assay robustness needs to be addressed.

    e. For SEC-HPLC assay linearity, the standard deviation (SD) and percent relative standard deviation (% RSD) were not reported in Table 2 (page 12 of the validation report QCTR-06006). This table should be updated to include the missing data.

4. In relation to your release and stability programs, the following issues should be addressed:

    a. Measurements of K_m and k_{cat} using a physiologically relevant substrate should be included in your release and stability program for drug substance and drug product to assure potency.

    b. The cellular uptake assay should be included in your stability testing for drug substance, and in the release and stability program for drug product to assure biological activity of velaglucerase.

    c. IEX-HPLC or IEF should be added to drug substance and drug product stability program to monitor for changes in velaglucerase charge.

    d. The acceptance criteria for the RP-HPLC assay used in the release and stability program should include measurements of peaks [redacted] to ensure product quality and consistency. b(4)

    e. The acceptance criteria for the SEC-HPLC assay used in the release and stability program should include a measurement of the shoulder peak to ensure product quality and consistency.

f. Provide the tables used to determine the k index for calculating the tolerance interval for acceptance criteria in quantitative release tests.

g. Justify the differential use of Silver and Coomassie staining of SDS-PAGE gels in the release and stability programs, respectively.

h. Acceptance criteria for the qualification of your reference standard should be set to avoid product drift over time. The current acceptance criteria for the qualification of a new reference standard should be based on historical manufacturing results and be tighter than release testing acceptance criteria.

5. Regarding the drug product evaluation (Section 3.2.P.3.5), only summaries for the following studies were provided:

   a. Enhancement and inhibition study for method suitability.

   b. study for the sterility method suitability.

   c. Container Closure integrity testing.

   b(4)

   Provide the complete reports for each of these studies.

Clinical

6. Regarding your immunogenicity assessment, provide the following information:

   a. Any IgE and/or skin prick data that are available for the treatment-naïve patient who experienced an SAE of allergic dermatitis, as well as for the second patient who experienced an SAE involving an anaphylactic reaction after transitioning from imiglucerase to velaglucerase.

   b. Any data you may have bearing on the reactivity of patient and/or animal anti-velaglucerase antibodies toward glycan side chains versus the peptide backbone.

   c. A calculation of the cutpoint for the IgE anti-velaglucerase assay in terms of nanograms/mL.

7. Regarding all abnormal electrocardiogram (ECG) results for study TKT032, provide the specific abnormality in each ECG result and whether the change was thought to be clinically significant.

8. Provide graphs for trial HGT-GCB-039 with the following information (where the X-axis is each study week and the Y-axis is the mean change from baseline at that week):

   a. Mean hemoglobin change from baseline to each week through the end of the study, comparing the velaglucerase and imiglucerase arms.

b. Mean platelet change from baseline to each week through the end of the study, comparing the velaglucerase and imiglucerase arms.

c. Include error bars (preferably 1.5 standard error of the mean [SEM]).

d. Include a table showing the values that are plotted.

9. For each of the trials TKT032, TKT034, and HGT-GCB-039, provide a separate scatter plot of hemoglobin values at baseline versus hemoglobin values at completion of study. Also, provide the corresponding electronic dataset with study number, patient identifier, and hemoglobin values at baseline and end of study. Include patients in datasets even if there are missing values.

10. In regard to the financial disclosure certifications provided where a single investigator was involved in multiple studies, clarify whether the reported financial arrangements are for each study separately or are cumulative amounts from all involved studies for that year.

Statistical

11. Study TKT032 uses covariate adaptive randomization to balance treatment allocation to patients in the age (2-17 or ≥18) and gender (Male or Female) subgroups. In general, adaptive randomization techniques compromise the independence assumption applied to data captured during the study. Consequently, a permutation/re-randomization test needs to be conducted where possible, as a sensitivity analysis, for all appropriate efficacy endpoints.

12. The missing data handling strategy for both studies TKT032 and HGT-GCB-039 was insufficient. Both studies utilized last observation carried forward (LOCF) to handle missing data for their respective primary efficacy analyses. The LOCF approach is only valid for data whose missingness mechanism is assumed to be Missing Completely at Random (MCAR). However, MCAR is an unrealistic assumption; hence other approaches for handling missing data in a primary analysis context should be considered under more realistic assumptions for the missingness mechanism. Multiple Imputation, under a Missing at Random (MAR) assumption, is an acceptable approach and should be conducted to handle missing data in these primary efficacy analyses. The previously specified LOCF approach and also an additional worst-case imputation (no change from baseline) should be used as sensitivity analyses.

13. No subgroup analyses were conducted for studyHGT-GCB-039. Primary efficacy results in this study should be further investigated for gender, racial, and appropriate age subgroups.

Labeling

The following issues/deficiencies have been identified in your proposed labeling.

14. Highlights of Prescribing Information (in Highlights section):

    a. The information summarized in the Highlights section should be presented in direct language (i.e., "command" language).

    b. Include for each bulleted statement a numerical reference to the corresponding section or subsection in the full prescribing information (FPI).

15. Full Prescribing Information: Table of Contents (in Table of Contents):

    a. The section or subsection headings and the section or subsection numerical identifier must be separated by two square em's (i.e., two squares the size of the letter "m" in 8 point type) [21 CFR 201.57(d)(7)]. In addition, periods should not be used after the number for each section or subsection heading.

16. Full Prescribing Information:

    a. The section or subsection headings and the section or subsection numerical identifier must be separated by two square em's (i.e., two squares the size of the letter "m" in 8 point type) [21 CFR 201.57(d)(7)]. In addition, periods should not be used after the number for each section or subsection heading.

    b. Bold type should not be used in the body of the Full Prescribing Information except as required (e.g., section and subsection headings). Other methods may be used, such as italics.

    c. Cross-references within the labeling should identify the section (not subsection) followed by the numerical identifier of the section or subsection, as appropriate. For example, under subsection 13.1, Carcinogenesis, Mutagenesis, Impairment of Fertility, references are made to the Pregnancy subsection (i.e., subsection 8.1) of section 8, Use in Special Populations. The appropriate reference is as follows:

        [see Use in Specific Populations (8.1)]

We are providing the above comments to give you preliminary notice of potential 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 review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Wes Ishihara, Regulatory Project Manager, at (301) 796-0069.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

BRIAN K STRONGIN
10/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Office/Division)*: OMP/DDMAC (Wayne Amchin)			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Wes Ishihara, ODEIII/DGP, 301-796-0069	
DATE 10/23/09	IND NO.	NDA NO. 22575	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 8/31/09
NAME OF DRUG VPRIV (velaglucerase alfa)	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG Inborn Errors of Metabolism	DESIRED COMPLETION DATE 1/29/10
NAME OF FIRM: Shire Human Genetic Therapies, Inc.				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DDMAC labeling review consult is requested. Below is the information regarding this application:
EDR link: \\CDSESUB1\EVSPROD\NDA022575\022575.enx (seq#: 0001)

Application includes package insert and FDA approved patient labeling (attached to PI). Please note that the patient labeling inclusion may be due to sponsor's misunderstanding of the PLR requirements as patient labeling is usually not necessary for these enzyme replacement therapy products since it is administered by trained providers.

Currently scheduled meetings:
Team meeting: 10/30/09
Midcycle: 10/3/09
Team meeting: 1/5/09
Labeling meeting: 1/22/09
Labeling meeting: 1/28/09

Wrap up meeting: 1/29/09 PDUFA: 2/26/09	
SIGNATURE OF REQUESTOR R. Wesley Ishihara	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
10/23/2009

MEMORANDUM

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

DATE: October 22, 2009

TO: File

THROUGH : Jang-Ik Lee
Ii-Lun Chen

FROM: Wes Ishihara

SUBJECT: Teleconference Regarding Pharmacokinetic Assay Validation Reports for NDA 022575

APPLICATION/DRUG: VPRIV (velaglucerase alfa)

FDA Participants:
Ii-Lun Chen, M.D., Medical Officer, Division of Gastroenterology Products (DGP)
Wes Ishihara, Project Manager, DGP
Jang-Ik Lee, Pharm.D., Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP3)
Lanyan Fang, Ph.D., Clinical Pharmacology Reviewer, DCP3
Wayne Amchin, Project Manager, Division of Drug Marketing, Advertising, and Communication

Shire Participants:
Dr. Nikhil Mehta VP Regulatory Affairs (RA)
Dr. Andrew Papas Sr. Director RA
Ms. Jeannine Firestone Assoc. Director RA
Dr. Juan Ruiz, Sr. Director, Bioanalytical & Biomarker Development
Dr. Perry Calias, Sr. Director Nonclinical Development
Dr. Zahra Shahrokh, Sr. Director Analytical Development
Dr Steven Troy, Senior Director, Clinical Pharmacology and Pharmacokinetics

On September 30, 2009, FDA requested Shire to provide in-process assay performance reports for pharmacokinetic (PK) studies TKT025, TKT025EXT, and TKT032. Shire responded to FDA's request on October 12, 2009; however, upon review of the information submitted, it was determined that the information was inadequate. On October 15, 2009, FDA requested that Shire perform and include additional analyses (standard curves, accuracy, precision, and inter-assay and intra-assay performance) and pertinent raw data. To ensure that the submission included all the requisite information, Shire emailed draft reports on October 21, 2009 (see attached), and

requested FDA feedback on whether the information contained was complete.

On October 22, 2009, FDA contacted Shire to discuss their proposed submission. FDA stated that in general Shire's proposed submission is sufficient to address any issues that may preclude NDA filing from a clinical pharmacology standpoint; however, there is additional clarification needed.

FDA pointed Shire to Table 22, page 76, and asked for clarification on what the reference number corresponds to under the first column of the table. Shire stated that a number is assigned for each assay run as opposed to each sample. Shire also stated that the assay controls were run in duplicate. FDA asked Shire how the standard deviation was calculated if the controls were run in duplicate. Shire stated that the standard deviation was calculated using Microsoft Excel. FDA stated that duplicate samples are usually not acceptable and that the assay controls should have been run at least in triplicate (most companies do five replicates). FDA further added that calculations should not be based on mean values of the duplicate samples, but rather based on all values. FDA requested that Shire include in the submission the date of each assay run and the actual values of each duplicate, recalculate all statistics, and verify that the tables (on page 76 through page 86) be updated accordingly. Shire agreed and stated that the response would be submitted the following day.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
12/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Mail: OSE (Nina Ton); CDER OSE CONSULTS			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Wes Ishihara, ODEIII/DGP, 301-796-0069	
DATE 10/22/09	IND NO.	NDA NO. 22575	TYPE OF DOCUMENT Original NDA	DATE OF DOCUMENT 8/31/09
NAME OF DRUG VPRIV (velaglucerase alfa)	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG inborn error of metabolism	DESIRED COMPLETION DATE 1/15/09

NAME OF FIRM: Shire Human Genetic Therapies, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please conduct a carton and container labeling review. The carton and container was submitted to the application, with the updated proposed trade name VPRIV on 10/1/09. This link to the eCTD submission is <\\CDSESUB1\EVSPROD\NDA022575\022575.enx> and the sequence number is 0005. The package insert is located under the same link, but under sequence number 0001.
PDUFA: 2/26/09
Attachments: see links above.

SIGNATURE OF REQUESTOR Wes Ishihara	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Additional Information:
Proposed name: **VPRIV**
Established name: **velaglucerase alfa**
Indication of use: **velaglucerase alfa is indicated for the long-term use as an enzyme replacement therapy (ERT) for pediatric and adult patients with type I Gaucher disease.**
Dosage forms: **Lyophilized powder for injection**
Strength: **200 unit/vial; 400 unit/vial**
Usual dose: **60 U/kg**
Frequency of administration: **Infusion every other week**
Prescribing population: **Physicians treating patients with type I Gaucher disease**
Packaging information (if injectable): **None**
Route of administration: **Intravenous Infusion**
Any unique product characteristics for the drug: **None noted**
Major adverse events that may have been identified that can result form a medication error: **None noted**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
10/22/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 15, 2009

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire Human Genetic Therapies, Inc.	Division of Gastroenterology Products
Fax number: 617-613-4444	**Fax number:** (301) 796-9905
Phone number: 617-613-4531	**Phone number:** (301) 796-0069

Subject: (NDA 22575) velaglucerase alfa – Information Request

Total no. of pages including cover: 3

Comments:
Please see the attached.

Document to be mailed: ☐ YES X NO

Clinical Pharmacology Information Request to Shire for Velaglucerase alfa (NDA 22-575)

1. Submit a complete pharmacokinetic report for Study TKT025.

2. You have submitted in-process assay performance summary for velaglucerase alfa (October 12, 2009). Our preliminary review indicates that the summary is not sufficient. Particularly, your summary does not provide pertinent raw data and statistical information on standard curves, accuracy, precision, and inter-assay (i.e., between assay) and intra-assay (i.e., within assay) performance. Furthermore, Module 5.3.3.2 in eCTD sequence 0001 does not include full in-process performance assay reports but an incomplete one-page assay summary for Study TKT032 only (section 3.3, page 7). So that our review may proceed, provide information on the items listed below, as part of a complete in-process performance report for each of the three studies (TKT025, TKT025EXT, and TKT032).

    a. Provide the r^2 value that was obtained for each standard curve for each analytical run.

    b. Concentration values of the low-, medium- and high-concentration quality control samples.

    c. Provide the value that was obtained for each quality control sample in each assay run with summary statistics in a table format.

    d. The intra-assay (i.e., within assay) accuracy and precision values of the quality control samples and at the lower limit of quantitation in each assay run.

    e. The inter-assay (i.e., between assay) accuracy and precision values of the quality control samples and at the lower limit of quantitation in all assay runs.

    f. A copy of Shire HGT binder #735-1053 for Study TKT032 and similar copies of Shire HGT binder for Studies TKT025 and TKT025EXT.

The above items relate to the first 3 bullet points on page 18 of the FDA Guidance on Bioanalytical Method Validation, which can be located at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf. We strongly recommend that you refer to this Guidance in your preparation of the assay performance reports. In the calculation of accuracy and precision, include only the quality control sample data obtained during subject sample runs for the corresponding study. In the report, we recommend that you also include a table for the analyte that contains the overall summary information on the assay (see Appendix for a sample table format).

Appendix

An example of the composite **minimum** information that must be provided along with documentation for each type of analysis:

Method	XXXXX
Compound	XXXXX
Matrix	Human XXXXX (e.g. plasma, serum, urine)
Accuracy (% Nominal) ***Intra-assay*** ***Inter-assay***	 XX.X to XX.X % XX.X to XX.X %
Precision (% CV) ***Intra-assay*** ***Inter-assay***	 X.X% to X.X % X.X % to X.X %
Standard curve range	X.XX xx/mL to XX.XX xx/mL (%CV = X.X to XX.X %, Accuracy = XX.X to XXX.X %)
Sensitivity (LOQ)	XX xx/mL
Specificity	Demonstrated with xxxxxxxxxx in the presence and absence of XXXXX. xxxxxxxx did not interfere with the detection of XXXXX, nor was recognized in the XXXXX assay.
Stability of XXXXXX in Human XXXX	XXXXX was demonstrated to be stable in human XXXX following three freeze/thaw cycles. The mean (SD) recovery after 1, 2, or 3 freeze (-70° C) – thaw (37° C) cycles was XX.X (X.X) %, XX.X (X.X) % and XX.X (X.X) %, respectively. Stability@ -20° C for 40 days was also demonstrated.
Conclusion	**xxxxxxxxxxxxxxxxx**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
10/15/2009

DSI CONSULT: Request for Clinical Inspections

Date: 10/15/09

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Khairy Malek, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Ii-Lun Chen, M.D., Medical Officer, Division of Gastroenterology Products (DGP)
John Hyde, M.D., Ph.D., Clinical Team Leader, DGP
Donna Griebel, M.D., Director, DGP

From: Wes Ishihara, Project Manager, DGP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22575
Applicant/ Applicant contact information (to include phone/email):
Drug Proprietary Name:
NME or Original BLA (Yes/No): Yes (NME)
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): Yes
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Long-term enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease.

PDUFA: 2/26/2010
Action Goal Date: 2/26/2010
Inspection Summary Goal Date: 1/3/2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #: 071 Name: Dr. Ari Zimran Address: Gaucher Clinic The Hebrew University Haddassah Medical School Shaare Zedek Medical Center 12 Hans Bayt Jerusalem 91031, Israel Phone: 972 2-6555143 Cell: 972 55 728284 Email: azimran@gmail.com Email: gaucher@szmc.org.il Fax: 972 2 6517979	TKT025	12/12 patients	Long-term enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease.
	TKT025EXT	8/10 patients	
	TKT032	7/25 patients	
	TKT034	9/40 patients	
	HGT-GCB-039	3/34 patients	
Site #: 152 Name: Derlis Emilio Gonzales Rodriguez, M.D. Address: Sociedad Espanola de Socorros Mutuos (Santorio Espanol) Gobernador Irala y Coronel Lopez Barrio Sajonia, Asuncion, Paraguay Phone: (595)21-420.888 Direct: (595)21-423-603 Cell: (595)971-223286 Email: degonzal@conexion.com.py Email: gderlis@conexion.com.py Fax: (595)21-420.888	TKT032	11/25 patients	Same as above
	HGT-GCB-039	5/34 patients	

III. Site Selection/Rationale

First, the pivotal phase 3 and the major supportive trials all took place outside the US. The reason for requesting inspection for Israel is that this is the sole site for the supportive Trial 25 and had a large portion of the patients enrolled in the pivotal Trial 32. Furthermore, the principal investigator, Dr. Zimran, has received over a million dollars in funding from the sponsor since the early 2000s.

Second, the request for inspection at the Portugal site stems from the fact that almost half the patients in the single pivotal Trial 032 come from this site.

Lastly, the other important supportive trials (34 and 39) also have patients from Israel and Paraguay.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

_X_ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

The primary efficacy endpoint was the change in hemoglobin value from baseline to end of study, please pay particular attention to this laboratory information on the case report forms. The key secondary endpoints were: platelet count improvement, decrease in liver and spleen volumes.

Should you require any additional information, please contact Wes Ishihara at 301-796-0069 or Ii-Lun Chen at 301-796-2716.

Concurrence: (as needed)

J. Hyde	Medical Team Leader
I. Chen	Medical Reviewer
D. Griebel	Division Director (for foreign inspection requests or requests for 5 or more sites only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
10/15/2009

II-LUN CHEN
10/15/2009

JOHN E HYDE
10/15/2009

DONNA J GRIEBEL
10/15/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 8, 2009

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT, Inc.	Division of Gastroenterology Products
Fax number: 617-613-4444	**Fax number:** (301) 796-9905
Phone number: 617-613-4531	**Phone number:** (301) 796-0069

Subject: (NDA 22575) velaglucerase alfa; Information Request

Total no. of pages including cover: 1

Comments:
For each of your studies (TKT025, TKT025EXT, TKT032, TKT034, and HGT-GCB-039), identify each clinical site and provide for each clinical site the site number, name of principle investigator, site (street) address, phone number, fax number, and email address. Also indicate for each site, the number of patients enrolled at that particular site.

Document to be mailed: ☐ YES X NO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
10/08/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 30, 2009

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT, Inc.	Division of Gastroenterology Products
Fax number: 617-613-4444	**Fax number:** (301) 796-9905
Phone number: 617-613-4531	**Phone number:** (301) 796-0069

Subject: (NDA 22575) Information Request

Total no. of pages including cover: 1

Comments:
In order to facilitate a filing determination, the follow information is requested:

1. Provide the in-process assay performance reports for the pharmacokinetic studies TKT032 and TKT025EXT. These reports need to include assay performance during patient sample runs in Studies TKT032 and TKT025EXT. Please refer to FDA Guidance for Industry: Bioanalytical Method Validation (http://www.fda.gov/cder/guidance/4252fnl.pdf), which describes the information to be included in the reports. Please pay special attention to Subsection C (Application to Routine Drug Analysis) on pages 17 and 18.
2. Financial disclosure forms FDA 3454 and/or 3455 for studies HGT-GCB-039, TKT034, and TKT025EXT.
3. Patent information submitted on FDA form 3542a and per 21 CFR 314.53.

Document to be mailed: ☐ YES X NO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	GI-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA
NDA-22575	ORIG-1	SHIRE HUMAN GENETIC THERAPIES INC	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
09/30/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 23, 2009

To: Nikhil Mehta, Ph.D.	**From:** Wes Ishihara
Company: Shire HGT	Division of Gastroenterology Products
Fax number: 617-613-4444	**Fax number:** (301) 796-9905
Phone number: 617-613-4531	**Phone number:** (301) 796-0069

Subject: (NDA 22575) velaglucerase alfa; Information Request

Total no. of pages including cover: 1

Comments:
For Trial HGT-GCB-039, we seek clarification whether a written summary of safety data is provided. If this information has been provided, indicate the date of submission and the specific location of this information. The narratives of several serious adverse events and raw safety data tables have been located; however, a brief overview of the safety data is requested if this information has not been provided for Trial HGT-GCB-039. We understand a full clinical study report is not available at this time. Your submission should include, but not be limited to, numbers and reports of any deaths and serious adverse event, as well as a general adverse event profile between treatment and placebo groups.

Document to be mailed: ☐ YES X NO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HGT INC.	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
09/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22575

NDA ACKNOWLEDGMENT

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

Dear Dr. Mehta:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: TRADENAME (velaglucerase alfa)

Date of Application: August 31, 2009

Date of Receipt: August 31, 2009

Our Reference Number: NDA 22575

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 30, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-0069.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22575	ORIG-1	SHIRE HGT INC.	VELAGLUCERASE ALFA

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

/s/

RICHARD W ISHIHARA
09/14/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 61,220

MEETING MINUTES

Shire Human Genetic Therapies, Inc.
Attention: Howard Yuwen, Ph.D.
Senior Director, Regulatory Affairs
700 Main Street
Cambridge, MA 02139

Dear Dr. Yuwen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gene-Activated glucocerebrosidase (velaglucerase alfa; GA-GCB; DRX008A).

We also refer to the meeting between representatives of your firm and the FDA on August 10, 2009. The purpose of the meeting was to discuss the contents of your NDA submission for velaglucerase alfa.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0069.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 10, 2009
Meeting Location:	White Oak, Building 22, Room 1309
Application Number:	IND 61220
Product Name:	velaglucerase alfa
Indication:	**Treatment of patients with type 1 Gaucher disease**
Sponsor/Applicant Name:	Shire Human Genetic Therapies, Inc.
Meeting Chair:	John Hyde, Ph.D., M.D.
Meeting Recorder:	Wes Ishihara

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology Products (DGP)
Anne Pariser, M.D., Acting Deputy Director, DGP
John Hyde, Ph.D., M.D., Medical Team Leader, DGP
Ii-Lun Chen, M.D., Medical Officer, DGP
Wes Ishihara, Project Manager, DGP
Lynne Yao, M.D., Acting Medical Team Leader, DGP
Cristi Stark, M.S., Acting Chief, Project Management Staff, DGP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGP
Tamal Chakraborti, Ph.D., Pharmacology Reviewer, DGP
Emanuela Lacana, Ph.D., Product Quality Team Leader, Division of Therapeutic Proteins
Mike Welch, Ph.D., Statistical Team Leader, Division of Biostatistics III (DBIII)
Behrang Vali, M.S., Statistical Reviewer, DBIII
Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3 (DCP3)
Lanyan Fang, Ph.D., Clinical Pharmacology Reviewer, DCP3
Shawn Gould, Facility Reviewer, Division of Manufacturing and Product Quality (DMPQ)
Elizabeth McNeil, M.D., Medical Reviewer, Office of Orphan Product Development (OOPD)
Steven Bird, OOPD

SPONSOR ATTENDEES

Nikhil Mehta, Ph.D., Vice President, Global Regulatory Affairs
Howard Yuwen, Ph.D., Senior Director, Regulatory Affairs

Lynn E. Bayless, M.S., Associate Director, Regulatory Affairs
Jeannine L. Firestone, Associate Director, Global Regulatory Affairs
Ferdinand Massari, M.D., Global Head and Vice President, clinical and Medical Affairs
Kiran Bhirangi, M.D., FRCS, Senior Director, Clinical Research
Eric A. Crombez, M.D., Medical Director, Clinical Research
Divakar Sharma, Ph.D., Senior Director, Biometrics
David Zahrieh, M.S., Senior Biostatistician I
John Anthony, Associate Director, Application Programming and Development
Marcio Voloch, Ph.D., Vice President, Process Development
Kathir Swamy, Ph.D., Senior Director, Quality
Joyce P. Whitehead, Ph.D., Director, Manufacturing Technical Services
Pericles Calias, Ph.D., Senior Director, Nonclinical Development

1.0 BACKGROUND

On June 8, 2009, Shire Human Genetic Therapies, Inc. (Shire) submitted a Type B, Pre-NDA meeting request to discuss an upcoming NDA submission for velaglucerase alfa for the treatment of type 1 Gaucher disease. This meeting request was granted by the FDA on July 1, 2009. Subsequently, Shire accelerated the NDA submission schedule for velaglucerase alfa as a result of an unexpected enzyme replacement therapy shortage with the currently marketed product for patients with type 1 Gaucher disease. Shire also requested fast track designation on June 30, 2009, which was granted by the FDA on July 15, 2009. Additionally, the FDA agreed to accept submission of portions of the NDA for review (i.e., a rolling review). On July 30, 2009, Shire submitted the first portion of the NDA for velaglucerase alfa, which included full Modules 3 and 4 and a partial Module 5. Submission of the final portion of the NDA for review is planned for August 31, 2009.

Shire's stated purpose for the meeting was to obtain agreement from the FDA that the information that has been included, as well as the forthcoming information to be included in the NDA will be appropriate and supportive for approval of velaglucerase for treatment in patients with type 1 Gaucher disease.

Shire submitted a meeting package on July 14, 2009, which was received by the FDA on July 15, 2009. The FDA provided preliminary responses to questions in the meeting package via E-mail on August 7, 2009. On August 10, 2009, prior to the meeting, Shire sent written responses via E-mail to some of the FDA's preliminary responses (see Attachment 1).

2. DISCUSSION

QUESTIONS AND RESPONSES

Questions in the meeting package are shown in plain font. The FDA's preliminary responses are shown in **boldface**. Discussion during the meeting is shown in ***bold italics***.

Nonclinical

1. Is the Agency in agreement that the nonclinical studies as summarized in this document are appropriate to support the approval of a marketing application for velaglucerase alfa?

   FDA Response:
   Yes. We agree that your nonclinical studies are appropriate to support filing of your marketing application for velaglucerase alpha.

Clinical

2. Is the Agency in agreement that the clinical trial data to be included in the NDA are sufficient to support the approval of velaglucerase alfa for long-term enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease.

FDA Response:
On page 10 of your Type B Meeting Briefing Package, you state that only safety data will be presented for HGT-GCB-039. Please explain why additional information about this trial will not be provided. We do not feel your proposal is adequate. As this trial is a controlled trial pertinent to the use of velaglucerase, it is important that you provide at least the protocol and a description of results, as per 21 CFR 314.50(d)(5)(ii).

Additional Discussion:
Shire stated that the reason trial HGT-GCB-039 was not included in the original proposal was due to a late completion date of the trial relative to submission timing for the NDA. Shire added that this trial was powered. The FDA stated that this is an important Phase 3 trial that should be considered in the evaluation of velaglucerase alfa. The FDA asked whether submission of information for HGT-GCB-039 would delay submission of the complete NDA. Shire stated that providing a final clinical study report would likely delay submission of the complete NDA; however, the study protocol, safety data, and top-line efficacy data could be provided without any delay in completing the NDA submission.

Shire agreed to include the study protocol, safety data, and top-line efficacy results in the Original NDA submission.

The data otherwise appear appropriate to support filing of your NDA. However, there are a few additional items that are necessary for an adequate and efficient review of your application. Please be certain to address the following requests:

a) Include a detailed regulatory history of the clinical development of velaglucerase alfa.

Additional Discussion:
In its written responses (Attachment 1), Shire stated it will include the full regulatory history of velaglucerase alfa with the NDA submission. There was no additional discussion at the meeting.

b) Provide a thorough literature review regarding the safety of velaglucerase alfa and the safety of any other similar products (e.g., imiglucerase) currently on the market, as per 21 CFR 314.50(d)(5)(vi)(a).

Additional Discussion:
It its written responses (Attachment 1), Shire stated it will provide a literature search and a review of the safety of velaglucerase alfa and imiglucerase. The review of

velaglucerase alfa and imiglucerase will be provided in Module 2.5 of the NDA. Copies of literature references will be provided in Module 5.4 of the NDA. There was no additional discussion at the meeting.

c) **Include historical control data regarding Type 1 Gaucher disease for comparison with the results of your study TKT032.**

Additional Discussion:
In its written responses (Attachment 1), Shire stated it will perform a literature search on the natural history of Gaucher disease and relevant references will be provided in Module 5.4 of the NDA. There was no additional discussion at the meeting.

d) **For each trial you plan to include in your NDA submission (studies TKT032, TKT034, HGT-GCB-039, TKT025, and TKT025EXT), please provide the following:**

i) **All clean raw/CRF data presented in appropriate electronic datasets along with a copy of the annotated case report form (aCRF). We recommend that these datasets fully comply with SDTM standards.**

Additional Discussion:
Shire stated that all datasets will comply with CDISC standards except study TKT025. The FDA stated that at this time submission of datasets for study TKT025 in non-CDISC format was acceptable.

ii) **All corresponding analysis datasets along with an appropriate and complete data definition file (i.e. DEFINE.pdf or DEFINE.xml). We recommend that these datasets fully comply with ADaM standards.**

Additional Discussion:
In its written responses (Attachment 1), Shire agreed to provide all corresponding analysis datasets along with the appropriate and complete data definition file according to ADaM standards in the NDA. There was no additional discussion at the meeting.

iii) **A well commented, organized, and clean SAS program written for each analysis dataset created.**

Additional Discussion:
In its written responses (Attachment 1), Shire agreed to provide well commented, organized, and clean SAS programs for each analysis dataset. At the meeting, Shire also agreed to provide SAS programs for the primary efficacy tables.

iv) **A description of each amendment made to the protocol.**

Additional Discussion:
In its written responses (Attachment 1), Shire agreed to provide a description of each protocol amendment in the NDA. There was no additional discussion at the meeting.

e) **We request that you provide case report forms for all patients reporting serious adverse events.**

Additional Discussion:
In its written responses (Attachment 1), Shire stated it will provide case report forms (CRFs) for all patients reporting serious adverse events (SAEs) in the NDA. There was no additional discussion at the Meeting.

f) **Perform standardized MedDRA queries on the safety data to identify and evaluate adverse reactions of specific interest for therapeutic proteins, such as: anaphylactic reactions, anaphylactic shock conditions, immunogenicity, pulmonary hypertension, pneumonia, infusion reactions, and injection site reactions.**

Additional Discussion:
In its written responses (Attachment 1), Shire stated it will perform standardized MedDRA queries on the safety data. There was no additional discussion at the meeting.

g) **You state that a Safety Update will be provided approximately three months into the review of the NDA, but that the data will be presented individually for each study. As per 21 CFR 314.50(d)(5)(vi), you should submit your update in the same format as the integrated summary of all available information about the safety of the drug product.**

Additional Discussion:
Shire agreed to provide the safety update in the same format as the Original NDA, with a cutoff date of August 31, 2009. Any significant adverse events after that date will be provided to the FDA, individually. The FDA agreed with this approach and the data inclusion cutoff date.

Please note our Additional FDA Comment 10, below.

Chemistry, Manufacturing, and Controls

3. Shire is providing stability data in support of the proposed shelf-life that is based on real-time, long-term storage data from drug substance manufactured using the AF1 process. Based on demonstrated comparability of the AF1 and AF2 process and additional stability

data which will be submitted during the end of the review period of the NDA, does the Agency agree that it will support the proposed commercial drug substance and drug product shelf-life?

FDA Response:
A final recommendation on drug substance and drug product shelf-life will be made only after the review of the data submitted in the application is completed. Your proposal to submit additional stability data during the end of the review period is acceptable.

ADDITIONAL FDA COMMENTS:

4. **Regarding your drug substance and drug product release and stability protocol, please include:**

   a) **A potency assay that measures the kinetic parameters of velaglucerase (K_m and k_{cat}) using a physiologically relevant substrate.**

   Additional Discussion:
   Shire proposed using the current surrogate substrate for the specific activity assay and the natural substrate assay to characterize significant process changes. Shire expressed concern with developing a potency assay to measure K_m and k_{cat} using a physiologically relevant substrate because of technical issues with implementing the assay as well as the complexity with performing the assay. Shire added that an investigation of an enzyme kinetic method revealed that there has been no observed change in drug parameters up to 24 months. Additionally, Shire noted that k_{cat} remained constant between the surrogate substrate and the physiologically relevant substrate, although, K_m was lower for the surrogate substrate. The FDA disagreed with Shire's proposal due to observed significant differences between K_m measured using the physiologically relevant substrate and the surrogate substrate (~50 fold difference). The FDA added that this observation reinforces that using the physiologically relevant substrate yields greater assay sensitivity to changes in the protein. In addition, measuring K_m involves using multiple concentrations of substrate, which further enhances the ability to detect important changes in the protein. Shire asked the FDA for clarification on the need for a standardized assay since dosing is usually titrated for each patient. The FDA clarified that although an assay to measure K_m is not needed for dosing purposes, it is necessary for product release testing.

   Shire committed to make good faith efforts to provide updates to the NDA on the use of K_m and k_{cat} using a physiologically relevant substrate for release and stability.

b) **A cellular uptake assay and/or a receptor binding assay that directly correlates with cellular uptake.**

Additional Discussion:
Shire stated that they have implemented a dose-response cellular uptake assay that is used for drug substance release. Shire added that changes in the drug product are not expected and, therefore, not necessary for routine drug product release testing; however, this assay is used for drug product stability testing (i.e., initial samples). The FDA stated that lyophilization can impact the protein structure and assurance needs to be provided that patients are consistently receiving a quality product, which can only be demonstrated at drug product release.

Shire will implement this as part of drug substance release and drug product stability testing. Additional data will be provided to support drug product release justifying that there is no change in product attributes. The FDA and Shire will continue discussions during the review of the NDA (i.e., product specification discussions).

5. **Regarding your drug substance release protocol:**

a) **Specify the molar ratio of mannose and other monosaccharides relative to protein.**

Additional Discussion:
Shire stated that their proposed method to determine molar ratios of mannose and other monosaccharides is to compare the area under peaks — of the drug substance glycan map to the reference standard. The FDA asked whether Shire has experienced any difficulty measuring sialic acid and mannose-6-phosphate (M6P) molar ratios. Shire stated that the majority of the carbohydrates are mannose-containing glycans and there is very little sialic acid to measure. The FDA asked whether an assessment of moles of mannose per mole of protein will be included in release testing. Shire stated that Module 3 of the NDA currently includes percent mannose as release specification.

Shire will submit additional data supporting use of percent mannose as release specification rather than molar ratio mannose/protein.

b) **Specify limits for — content, or provide validation data that demonstrate removal by the process.** b(4)

Additional Discussion:
Shire stated that three recent process validation lots demonstrated a concentration of — below the limit of quantitation. Therefore, Shire does not recommend that routine testing — be conducted. The FDA agreed.

6. **Please provide batch numbering and the pooling protocol for drug substance and drug product.**

   Additional Discussion:
   Shire clarified that the drug product and drug substance numbers are the same.

7. **Please provide shipping validation studies for drug substance and drug product.**

   Additional Discussion:
   In its written responses (Attachment 1), Shire stated it will provide the shipping study reports under Module 3 of the NDA. There was no additional discussion at the meeting.

8. **Please provide DMF references for container closure systems for drug substance and drug product.**

   Additional Discussion:
   In its written responses (Attachment 1), Shire stated it will provide the Letters of Authorization to the DMF for the container closures systems under Module 1 of the NDA. There was no additional discussion at the meeting.

9. **Please clarify which patients received AF1 and AF2 in your clinical trials, including TKT032 and HGT-GCD-039.**

   Additional Discussion:
   Shire stated that the only patients who received AF2 material were those in trials TKT034 and HGT-GCB-044. Patients in both study TKT032 and study HGT-GCB-039 received AF1 material. Shire clarified that clinical material included material manufactured

   however, patients in study TKT032 did not receive any material manufactured in the . The FDA stated that data from studies that used the material may not be supportive of the NDA, as stated in a letter sent to Shire in December 2006. The FDA stated that if analytical comparability of AF1 and AF2 material is not established, additional clinical and clinical pharmacology data may need to be collected (e.g., pharmacokinetic and pharmacodynamic comparability data).

b(4)

10. Be aware that, should our assessment of your physicochemical comparability studies conducted on drug substances manufactured with the AF1 and AF2 processes determine that the drug substances manufactured with the two processes are not comparable, additional nonclinical data and, potentially, clinical data may be required.

Additional Discussion:
See discussion under Additional FDA Comment 9.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

See the discussion above (Section 2.0).

5.0 ATTACHMENTS AND HANDOUTS

Attachments: 1) Shire E-mail of 8/10/09 with written responses sent prior to the meeting.
2) Shire slides presented at meeting.

Attachment 1

From: Bayless, Lynn [lbayless@shire.com]
Sent: Monday, August 10, 2009 10:18 AM
To: Ishihara, Richard
Cc: Stark, Cristi L
Subject: IND 61,220-Pre-NDA meeting
Attachments: emfinfo.txt

Dear Wes,

Shire has reviewed FDA preliminary responses to Shire pre-NDA questions, sent via email on August 7th, and would like to further discuss the following questions at the pre-NDA meeting scheduled for today:

Question 2
Question 2di
Question 2g
Question 4
Question 5
Question 6
Question 9

Shire hereby commits to complying with the following FDA requests noted in the preliminary responses sent via email on 7 August 2009. These questions will not be discussed at the meeting time.

FDA Question 2a:
Include a regulatory history of the clinical development of velaglucerase alfa.

Company Response:
A full regulatory history of velaglucerase alfa will be included in the NDA.

FDA Question 2b
Provide a thorough literature review regarding the safety of velaglucerase alfa and the safety of any other similar products (e.g., imiglucerase) currently on the market.

Company Response:
- A literature search and review regarding the safety of velaglucerase alfa and imiglucerase will be performed.
- Review of the results will be provided in Module 2.5.
- Copies of literature references will be included in Module 5.4.

FDA Question #2c:
Include historical control data regarding Type 1 Gaucher disease for comparison with results of your study TKT032.

Company Response:
Shire will perform a literature search on the natural history of Gaucher disease and relevant references will be included in Module 5.4.

FDA Question #2d-ii:
All corresponding analysis datasets along with an appropriate and complete data definition file (i.e.-

DEFINE.pdf or DEFINE.xml). We recommend that these datasets fully comply with ADaM standards.

Company Response:
Shire agrees to provide all corresponding analysis datasets along with the appropriate and complete data definition file according to ADaM standards in the NDA.

FDA Question #2d-iii:
A well commented, organized, and clean SAS program written for each analysis dataset created.

Company Response:
Shire agrees to include a SAS program for each analysis dataset created in the NDA.

FDA Question #2d-iv:
A description of each amendment made to the protocol.

Company Response:
Shire agrees to provide a description of each protocol amendment in the NDA.

FDA Question #2e:
We request that you provide case report forms for all patients reporting serious adverse events.

Company Response:
Shire will provide CRFs for all patients reporting serious adverse events (SAEs) in the NDA.

FDA Question #2f:
Shire will perform standardized MedDRA queries on the safety data.

FDA Question #7
Please provide shipping validation studies for drug substance and drug product

Company Response:
Shire will provide the shipping study reports to Module 3

FDA Question #8
Please provide DMF references for container closure systems for drug substance and drug product

Company Response:
Shire will provide the Letters of Access to the DMF for the container closures systems to Module 1

Should you have any questions in advance of our arrival please feel free to contact either myself (617) 710-2829 or Howard Yuwen (617) 595-2721.

Kind regards,

Lynn

Lynn E. Bayless, M.S., RAC
Associate Director
Shire Human Genetic Therapies, Inc.
700 Main Street
Cambridge, MA 02139

Phone: 617-613-4219
Blackberry: 617-710-2829
Fax: 617-613-4009

lbayless@Shire.com

Attachr. 2

Velaglucerase alfa: Pre-NDA Meeting

August 10, 2009

Shire

Our purpose

We enable people with life-altering conditions to lead better lives

FDA Question 2:

On page 10 of your Type B Meeting Briefing Package, you state that only safety data will be presented for HGT-GCB-039. Please explain why additional information about this trial will not be provided. We do not feel your proposal is adequate.

Company Response:

- In the original NDA Shire will present the following information:
  - Study protocol
  - Safety data from HGT-GCB-039 to be included in the safety summary
  - Efficacy report covering primary (hemoglobin concentration) and secondary endpoints (platelet counts, liver and spleen volume, chitotriosidase and CCL18) included in Module 5

HGT-GCB-039 Primary Efficacy Assessments
Mean Change at Week 41 from Baseline in Hemoglobin
One-sided 97.5% CI for Non-inferiority (velaglucerase alfa - imiglucerase)

Pop.	Treatment Group	N	Baseline Mean/ (Median)	Mean Change from Baseline to Week 41	Mean Treatment Difference (velaglucerase alfa – imiglucerase)	97.5% One-sided CI[a] (L, U)
ITT	velaglucerase alfa 60 U/kg	17	11.5 (11.4)	1.624	0.135	**(-0.596, inf)**
	imiglucerase 60 U/kg	17	10.5 (10.6)	1.488		
PP	velaglucerase alfa 60 U/kg	15	11.3 (11.4)	1.677	0.157	**(-0.599, inf)**
	imiglucerase 60 U/kg	15	10.4 (10.6)	1.520		

a-obtained from a two-sample t-test

HGT-GCB-039 Secondary Efficacy Assessments – Difference in Mean Change at Week 41 from Baseline (velaglucerase alfa - imiglucerase)

		Change from Baseline to Week 41		
Parameter	n	Mean Treatment Difference	95% CI	Treatment Difference (includes 0)
Platelets[a] (x10^9/L)	34	-38.71	(-88.42, 10.99)	No
Normalized Liver Volume[a] (% of Body Weight)	34	-0.07	(-0.43, 0.29)	No
Normalized Spleen[b] Volume[c] (% of Body Weight)	14	0.08	(-0.52, 0.68)	No
Chitotriosidase[a d] (nmol/mL/h)	21	-703.6	(-11762.3, 10355.1)	No
Chemokine (C-C motif) Ligand 18 (ng/mL)	34	145.7	(-188.6, 480.0)	No

a Based on a mixed model adjusting for age at informed consent, splenectomy status and baseline values.
b There are 20 splenectomized patient(s) excluded (10 velaglucerase alfa 60 U/kg; 10 imiglucerase 60 U/kg).
c Based on a mixed model adjusting for age at informed consent and baseline values.
d There are 13 patient(s) deficient in chitotriosidase activity excluded (7 velaglucerase alfa 60 U/kg; 6 imiglucerase 60 U/kg).

FDA Question 2d-i:

For each trial you plan to include in your NDA submission (studies TKT032, TKT034, HGT-GCB-039, TKT025, and TKT025EXT), please provide the following:

i) All clean raw/CRF data presented in appropriate electronic datasets along with a copy of the annotated case report form (aCRF). We recommend that these datasets fully comply with SDTM standards.

Company Response:

- Raw/CRF data presented in the appropriate electronic datasets along with a copy of the annotated CRF in the NDA in compliance with SDTM standards with the exception of the legacy study TKT025.

For Ease of the Review TKT025 Non-CDISC

- TKT025: Office of Regulatory Review Support at the FDA informed Shire it was acceptable to submit TKT025 data in non-CDISC format
  - TKT025EXT CRT includes key efficacy data and all safety data from TKT025 stored in CDISC format.
  - ISE CRT includes key efficacy data from TKT025 and all efficacy data from TKT025EXT for stand-alone analysis stored in CDISC format.
  - ISS CRT includes all safety data from TKT025 and TKT025EXT for stand-alone analysis stored in CDISC format.

FDA Question 2g:

You state that a Safety Update will be provided approximately three months into the review of the NDA, but that the data will be presented individually for each study. As per 21 CFR 314.50 (d)(5)(vi), you should submit your update in the same format as the integrated summary of all available information about the safety of the drug product.

Company Response:

- Shire agrees to provide integrated safety data in the Safety Data Update during the review of the NDA.
  - Shire intends to have a data cut off of August 31, 2009.

CMC Responses

Shire

Our purpose

We enable people with life-altering conditions to lead better lives

4a Regarding your drug substance and product release and stability protocol, please include;

- A potency assay that measures the kinetic parameters of velaglucerase alfa (Km and kcat) using a physiologically relevant substrate:

Company Response

- There is variability in the clinical dosing for ERT in Gaucher patients (15 to 60 U/kg)
  - To provide a consistent measurement of activity for velaglucerase alfa, Unit of activity was defined using the same surrogate substrate p-Nitrophenyl β-D-Glucopyranoside as was used for imiglucerase.
- Investigation of an enzyme kinetic method using glucosylceramide with C18 acyl chain showed:
  - No changes in kinetic parameters for drug product stored up to 24 mo at 2 to 8°C
  - k_{cat} correlated well with specific activity using surrogate substrate in forced degradation studies and provides no additional information
  - A decrease in K_m was associated with product degradation (indicating tighter binding)
- Details of the kinetic assay evaluation are included in Section 3.2.S.3.1 Characterization
- We are proposing to maintain the current substrate for the specific activity assay and will utilize the natural substrate assay to characterize significant process changes

4b Regarding your drug substance and product release and stability protocol, please include;

- A cellular uptake assay and/or a receptor binding assay that directly correlates with cellular uptake

Company Response

- We have developed a dose-response, mannose-receptor mediated, cell uptake bioassay (as shown to be uptake inhibited by mannan)
- The assay is part of drug substance lot release and drug product stability program, as justified by;
  - DS stability is stored frozen where no changes in quality attributes occur
  - There are no changes in the glycosylation, protein structure, or activity introduced by the manufacture of drug product

	Release	Stability
Drug substance	Yes	No
Drug product	No	Yes

5a Regarding your drug substance release protocol:

- Specify the molar ratio of mannose and other monosaccharides relative to protein

Company Response

- There are approx. 15 mannose and 1 M6P per mole, with only trace levels of sialic acid
- Glycan map is run routinely for release of drug substance. There are three peak groups.
  - Currently % peak group area for 1 and 3 are reported
    - Peak group 1 consists of high mannose glycans
    - Peak group 3 monitors M6P containing glycans
- Additional details are provided in Section 3.2.S.3.1 Characterization
- To monitor mannose and total carbohydrate content:
  - Percent peak group area of 1 and 3 will be compared against reference standard
  - Total peak group area will be compared against reference standard

5b Regarding your drug substance release protocol:

- Specify limits for [redacted] content, or provide validation data that demonstrate removal by the process b(4)

Company Response

- Data regarding the clearance of [redacted] for the three Process Validation lots is provided in Section 3.2.S.3.2 Impurities b(4)
  - The [redacted] levels in the three PV Lots were below LOQ for the SP and HA load (LOQs of 0.1 µg/mL and 0.2 µg/mL, respectively)

- In addition, spiking experiments were carried out to assess potential clearance [redacted]. This information is provided in Section 3.2.S.2.5 Process Evaluation b(4)
  - Observed [redacted] LRVs:
    - MEP Chromatography Step
    - SP Chromatography Step [redacted]
    - Total
- Based on the cumulative data, routine testing for [redacted] is not required

6 Manufacturing

- Please provide batch numbering and the pooling protocol for drug substance and drug product

Company Response

- Drug substance and drug product lots receive a unique batch number per Shire SOP
- Batch and scale definition including batch numbering for drug substance is provided in Section 3.2.S.2.2. The drug product numbering follows the same numbering scheme
- The criteria for pooling of drug substance is described in Section 3.2.S.2.2
  - Drug substance is pooled based on average harvest number and total grams of velaglucerase alfa per liter of [redacted] b(4)
- Multiple lots of drug substance are pooled to manufacture drug product as stated in Section 3.2.P.3.3.

9 Process Development

- Please clarify which patients received AF1 and AF2 in your clinical trials, including TKT032 and HGT-GCD-039

Company Response

- As part of commercialization of velalglucerase alfa, the purification process was scaled up (AF1 to AF2)
  - No change in cell culture process
  - Key process changes in purification included:
    - An approximate 2-fold scale up
    - Tightening of column load specifications and operational controls to improve process robustness
    - Details are included in Section 3.2.S.2.6.1
  - Based on comprehensive comparability studies of AF1 and AF2 materials, the processes were found to be comparable
  - Details are included in Section 3.2.S.2.6.2

9 Process Development

- Please clarify which patients received AF1 and AF2 in your clinical trials, including TKT032 and HGT-GCD-039

Company Response

Clinical Study	Patients	
	Received AF1	Received AF2
TK025	12	-
TK025EXT	10	-
TK032	25	-
HGT-GCB-034	40	18*
HGT-GCB-039	34	-
HGT-GCB-044	95 patients received AF2	

* Patients were transitioned from AF1 to AF2

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-61220	GI-1	SHIRE HUMAN GENETIC THERAPIES INC	GENE-ACTIVATED (GLUCOCEREBROSIDASE)

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

/s/

RICHARD W ISHIHARA
09/10/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,220

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

Dear Dr. Mehta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gene Activated® Glucocerebrosidase (GA-GCB, DRX008A).

We refer to your May 2, 2006, correspondence requesting a meeting to further discuss and obtain concurrence from the FDA on the adequacy of your nonclinical development program to initiate Phase 3 clinical studies and support a NDA for GA-GCB.

The date scheduled for this meeting was June 16, 2006.

We further refer to our correspondences sent to you by facsimile on June 15, 2006, (see attachment 1) which contained our initial responses to the questions submitted in your meeting background package.

We acknowledge your decision to accept our written responses in lieu of a meeting.

Therefore, the attached responses, sent to you by facsimile on June 15, 2006, represent the official minutes of the scheduled meeting.

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

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., Ph.D.
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment 1

Questions and Responses:

1. In combination with the clinical safety data, are the nonclinical safety data as summarized in the End of Phase 2 briefing package (Serial No. 024) and the subsequent pharmacology and toxicology information amendment (Serial No. 030) adequate to initiate phase 3 studies in the U.S.?

   Response:

   After further consideration, the information available is adequate to initiate the phase 3 clinical study with female patients of child-bearing potential electing to participate in the study agreeing to use a medically acceptable method of contraception at all times during the study and must have negative results to a pregnancy test performed at the time of enrollment and as required throughout their participation in the study.

2. Are the results from the completed chronic toxicology studies adequate to support an NDA for GA-GCB?

   Response:

   There is no need for further chronic toxicology studies.

3. Are the proposed designs of the reproductive toxicology studies adequate to support an NDA for GA-GCB? Specifically,

   a. Segment I and Segment II studies will be conducted separately in two species (rats and rabbits)
   b. The maximum dose administered will be 17 mg/kg
   c. Segment III studies will not be conducted

   Response:

   - **Your proposal to conduct separate Segment I (rats) and Segment II (rats and rabbits) studies is acceptable.**

   - **The 17 mg/kg appears to be an appropriate dose for rats, however, you may need to conduct a dose ranging study in rabbits to support dose selection for the Segment II study. Submission of the reproductive toxicology battery will be needed with NDA submission.**

   - **It would be desirable for you to conduct pre- and postnatal development study (Segment III) in rats as recommended in the Division meeting minutes dated February 7, 2006.**

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

/s/

Joyce Korvick
7/12/2006 10:49:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,220

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gene Activated® Glucocerebrosidase (GA-GCB).

Please refer to the meeting between representatives of your firm and the FDA on January 11, 2006. The purpose of the meeting was to obtain agreement from the FDA on the proposed clinical development plan and chemistry, manufacturing, and control (CMC) plans to ensure that meaningful data will be generated to support a marketing application for GA-GCB.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Ryan Barraco
Regulatory Project Manager
Division of Gastroenterology
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 11, 2006

TIME: 10:00 – 11:30 AM

LOCATION: White Oak, Bldg 22, Conference Room 1313

APPLICATION: IND 61,220

DRUG NAME: Gene Activated® Glucocerebrosidase (GA-GCB)

TYPE OF MEETING: B, End-Phase-2

MEETING CHAIR: Dr. John Hyde

MEETING RECORDER: Ryan Barraco

FDA ATTENDEES:

Brian E. Harvey, M.D., Ph.D., Director, Division of Gastroenterology Products (DGP)
Joyce Korvick, M.D., M.P.H., Deputy Director, DGP
John Hyde, M.D., Ph.D., Medical Team Leader, DGP
Anne Pariser, M.D., Medical Officer, DGP
Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist, DGP
Ryan Barraco, Regulatory Project Manager, DGP
Stella Grosser, Ph.D., Biometrics Team Leader, Division of Biometrics II
Maria Ysern, M.S., Review Chemist, Division of Pre-Marketing Assessment II
John Hill, Ph.D., Review Chemist, Division of Pre-Marketing Assessment I

EXTERNAL CONSTITUENT ATTENDEES (Transkaryotic Therapies Inc.):

Kip Martha, M.D., Sr. Vice President and Chief Medical Officer
Suzanne L. Bruhn, Ph.D., Vice President, Global Regulatory Affairs
Kathryn McNaughton, Ph.D., Program Executive
Marcio Voloch, Ph.D., Vice President, Process Development
Zahra Shahrokh, Ph.D., Sr. Director, Pharmaceutical and Analytical Development
Candida Fratazzi, M.D., Sr. Medical Director
Michael Hall, M.D., Vice President, Clinical Research
Howard H. Yuwen, Ph.D., Sr. Director, Regulatory Affairs
Marc Wiles, Ph.D., Sr. Director, Preclinical Research
Robert Corcoran, Vice President, Quality
Robert Mensah, Ph.D., Director, Biometrics
Lynn E. Bayless, Regulatory Project Manager
Jeannine Lennihan, Regulatory Affairs Associate II
Ari Zimran, M.D., Director, Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel

BACKGROUND:

Transkaryotic Therapies Inc. (TKT) submitted a meeting request (MR) on November 4, 2005, received November 7, 2005, for a Type B, End-of-Phase 2 meeting for Gene Activated® Glucocerebrosidase (GA-GCB). TKT submitted twelve questions in their background package submitted December 12, 2005, received December 13, 2005. Transkaryotic Therapies Inc. requested the meeting to obtain agreement from the FDA on the proposed clinical development plan and chemistry, manufacturing, and control (CMC) plans to ensure that meaningful data will be generated to support a marketing application for GA-GCB.

MEETING OBJECTIVES:

To reach an agreement with the Agency on the responses to the questions posed in the sponsor's background package.

DISCUSSION POINTS:

In response to the sponsor's questions in their background package for the meeting, the following agreements were reached after discussion. The format provides for the sponsor's questions, followed by the Agency's responses in bold lettering. The sponsor's presentation slides follow the questions and responses.

IND 61,220/(GA-GCB)
Transkaryotic Therapies Inc.
End-of-Phase 2 Meeting
January 11, 2006

Questions and Responses:

1. Would the FDA consider the future marketing application for GA-GCB to be reviewed as an NDA or a BLA?

   Agency Response:

   Given that Cerezyme and Ceredase were approved under the NDA process, GA-GCB will be reviewed as a NDA under current plans.

2. Does FDA agree that the primary and secondary endpoints for the treatment-naïve patient study (TKT032) are acceptable to test the effectiveness of GA-GCB as a first line therapy in patients with Gaucher disease?

   Agency Response:

   No. Study TKT032 must be at least 12 months in duration to support a long-term indication. If pediatric patients are to be included as planned, growth and bone development will need to be assessed.

Discussion: Proposed endpoints are otherwise acceptable. TKT will build growth and development assessments into protocol.

3. If statistical significance ($p \leq 0.05$) is achieved for the primary endpoint for the treatment-naïve patient study (TKT032), would FDA consider the finding to be sufficient demonstration of efficacy to support approval of a marketing application?

Agency Response:

Clinical findings must be reviewed in addition to the p-value.

Discussion: Study power was based on change in hemoglobin. This is adequate for design, but review of application will need to look at size of changes and other clinical outcomes.

4. Does FDA agree that the total number of patients included in the efficacy database will be sufficient to demonstrate effectiveness of GA-GCB?

Agency Response:

It will be your decision as to how many patients to include for the assessment of efficacy, as long as you have adequate precision and power to demonstrate a treatment effect. We note that 24 patients in treatment-naïve study (TKT032) and 20 patients in maintenance study (TKT034) are sample sizes comparable to those of the Cerezyme and Zavesca trials.

5. Does FDA agree that in the trial (TKT034) to demonstrate safety in patients switched from imiglucerase therapy to GA-GCB, the minimum number of 20 patients is sufficient?

Agency Response:

No. We would like to see at least 40 patients treated for 12 months to more adequately assess safety and maintenance of treatment effect, especially platelet counts. We recommend that the inclusion criteria be as broad as possible; in particular, we recommend that you enroll patients on maintenance Cerezyme treatment regardless of antibody (Ab) status, as this may more accurately reflect the expected clinical use of your product.

Discussion: TKT is amendable to including patients with antibodies, but would probably still exclude patients who have had anaphylaxis.

6. Does FDA agree that the proposed clinical development plan is sufficient to demonstrate safety and efficacy and support approval of GA-GCB for the indication of the long-term treatment of patients with Gaucher disease?

Agency Response:

No. The indication needs to be supported by what is being studied. Since you are proposing to study the treatment of Type 1 Gaucher disease patients over 6 years of age for the treatment of anemia, thrombocytopenia, hepatosplenomegaly, etc. as described in the Cerezyme indication, we would expect your product to have a similar indication.

We are concerned that you propose to exclude all subjects with pre-existing Ab formation. As proposed, six-month studies would be inadequate to support an indication of long-term treatment.

Additional Clinical Comments:

- **Your clinical plan needs to reflect more accurately the expected clinical use. We think it would be likely to have patients transitioned from Cerezyme if they are Ab positive and possibly experiencing infusion reactions.**

  Discussion: TKT noted that history of infusion reaction is not an exclusion criterion.

- **Your Ab testing needs to have performance characteristics defined and should be fully validated.**

- **Your current experience is in adults with a median age of 56 years (range, 25-63 years). Given the older ages, those patients likely represent an attenuated disease population. The findings in those patients may not necessarily reflect what will be seen with the more severely effected treatment-naïve patients you plan on enrolling in Study TKT032. Your protocol needs to include an advance safety plan to address infusion reactions and other more serious manifestations.**

  Discussion: TKT intends to have plans in the protocol to address infusion reactions.

- **What are your plans for studying pediatric patients less than 6 years old? The Cerezyme labeling currently provides information about patients down to 2 years of age.**

  Discussion: TKT does have plans to study patients down to two years of age.

- **Studies that involve pediatric patients should include plans to monitor growth.**

- **A bone monitoring plan needs to be included in your development plan. Bone marrow changes should be detectable on MRI as early as one year after starting treatment, and changes should be followed for at least 3 to 5 years. This is especially important if you intend to explore lower doses.**

  Discussion: TKT noted the imaging technology was not widely available. FDA was agreeable with evaluating a subset of patients, but it would still be important to monitor over a long period of time.

- **We recommend that you consider including plans in your study design for any dose-escalation and dose-reduction to be done according to defined clinical criteria.**

  Discussion: The plan is to keep dose steady in the primary efficacy study. In a European study the effect of a high dose was seen on markers but not clinical outcomes. TKT noted that the doses 60 and 45 were widely used. TKT will look at 30 in extension study.

- **It should be feasible to obtain a safety data base of approximately 80 patients exposed for one year.**

7. Does the FDA agree that the proposed designs of the reproductive toxicology studies are adequate to support a marketing application for GA-GCB?

   Agency Response:

   No.

   - **The dose ranges proposed for all these studies should be expanded to accommodate higher doses that provide sufficient margins to the highest human dose on a surface area basis.**

     Discussion: TKT stated that the dose ranges were based on a 10-fold margin on a mg/kg basis instead of surface area. TKT noted that there is a limitation to how much protein can be given to the animals.

   - **Female fertility and teratology study in rats should be two separate studies. This will provide clarity for effects on fertility of the dams and teratological effects on the fetuses.**

     Discussion: TKT stated that they proposed to do the studies together as recommended in the ICH guidance. FDA noted that it may be more practical to separate them.

   - **A Segment III Prenatal and Postnatal study in rats should be conducted to assess the effects on pre- and postnatal development.**

   - **Male and female fertility studies in rats and teratology studies in rats and rabbits should be completed and submitted to the IND prior to initiating the large scale Phase 3 clinical study.**

8. Are the nonclinical studies as summarized in this document adequate to support the approval of a marketing application for GA-GCB?

   Agency Response:

   No. An adequate number of animals or sufficiently high doses have not been employed in the rat toxicology studies. Please conduct a 12-month chronic toxicity study in rats with at least 10 animals/sex/group and expanded dose range. Provision should also be made for recovery groups.

   Discussion: FDA and TKT felt that additional follow-up discussions for Questions 7 and 8 would be important for reaching agreement.

9. Does the FDA concur with TKT's position that the proposed Phase I/II to Phase III Drug Substance comparability plan is sufficient to support use of this material in clinical trials?

Agency Response:

As proposed, the comparability plan is acceptable. We have the following comments concerning Table 12-2 of this meeting package, page 75, which proposes tests and acceptance criteria that will be used for assessing comparability:

- **Please clarify which reference standard will be used for the identity test.**
- **For the reversed phase HPLC, please provide a comparison of overlapping chromatograms, using the Phase 1/2 material, a 50:50 mixture of the old and the new material to verify they overlap (co-mixture analysis).**
- **Indicate which 4 species of comparable retention times are going to be compared in the ion Exchange HPLC.**
- **If possible, perform the host cell protein test on reserve samples to compare the old product to the new product.**

Additional comments about this comparability plan may be provided by the Office of Biotechnology Products (OBP) at a later time. For any additional details regarding comparability issues, please refer to "Guidance for Industry Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process."

Discussion: TKT plans to respond to these requests.

10. Does the FDA agree with TKT's overall Drug Substance and Drug Product comparability plan for the post-Phase III clinical trial changes?

Agency Response:

Yes, we agree with the overall comparability plan. Please refer to our recommendations in question 1.

11. Does the FDA agree with the proposed Drug Product Process Validation and Stability plans, specifically the use of active and placebo vials in the lyophilizer load?

Agency Response:

We recommend discussing this issue with your assigned District Office. They will be responsible for verifying your proposed drug product process validation and stability plan.

Discussion: FDA clarified that while the plan appears acceptable, the field office may have its own approach, so that it would be wise to check with them too.

12. Does the FDA agree with TKT's testing strategy to monitor for potency and bioactivity?

Agency Response:

Your procedure for monitoring the bioactivity of the enzyme by its enzyme activity and by the glycosylation profile appears adequate.

Additional CMC Comments:

1. **Drug Substance:**

   a. **Establish acceptable criteria and in process intermediates as manufacturing experience allows.**

   b. **You claim that the drug substance manufacturing process has been engineered to produce a Glycoform that is high in mannose content. Routine lot release test would serve to verify and monitor this claim as well as the internalization of the API into the target cell via the cell surface mannose receptor.**

2. **Drug product:**

   a. **The infusion bag label claims that the drug product is to be used within 3 hours of dilution. Please provide stability data for the reconstituted drug product (vial) and the diluted drug product (infusion bag).**

      Discussion: TKT will provide this.

3. **Stability data need to be updated as they become available.**

   Discussion: This CMC advice represents current thinking, but the Office of Biotechnology Products has not had input yet, so there may be additional comments.

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

/s/

Ryan Barraco
2/7/2006 01:15:01 PM

John Hyde
2/7/2006 01:25:18 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22575 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: VPRIV Established/Proper Name: velaglucerase alfa Dosage Form: for injection		Applicant: Agent for Applicant (if applicable):
RPM: Wes Ishihara		Division: Division of Gastroenterology Products

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ Actions	
• Proposed action 2/26/10 • User Fee Goal Date is 2/28/10	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 1: NME

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: 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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric 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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [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.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (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))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (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)? ☐ Yes ☐ No

  *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 the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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**," 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

  *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 section below (*Summary Reviews*).*

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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 section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist[3]	3/2/10
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 2/26/10
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	2/25/10
• Original applicant-proposed labeling	11/20/09
• Example of class labeling, if applicable	Aldurazyme (8/25/09) Fabrazyme (12/17/08) Myozyme (12/8/08)

[3] Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	2/19/09
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 12/16/09 12/10/09
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 2/26/10, 11/24/09, 10/30/09 ☒ DMEPA 1/27/10 ☐ DRISK ☒ DDMAC 1/28/10 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	12/23/09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Designation • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	2/25/10, 2/24/10, 2/24/10, 2/22/10, 2/19/10, 2/19/10, 2/19/10, 2/18/10, 2/17/10, 2/10/10, 2/4/10, 1/29/10, 1/27/10, 1/22/10, 1/19/10, 1/7/10, 12/23/09, 12/11/09, 11/19/09,

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	11/13/09, 10/30/09, 10/15/09, 10/8/09, 9/30/09, 9/23/09, 9/14/09
❖ Internal memoranda, telecons, etc.	10/22/09
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 8/10/09
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 1/11/06
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) *(indicates dates)*	6/15/06
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 2/26/10
Division Director Summary Review *(indicate date for each review)*	☐ None 2/26/10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 2/26/10
PMR/PMC Development Templates *(indicate total number)*	☐ None 3/2/10
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review
• Clinical review(s) *(indicate date for each review)*	2/23/10, 2/5/10, 10/5/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Section 3.3 of MO Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 1/29/10

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 2/25/10, 10/27/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2/1/10, 10/28/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 2/22/10
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 2/19/10, 1/28/10, 9/28/09
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 2/25/10, 2/25/10, 9/25/09
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 2/3/10, 9/17/09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See Section 4 of the CMC Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date)*	Date completed: 2/25/10, 2/22/10 ☒ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

›pendix A to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.