CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761047Orig1s000

PRODUCT QUALITY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date:	**November 13, 2017**
To:	Administrative File, **STN 761047/0**
From:	Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement:	Patricia Hughes, Ph.D., Acting Branch Chief, CDER/OPQ/OPF/DMA/Branch IV
Subject:	Second addendum to review memo for New Biologic License Application (BLA) STN 761047 dated August 15, 2017
Applicant:	Ultragenyx Pharmaceutical Inc.
US License:	**2040**
Facility:	Rentschler Biotechnologie GmbH, Laupheim, Germany FEI: 1000291122
Product:	Mepsevii (vestronidase alfa, recombinant human beta-glucuronidase, rhGUS, UX003)
Dosage:	2 mg/mL, solution for intravenous infusion
Indication:	Treatment for Mucopolysaccharidosis type VII (MPS VII, Sly syndrome)
FDA Receipt Date:	March 16, 2017
Action Date:	November 16, 2017

Recommendation: New information regarding the completed rabbit pyrogen tests conducted on three lots of drug product was provided by the applicant. The information was reviewed and considered not to impact the approval recommendation for the drug product section of the BLA. The drug product part of this BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval with the following post-marketing commitment:

Repeat the rabbit pyrogen test with three Mepsevii drug product lots at the maximum human equivalent dose of 4 mg/kg. Provide summary data and study report.

Review Addendum

In amendment dated 11/13/2017 (sequence 59), the applicant provided follow-up information for response to Question 17 provided in amendment dated June 28, 2017 (Sequence 26) regarding the completed rabbit pyrogen test conducted on three lots of Mepsevii DP. A miscalculation was discovered during a recent review of the study reports and the laboratory preparation source records for the completed rabbit pyrogen study. It was discovered that the dose administered to the rabbits was 3 mg/kg, not the intended maximum human equivalent dose of 4 mg/kg. The applicant acknowledges the rabbit pyrogen test was not conducted in full compliance with

21CFR610.13(b) and proposed to repeat the rabbit pyrogen test with three DP batches at the maximum human equivalent dose of 4 mg/kg as a post-marketing commitment (PMC).

The following will be reviewed as a PMC:
Repeat the rabbit pyrogen test with three Mepsevii drug product lots at the maximum human equivalent dose of 4 mg/kg. Provide summary data and study report.

Reviewer comment: Based on our recent experience, the risk of having pyrogenic substances other than bacterial endotoxin in the final DP is relatively low. In addition, the rabbit pyrogen test results using three Mepsevii DP batches at the 3 mg/kg dose (75% of the maximum dose) were all negative. Therefore, it is acceptable to repeat the rabbit pyrogen test with three DP batches at the 4 mg/kg dose as a PMC.

Satisfactory

Conclusion

I. The drug product part of the BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval with the following post-marketing commitment:

   Repeat the rabbit pyrogen test with three Mepsevii drug product lots at the maximum human equivalent dose of 4 mg/kg. Provide summary data and study report.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. No inspection follow-up items were identified.

Bo Chi

Digitally signed by Bo Chi
Date: 11/14/2017 10:41:02AM
GUID: 508da71600029713f321cfd33c82d8d4

Patricia Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 11/14/2017 12:34:02PM
GUID: 508da717000297bcbfce0919f8c09594

First Approval for Indication

Recommendation: **Approval**

BLA Number: 761047
Review Number: 2
Review Date: 10/31/2017

Drug Name/Dosage Form	Vestronidase alfa-vjbk / injection
Strength/Potency	2 mg/mL (10 mg/5 mL)
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	Mucopolysaccharidoses VII (MPS VII, Sly Syndrome)
Applicant/Sponsor	Ultragenyx Pharmaceutical Inc.

Submissions Reviewed:

Submission(s) Reviewed	**Document Date**
STN 761047/0057	10/30/2017

Executive Summary

In BLA amendment 0057, received on October 30, 2017, Ultragenyx informed the Agency of a name change of the vestronidase alfa-vjbk drug substance and drug product manufacturer due to a change in the corporate structure. All business operations have been transferred to Rentschler Biopharma SE, a wholly owned subsidiary of Rentchsler Biotechnologie GmbH, effective October 1st, 2017. The address and contact information have not changed, except for the email address. This business change is not expected to affect product safety or efficacy. Therefore, OPQ's recommendation for this BLA is still approval.

Updated Approval Action Letter Language:

- Manufacturing location:
  - Drug substance and Drug Product– Rentschler **Biopharma SE**, Erwin-Rentschler-Strasse 21, 88471 Laupheim, Germany

Updated Establishment Information:

Overall Recommendation:		
DRUG SUBSTANCE		
Function	Site Information	DUNS/FEI Number
(b) (4) Manufacture Release and Stability testing MCB and WCB manufacture and storage	Rentschler **Biopharma SE**, Laupheim, Germany	**313166479**/ 1000291122
DRUG PRODUCT		
Function	Site Information	DUNS/FEI Number
Manufacture of DP DP release and stability testing	Rentschler **Biopharma SE**, Laupheim, Germany	**313166479**/ 1000291122

Cristina Ausin-Moreno

Digitally signed by Cristina Ausin-Moreno
Date: 11/07/2017 09:40:25AM
GUID: 508da6d9000264f90aba0372cad7afa4

Joel Welch

Digitally signed by Joel Welch
Date: 11/08/2017 08:20:50AM
GUID: 508da6dc0002673d83d264d81364d6cf

First Approval for Indication

Recommendation: **Approval**

BLA Number: 761047
Review Number: 1
Review Date: 10/20/2017

Drug Name/Dosage Form	Vestronidase alfa-vjbk / injection
Strength/Potency	2 mg/mL (10 mg/5 mL)
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	Mucopolysaccharidoses VII (MPS VII, Sly Syndrome)
Applicant/Sponsor	Ultragenyx Pharmaceutical Inc.

Product Overview

Vestronidase alfa-vjbk is a human recombinant beta-glucuronidase (rhGUS). rhGUS catalyzes the hydrolysis of beta-D-glucuronic acid residues from the N-terminus of the glygosaminoglycans dermatan sulfate, chondroitin 6-sulfate, and heparan sulfate.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Rukman De Silva	DBRR IV/OBP
Drug Product	Rukman De Silva	DBRR IV/OBP
Assay Validation and Immunogenicity	Jacek Cieslak	DBRR IV/OBP
Facilities	Ruth Moore/Peter Qiu	DIA/OPF
Microbiology Drug Substance	Max Van Tassell/ Reyes Candau Chacon	DMA/OPF
Microbiology Drug Product	Bo Chi & Virginia Carroll/ Dupeh Palmer	DMA/OPF
Labeling	Vicky Border-Hemphill	OBP
Business Regulatory Process Manager	Truong Quach	OPRO
Application Technical Lead	Cristina Ausin-Moreno	DBRR IV/OBP

Mutidisciplinary Review Team:

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Jenny Doan	DGIEP
Cross-disciplinary Team Lead	Katie Donohue	DGIEP
Medical Officer	Dina Zand	DGIEP
Pharm/Tox	Yolanda Brach/Sushanta Chakder	DGIEP
Clinical Pharmacology	Christine Hon/Yow-Ming Wang	OCP
Statistics	Feiran Jiao/Yeh-Fong Chen	DB III

1. Names:
   i. Proprietary Name: Mepsevii
   ii. Trade Name: Mepsevii
   iii. Non-Proprietary/USAN: vestronidase alfa-vjbk
   iv. CAS name: 1638194-78-1
   v. INN Name: vestronidase alfa

vi. Common Name: UX003; Recombinant human beta-glucuronidase (rhGUS)
vii. OBP systematic name: RPROT P08236 (BGLR_HUMAN) beta-glucuronidase [UX003]

2. Pharmacological class: recombinant human lysosomal beta glucuronidase (lysosomal glycosaminoglycan specific enzyme)

Submissions Reviewed:

Submission(s) Reviewed	Document Date
STN 761047/0001	3/16/2017
STN 761047/0002 (updated FEI)	3/27/2017
STN 761047/0003 (response to IR #1)	3/30/2017
STN 761047/0004 (response to IR #2)	4/12/2017
STN 761047/0011 (response to IR #3)	5/11/2017
STN 761047/0017 (response to filing communication)	6/5/2017
STN 761047/0023 (response to IR#4)	6/21/2017
STN 761047/0026 (response to IR#5 and 6)	6/28/2017
STN 761047/0027 (response to IR#7)	6/30/2017
STN 761047/0028 (response to Q7 in IR#5)	6/30/2017
STN 761047/0029 (response to Q5 in IR#6)	7/14/2017
STN 761047/0030 (response to IR#10)	7/17/2017
STN 761047/0031 (response to IR#9)	7/18/2017
STN 761047/0034 (response to Q2 and Q4 in IR#8 and Q8 in IR#9)	7/25/2017
STN 761047/0035 (response to Q2 in IR#4 and Q6 in IR#9)	7/28/2017
STN 761047/0040 (response to IR#11 and IR#13)	8/11/2017
STN 761047/0042 (response to IR#15)	8/25/2017
STN 761047/0043 (response to Q5 in IR#8 and IR#14)	8/31/2017
STN 761047/0044 (response to Q1 in IR#13)	9/8/2017
STN 761047/0045 (response to Q1 and Q3 in IR#8)	9/15/2017
STN 761047/0049 (response to discussion regarding HCP PMC)	9/27/2017
STN 761047/0050 (response to IR#16)	10/2/2017
STN 761047/0052 (response to IR#12)	10/5/2017
STN 761047/0053 (response to IR#14)	10/10/2017
STN 761047/0054 (response to IR#15)	10/16/2017

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	3	N/A (Not reviewed because sufficient information was included in the submission)	N/A	None
	Type III			3	N/A	N/A	None
	Type III			1	Acceptable	N/A	None
	Type V			3	N/A	N/A	None
	Type II			1	Acceptable	N/A	None

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.
   IND 123788, IND (b) (4), eIND 119935, eIND 123764, spIND (b) (4).

3. Consults:
   None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761047 for MEPSEVII (vestronidase alfa-vjbk) manufactured by Ultragenyx Pharmaceutical, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of MEPSEVII is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

Approval Action Letter Language:

- Manufacturing location:
  - Drug substance and Drug Product– Rentschler Biotechnologies GmbH, Erwin-Rentschler-Strasse 21, 88471 Laupheim, Germany
- Fill size and dosage form – 2 mg/mL (10 mg/5mL) injection in single-dose vials
- Dating period:
  - Drug product – 24 months; 2-8°C
  - Drug Substance – (b) (4) months (b) (4) °C
    Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
  - For stability protocols:
    We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
  - Yes; Rationale for exemption – specified product (exempted according to 601.2a)

Benefit/Risk Considerations:

Treatment of Mucopolysaccharidoses VII (MPS 7, Sly syndrome) is an unmet medical need. It is an ultra-rare, progressively debilitating disease. Onset of symptoms may occur at birth or later in life during adolescence or adulthood. Most of MPS 7 patients die before the second or third decade of life due to several medical problems. On February 16, 2012, the product was granted orphan-drug designation for the treatment of MPS 7 (#11-3598). On July 15, 2015, the clinical development program was granted a Fast Track designation under IND 123788.

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The control strategy combined with in-process, release, and stability testing ensure process consistency and drug substance and drug product with appropriate quality attributes and free of adventitious agents.

Due to the limited demand of the product, the approval recommendation is supported by concurrent validation data for the drug substance manufacturing process. The submission

included an interim validation report with data corresponding to two drug substance process performance qualification (PPQ) lots. The third PPQ lot was manufactured at the time of the inspection of the Rentschler Biotechnologies site. The final process validation report including data for the third PPQ lot will be submitted in an annual report if all the pre-defined acceptance criteria are met or in a supplement if there are any out-of-specification results.

Environmental Assessment or Claim of Categorical Exclusion

The sponsor claims categorical exclusion under 21 CFR 25.31(a) and (c) based on the fact that filing of the BLA does not increase the use of the active moiety and its manufacture does not alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

The sponsor's claim of categorical exemption is accepted.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

1. To conduct the bioburden and endotoxin method qualification to include a total of three lots for the method qualification of (b) (4)
   Proposed timeline: December 2019

2. To re-evaluate all drug substance (DS) and drug product release and stability acceptance criteria when a statistically significant number of lots (25) of drug substance have been manufactured using the commercial manufacturing process and tested using the commercial specifications. The corresponding data, the analytical and statistical plan used to evaluate the specification, and any proposed changes to the specifications will be provided in the final study report.
   Proposed timeline: December 2035

3. To perform a leachable study to evaluate leachables in the UX003 drug product container closure system. The analysis will be performed using one drug product lot that has passed the end of shelf-life under the long term (5 ± 3°C) and accelerated (25°C/60% RH) storage conditions. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.
   Proposed timeline: January 2019

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategy that are relevant to both drug substance and drug product. For additional information see the Office of Biotechnology (OBP) Product Quality Review.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Enzymatic Assay (potency)	Directly linked to efficacy	Intrinsic to molecule	(b) (4)	
In vitro Cellular Uptake (potency)	Directly linked to efficacy	Intrinsic to molecule		
Mannose-6-Phosphate (potency)	Directly linked to efficacy	(b) (4)		
Glycosylation (potency and product related impurities)	Directly linked to efficacy and safety	Introduced during manufacturing process		
(b) (4) (potency)	Pharmacokinetics	Introduced during manufacturing process		
Aggregates – High Molecular Weight Impurities (product related impurities)	Efficacy and safety	Introduced during manufacturing process and storage		
Charge variants (product related variants)	Efficacy and safety	Intrinsic to molecule		
(b) (4) (product related variants)	Efficacy and safety	Introduced during manufacturing process and storage		
Higher Order Structure (potency)	Directly linked to efficacy and MOA	Intrinsic to molecule		
Fragments (product related impurities)	Safety	Introduced during manufacturing		

		process and storage		

B. Drug Substance vestronidase alfa-vjbk Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management
Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes. For additional information see the OBP Product Quality Review and Addendum and the Division of Microbiology Assessment (DMA) Microbiology Drug Substance Review.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other
Endotoxin (Contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process	(b) (4)	**PMC** to repeat the bioburden and endotoxin method qualification to include a total of three lots for the (b) (4)
Bioburden (Contaminant)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process.		
Host Cell Proteins (Process related impurity)	Safety and immunogenicity	Process; (b) (4)		The OBP primary review proposed a PMC (b) (4) According to the updated information the PMC is not necessary.

Host cell DNA (Process related impurity)	Safety	Process; (b) (4)	(b) (4)
(b) (4)	Safety	Formulation	
(b) (4) (Process related impurity)	Safety	(b) (4)	
(b) (4) (Process related impurity)	Safety		
(b) (4) (Process related impurity)	Safety	Introduced during manufacturing process	
Trace metals	Efficacy and safety	Introduced during manufacturing process	
Viruses (Process related impurity)	Safety	Contamination during manufacture	
Leachables and extractables (Process related impurity)	Safety	Entire process	

- Description:
  Vestronidase alfa-vjbk is a hydrolytic lysosomal beta-glucuronidase. The active enzyme is a homotetramer and each monomer contains 629 amino acids, including five cysteine residues (Cys 16, Cys374, Cys385, Cys478, and Cys622; Cys 622 may form an inter-monomer disulfide bridge) and four N-glycosylation sites (asparagines 151, 250, 398, and 609).

Molecular weight analysis confirmed identity and demonstrated lack of significant levels of post-translational modifications other than glycosylation. For additional information see the OBP Product Quality Review.

- Mechanism of Action (MoA):
  Mucopolysaccharidoses VII is characterized by a deficiency in beta-glucuronidase enzymatic activity. Lack of beta-glucuronidase activity causes accumulation of glycosaminoglycans (GAGs) in the lysosomes of several body tissues. This leads to several diseases including skeletal, cardiac, and pulmonary manifestations. Treatment with rhGUS replaces the inactive or missing enzyme. The enzyme is internalized in the lysosomes though the CI-M6P receptor. Hydrolysis of GAGs takes place inside the lysosomes. For additional information see the OBP Product Quality Review.

- Potency Assay:
  The substrate of the enzymatic activity assay is 4-methylumbelliferyl-glucuronide (4-MUG). The product of hydrolysis, 4-MU, is measured by fluorescence. One unit of activity corresponds to the amount of enzyme that cleaves 1 nmol of 4-MUG per hour at 37°C pH 4.8. Specific activity in MIU/mg is obtained by dividing the absolute activity by the protein concentration determined by UV A_{280}.

  The cellular uptake takes place through the cation-independent mannose-6-phosphate receptor. The sponsor uses beta-glucuronidase-deficient fibroblasts as the cell substrate. Cells are incubated with different concentrations of rhGUS. The intracellular rhGUS content is measured by enzymatic activity, after cell lysis. K_{uptake} is the concentration of rhTPP1 in medium that results in half saturation. Relative uptake is determined by comparing the absolute uptake of the sample to the uptake of the reference standard.

  For additional information see the OBP Product Quality Review.

- Reference Materials:
  (b) (4)
  For additional information see the OBP Product Quality Review and Addendum.

- Critical starting materials or intermediates:

Cell bank system: (b) (4)

The sponsor provided adequate CoA, EDMQ certificates of suitability, and TSE/BSE statements where necessary. For additional information see the OBP Product Quality Review.

- Manufacturing process summary: (b) (4)

The process is well controlled. Adequate procedures and controls are in place to maintain microbiological product quality during maximum hold periods and throughout manufacture.

For additional information see the OBP Product Quality Review and the DMA Microbiology Drug Substance Review.

- Container closure: (b) (4)

The applicant performed an evaluation of the vendor extractables support documentation and knowledge gained from the use of these containers during development to support their suitability. For additional information see the OBP Product Quality Review and the DMA Microbiology Drug Substance Review.

- Dating period and storage conditions:
  (b) (4)

C. Drug Product Mepsevii Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information see the OBP Product Quality Review and Addendum and the DMA Microbiology Drug Product Review and Addendum.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.	(b) (4)	
Endotoxins (Contaminant)	Safety and purity Can increase immunogenicity risk	Contaminants could be introduced throughout DP manufacturing or through a container closure integrity failure.		
Container Closure Integrity (sterility assurance)	Safety Failure in closure integrity may lead to contamination (loss of sterility) of DP or evaporation/leakage (impacting concentration or content)	Failure in closure integrity may lead to contamination (loss of sterility) of DP or evaporation/leakage (impacting concentration or content)		
Protein concentration (general)	Variable protein concentration causes variable dosage of the drug and may affect efficacy	(b) (4)		
Clarity and color (general)	Safety and efficacy	Clarity may be impacted by the		

		number of particles in solution; differences in color are indicative of contamination or degradation		
Particulate matter (Sub-visible particles (SVP)) (product or process related impurities)	Immunogenicity, patient safety	Container closure system (CCS) and process	(b) (4)	
Foreign matter (visible particles) (product and process related impurities)	Immunogenicity, patient safety	Manufacturing material and CCS		
Leachables/ extractables (Process related impurities)	Safety	Manufacturing equipment and CCS		**PMC** to report the results of analysis of leachables in long-term and accelerated stability DP samples
pH (general)	Safety and efficacy	Formulation		
Osmolality (general)	Safety	Formulation		
Extractable volume (general)	Essential for dosing	Manufacturing Process		
Identity (general)	Safety and efficacy	Intrinsic to molecule		

- Potency and Strength:
  Mepsevii is supplied at 2 mg/mL in a single use vial 10 mg of vestronidase alfa-vjbk

- Summary of Product Design:
  Mepsevii is supplied in single-use 10 mL vials

- List of Excipients:
  15.6 mg sodium dihydrogen phosphate dihydrate, 39.4 mg sodium chloride; 15.5 mg L-histidine, 0.5 mg polysorbate 20

- Reference Materials:
  The same reference material is used for drug substance and drug product

- Manufacturing process summary:
  The manufacturing process of drug product consists of pooling of (b) (4)

The control strategy is appropriate to ensure [redacted], consistently accurate fill and adequate critical quality attributes.
The maximum batch size is limited to [redacted] vials.

For additional information see the OBP Product Quality Review and Addendum and the DMA Microbiology Drug Product Review and Addendum.

- Container closure:
  The primary container closure system is a 10 mL Type I glass vial with a 20 mm [redacted] rubber stopper [redacted] and an aluminum seal with a [redacted] plastic cap.
  Appropriate compatibility studies were performed for the container closure system.
  For additional information see the OBP Product Quality Review and Addendum and the DMA Microbiology Drug Product Review and Addendum.

- Dating period and storage conditions:
  24 months at 2-8°C
- List of co-package components, if applicable:
  None

D. Novel Approaches/Precedents:
Concurrent validation of drug substance manufacturing process.

E. Any Special Product Quality Labeling Recommendations:
Store at 2-8°C. Protect from light. Do not freeze or shake. Diluted Mepsevii should be used immediately. If not used immediately, Mepsevii may be stored for up to 36 hours at 2-8°C followed by 6 hours at a maximum of 25°C.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
[redacted] Manufacture Release and Stability testing MCB and WCB manufacture and storage	Rentschler Biotechnologie GmbH, Laupheim, Germany	332952766/ 1000291122	VAI	- Failed to establish adequate system for maintaining equipment to control aseptic conditions - Procedures to prevent microbial contamination not established, written, validated, and/or followed - Deficient monitoring of environmental conditions in [redacted] areas - Inadequate qualification of controlled temperature units	Approval (VAI)

				- Inadequate qualification of critical equipment - Discrepancies in bioburden and endotoxin qualification from BLA content - Incorrectly reported bioburden results	
Cell Bank Characterization		(b) (4)	Approve Facility Based on Profile	N/A	Approval
Mycoplasma Testing (b) (4) Cell bank Characterization			Approve Facility Based on Profile	N/A	Approval
(b) (4)			Approve Facility Based on Profile	N/A	Approval
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of DP DP release and stability testing	Rentschler Biotechnologie GmbH, Laupheim, Germany	332952766/ 1000291122	VAI	See Drug Substance Section	Approval (VAI)
Testing for SVP		(b) (4)	Approve Facility Based on Profile	N/A	Approval
Testing for PS20			Approve Facility Based on Profile	N/A	Approval
Secondary Packaging and Labeling			Approve Facility Based on Profile	N/A	Approval

G. Facilities:

A pre-license inspection was conducted at Rentschler Biotechnologie GmbH, Laupheim, Germany, from May 15th -19th and May 22nd - 23rd 2017 by OPF/DMA (Maria Jose Lopez-Barragan, Diane Raccasi, and Maxwell Van Tassell), OBP (Rukman De Silva and Gerald Feldman), and DIA (Ruth Moore). A seven-item Form FDA 483 was issued.

For additional information see the Facilities Review: Division of Inspectional Assessment.

H. Lifecycle Knowledge Management:

a. Drug Substance:

   i. Protocols approved:
      1. Annual stability protocol
      2. Stability protocol for the extension of shelf-life
      3. Concurrent validation
      4. (b) (4) Validation Protocols
   ii. Outstanding review issues/residual risk:
   See Postmarketing commitments in section I.B
   iii. Future Inspections Points to Consider:
   None

b. Drug Product

   i. Protocols approved:
      1. Annual stability protocol
      2. Stability protocol for the extension of shelf-life
   ii. Outstanding review issues/residual risk:
   See Postmarketing commitments in section I.B
   iii. Future Inspections Points to Consider:
   None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material		X		
7.	Non-Mammalian Cell Substrate/Source Material			X	
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			x	
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]				X
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)		X		
17.	End of Phase II/Pre-NDA Agreements tem			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other [fill in]				
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods		X		
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}				X

Rukman De Silva
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Jacek Cieslak
Digitally signed by Jacek Cieslak
Date: 10/25/2017 02:38:27PM
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Ruth Moore
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Zhihao Peter Qiu
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Maxwell Van Tassell
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Date: 10/25/2017 12:36:51PM
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Reyes Candau-Chacon
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Virginia Carroll
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Dupeh Palmer-Ochieng
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Cristina Ausin-Moreno
Digitally signed by Cristina Ausin-Moreno
Date: 10/25/2017 12:29:28PM
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Joel Welch
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Date: 10/26/2017 10:29:31AM
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Bo Chi
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Date: 10/26/2017 05:50:58PM
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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date:	**October 20, 2017**
To:	Administrative File, **STN 761047/0**
From:	Virginia Carroll, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement:	Dupeh Palmer, Ph.D., Acting Quality Assessment Lead CDER/OPQ/OPF/DMA/Branch IV
Subject:	New Biologic License Application (BLA)
Applicant:	Ultragenyx Pharmaceutical Inc.
US License:	**2040**
Facility:	Rentschler Biotechnologie GmbH, Laupheim, Germany FEI: 1000291122
Product:	Mepsevii (vestronidase alfa, recombinant human beta-glucuronidase, rhGUS, UX003)
Dosage:	2 mg/mL, solution for intravenous infusion
Indication:	Treatment for Mucopolysaccharidosis type VII (MPS VII, Sly syndrome)
FDA Receipt Date:	March 16, 2017
Action Date:	November 16, 2017

Recommendation: The drug product part of this BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.

Review Addendum

The following studies and information were submitted to the Agency after the interim review and are reviewed herein:

1. Container closure integrity method validation with adequate sensitivity
2. Crimping study performed with the new container closure integrity method to support crimping parameters
3. Determination of worst-case location for [redacted] (b) (4) to support the validation study
4. Results from two additional media fills using the [redacted] (b) (4), performed in June 2017 and August 2017, including environmental monitoring data and process times
5. A post-dilution microbial hold time study to support the label's storage conditions

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0043	August 31, 2017	Response to IR
0045	September 15, 2017	Response to IR
0050	October 2, 2017	Response to IR
0053	October 10, 2017	Response to IR
0054	October 16, 2017	Response to IR

Module 3.2

FDA question:

(b) (4)

there are no adequate CCI data to support the UX003 DP container closure and the crimping parameter range. You have committed to develop and validate a CCI test with adequate sensitivity by September 29, 2017. Commit to provide the method validation data of the new CCI method and validation data using the new CCI method to support the integrity of the UX003 DP container closure and the crimping parameter range by September 15, 2017 to complete the review of this BLA within the set timeline.

Container Closure Integrity Test Method (3.2.P.2.5.3)

Section 3.2.P.2.5.3 was updated with a new CCIT method validation study in an amendment dated September 15, 2017 (sequence 0045). The dye leak test was validated (b) (4)

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FDA question:
Update Tables 3.2.P.3.4.4.1 and 3.2.P.3.4.4.3.1 (b) (4)

Process Controls for UX003 Drug Product Manufacture (3.2.P.3.4.4)

(b) (4)

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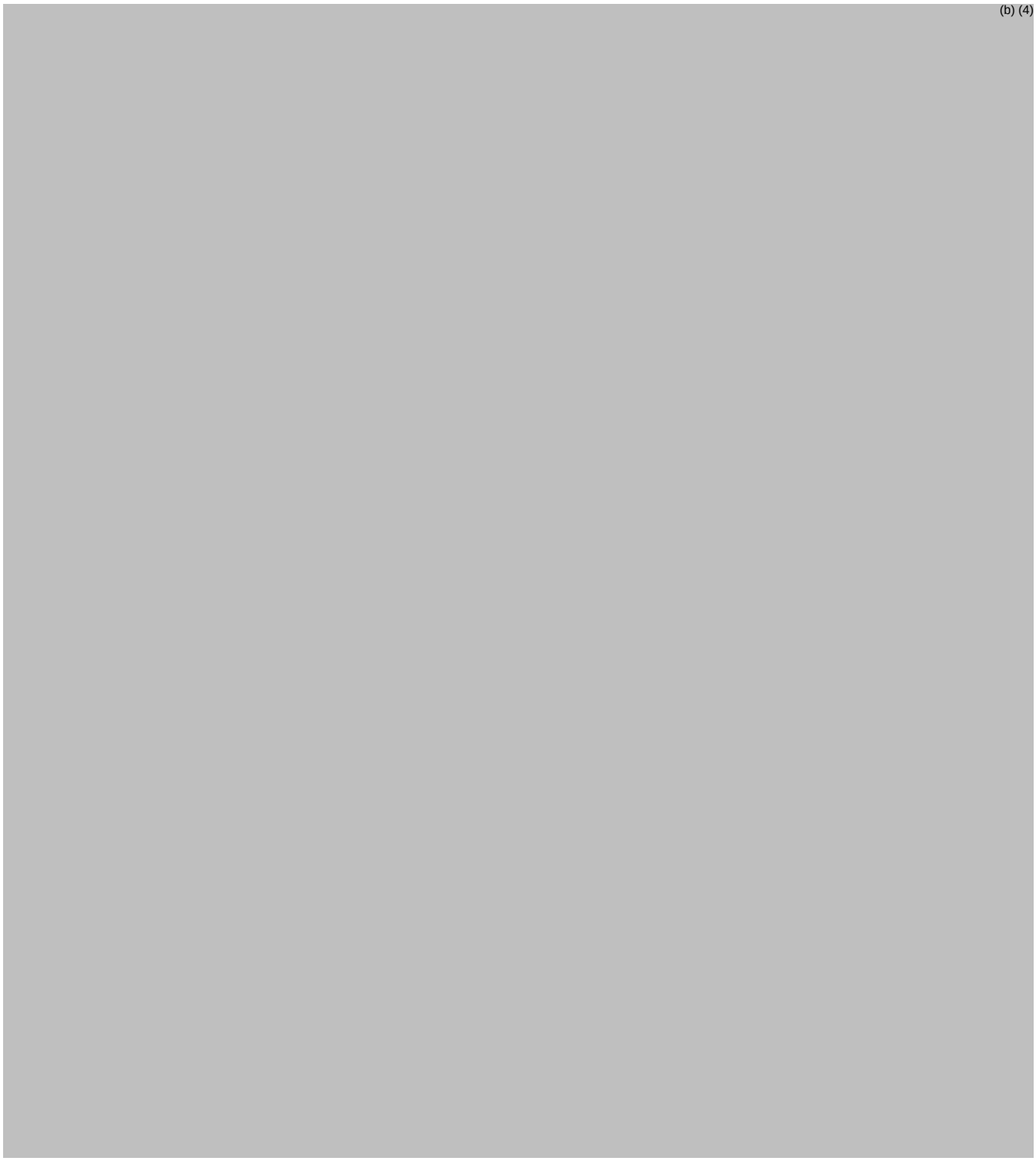
(b) (4)



SATISFACTORY

CGMP Status

The assessment of manufacturing facilities is documented in panorama.

Conclusion

I. The drug product part of the BLA, as amended, was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. No inspection follow-up items were identified.

DP Quality Microbiology Information Requests Sent and Date

August 15, 2017

1. The post-dilution microbial hold time study presented in the response dated August 11, 2017 (sequence 0040) is inadequate to support the label's post-dilution storage conditions of 36 hours at 2-8°C followed by (b) (4) °C. To support the hold time at (b) (4) °C following 2-8°C storage, conduct a post-dilution microbial hold time study with sequential incubation periods at 2-8°C followed by (b) (4) °C of at least twice the recommended storage time for both temperatures. Periodic intermediate sample times are recommended, including the (b) (4) time point at 20-25°C. Alternatively, reduce the label recommendation to a post-dilution storage time of 36 hours at 2-8°C or 6 hours at (b) (4) without storage at 2-8°C.

2. Update Tables 3.2.P.3.4.4.1 and 3.2.P.3.4.4.3.1 to reflect (b) (4) .

September 21, 2017

1. Explain how the two positive and two negative controls for the CCI test method are prepared for routine stability testing. Update section 3.2.P.2.5.3 accordingly.

2. Both visual and photometric detection methods are applied to test vials for CCI on stability, as described in section 3.2.P.2.5.3. The acceptance criteria in Table 3.2.P.2.5.3.3 appear to be based on visual detection. To avoid conflicting results between methods, select one detection method for the dye leak test and update section 3.2.P.2.5.3 accordingly.

3. Explain how the two positive and two negative controls for the container closure integrity (CCI) test method were prepared in the new crimping study for UX003 drug product presented in Table 3.2.P.3.5.5.5.1.1 (sequence 0045). Clarify whether the positive controls are drug product vials with (b) (4) . Update section 3.2.P.3.5.5.5 accordingly.

4. Regarding the information presented in Table 3.2.P.3.5.12.5.1 and the attached revalidation report (sequence 0045) for the media fill using the (b) (4) in June 2017:

    a. Based on the batch size of (b) (4) filled units for the PPQ runs, the minimum number of filled batch should be at least (b) (4) units to simulate actual production conditions. Justify why only (b) (4) vials were filled in the media fill study.

b. Clarify the rejection criteria during filling/capping for media fills on (b) (4)

c. (b) (4)

5. Clarify the results for anaerobic environmental monitoring (b) (4)

6. Clarify the following in reference to the media fill completed in August 2017, submitted in the amendment dated September 15, 2017 (sequence 0045):

a. (b) (4)

b.

The post-dilution hold time study submitted in the amendment dated October 10, 2017 (sequence 0053) does not support the label's storage conditions. The microbial counts at each time point should be compared to time 0, rather than (b) (4) To ensure a 2-fold safety factor, reduce the label's post-dilution storage conditions to 36 hours at 2-8°C followed by up to 6 hours at room temperature up to a maximum of 25°C.

Virginia Carroll

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Dupeh Palmer-Ochieng

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BLA STN 761047

Addendum

Mepsevii™ (vestronidase alfa-vjbk)

Manufacturer
Ultragenyx Pharmaceutical Inc.

Reviewer: Rukman De Silva, Ph.D.
ATL: Cristina Ausin, Ph.D.

`

Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

BLA 761047 Quality Addendum

Background:
At the time of finalization of the BLA 761047 primary CMC review there were information request items pending a response from the sponsor. This review addendum contains the review of the material the sponsor submitted after the BLA 761047 primary CMC review was finalized. This review only includes the updated CTD sections. All previous communications during the BLA review cycle are documented in the BLA 761047 primary CMC review uploaded into Panorama on August 14, 2017.

Primary Reviewer Summary Recommendation
The data submitted in this Biological License Application support the conclusion that the manufacture of Mepsevii™ (vestronidase alfa-vjbk) is well controlled and leads to a product that is pure and potent. Therefore, from the Chemistry, Manufacturing, and Controls perspective, it is recommended that Mepsevii™ (vestronidase alfa-vjbk) to be approved for human use (under conditions specified in the drug product label).

1. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request #14 (OBP)	8/3/2017
Information Request # 15 (OBP)	8/17/2017

2. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761047/0040	08/11/2017	Yes
STN 761047/0042	08/25/2017	Yes
STN 761047/0044	09/08/2017	Yes

III. List of Post-Marketing Commitments/Requirements

Draft PMC language to be updated upon discussion with the sponsor:

1) Re-evaluate all UX003 drug substance and drug product release and stability acceptance criteria when a statistically significant number of lots have been manufactured using the commercial manufacturing process and tested using the commercial specifications. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

2) Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the long term (5 ± 3 °C) and accelerated (25 °C/60% RH) storage conditions. The analysis will be performed at regular intervals and should include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UVMS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). This study will be performed as part of your annual stability program and results should be updated in the BLA Annual Report.

Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

3) (b) (4)

APPEARS THIS WAY ON ORIGINAL

Table of Contents

S. Drug Substance

3.2.S.4 Control of Drug Substance

(b) (4)

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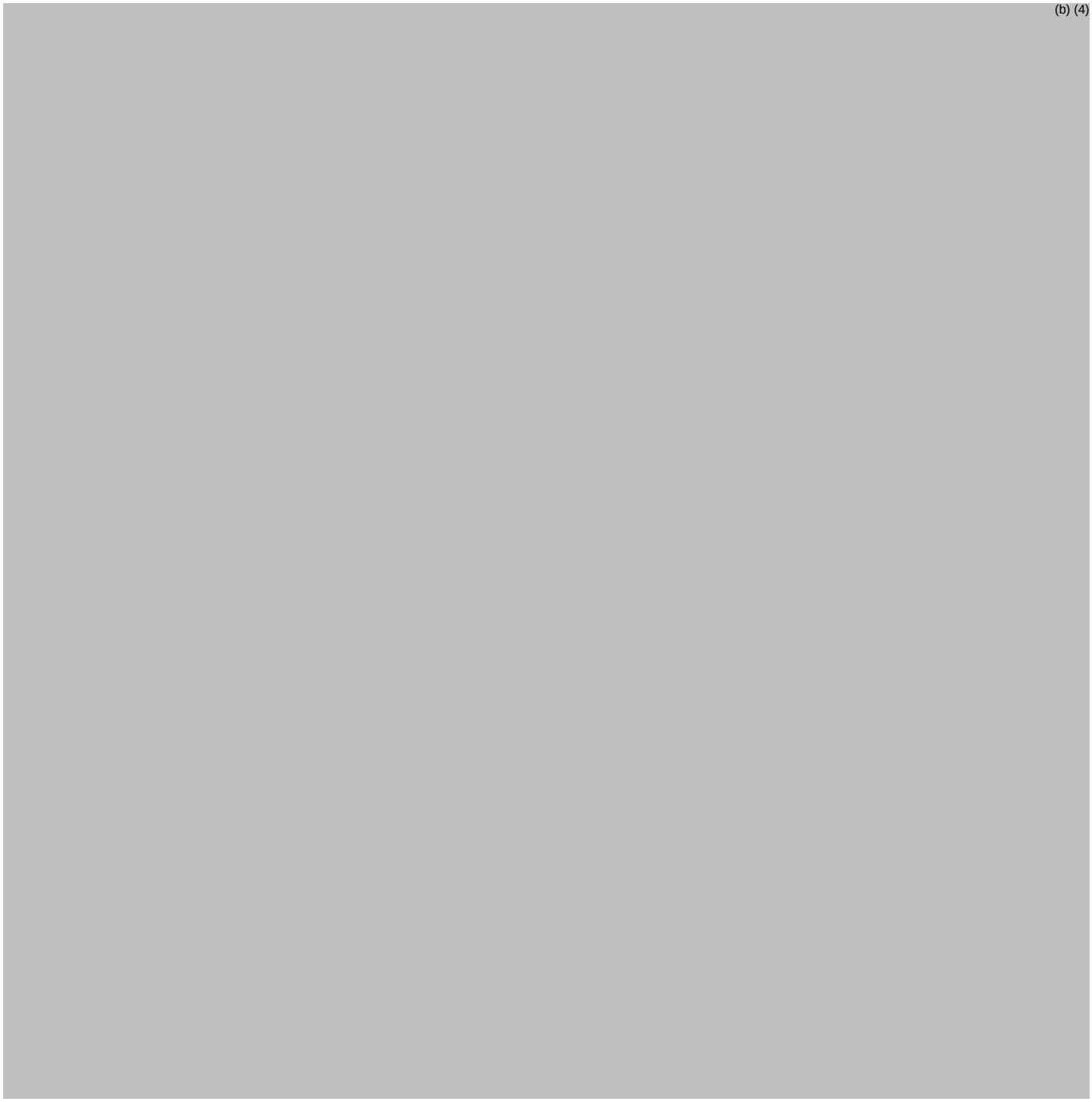

3.2.S.7 Stability

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

The original post-approval protocol did not include storing DS and DP under accelerated conditions. The following comment regarding the post-approval stability commitment for UX003 was communicated to the sponsor during the review cycle:

Your post-approval stability protocol indicates that you will add one representative DS lot and one DP lot at the long term conditions and you will evaluate their stability as part of your annual stability program. The purpose of the annual stability program is not only 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 (b) (4) *may not be adequate to address this issue. Therefore, we believe accelerated stability studies should be incorporated in the annual stability program for DS and DP the resulting data should be trended to establish whether changes occur in the degradation profile over time. Therefore, update your annual stability protocol to incorporate these suggestions, or provide a scientifically valid justification as to why these updates are not necessary.*

In response to our August 3, 2017 information request (Submission # 0040, dated August 11, 2017), the sponsor incorporated accelerated stability studies in the annual stability program for UX003 DS (Submission Table 3.2.S.7.2.2.2) and DP (Submission Table 3.2.P.8.2.2.2). In addition, the sponsor agreed to trend the accelerated stability data to establish whether the changes occur in the degradation profile overtime.

Reviewer's comments: *The sponsor's response is acceptable.*

P. Drug Product

3.2.P.3 Manufacture

(b) (4)

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The majority of the DP release and stability specifications are same as those proposed for control of the DS release and stability. Please see the Addendum section 3.2.S.4 above regarding the updated specifications of UX003 DS and DP.

The following comment regarding the identity test of the final DP was communicated to the sponsor during the review cycle:

In accordance to 21 CFR 610.14, identity testing on the final DP should be performed after all labeling operations have been completed. It is not clear if this is the current practice for UX003. Clarify at which point in the UX003 DP process samples are removed for identity testing and update the BLA accordingly.

In response to our August 3, 2017 information request (Submission # 0040, dated August 11, 2017), the sponsor proposed to perform identity testing (b) (4) , identity testing of each DP batch will be performed by the physical appearance characteristics of the DP primary packaging components (e.g. aluminum seal with (b) (4) colored flip cap) and the product (e.g. clear colorless liquid).

Reviewer's Comment: *The sponsor's proposed identity testing plan on the final DP after labeling operations is acceptable.*

3.2.P.7 Container/Closure System

During the review cycle, in response to an information request (Submission # 0026, dated June 28, 2017) the sponsor provided extractable study profile for UX003 DP (b) (4) glass containers (Submission # 0026, section 1.11.4, Table 10). The identified metal ions in the extractable profile were below the levels of toxicological concerns (< 0.001 mg/mL). Therefore, there is no safety concern due the metal ions below < 0.001 mg/mL. In addition, the extractable profile identified (b) (4) . However, no details of safety assessment of these extractables are provided in the submission. I have consulted non-clinical reviewer, Dr. Yolanda Branch to assess the safety of these compounds.

Reviewer's comments: *The non-clinical reviewer confirmed there is no safety concern regarding the identified extractables.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The sponsor monitors the stability of UX003 DP at long-term (5°C ± 3°C), accelerated (25 °C ± 2°C /60% RH) and stressed (40 °C ± 2°C /57% RH) storage conditions. The sponsor proposed a (b) (4) months expiry at long-term (5 °C ± 3°C) storage condition for commercial UX003 DP based on the stability data from the commercial and clinical lots representative of the commercial manufacturing process, container closure system and formulation. The following comment regarding the DP expiry was communicated to the sponsor during the review cycle:

You propose a shelf life of (b) (4) months at the long-term storage condition (5°C ± 3°C) for UX003 DP. The BLA contains 30 months of long-term storage condition stability data for clinical lot 1025264, stored in the intended commercial container closure system. Also, you provided up to 12 months of long-term stability data for the commercial process performance qualification batches 1032013, 1032014, and 1032015. You stated that the proposed shelf life for UX003 DP is based on the long-term and accelerated stability data of primary stability lots and it is supported by the long-term stability studies of UX003 DP formulated at pH (b) (4) You provided up to 36 months of long-term stability data for lot 1016656 and 24 months for lot 1020202, both formulated at pH (b) (4) According to ICH Q5C, the shelf life for biologics should be based on available real time, real temperature stability data in the intended container closure system from at least three batches. Thus, although the supportive stability data suggest that UX003 DP is stable under the long-term storage conditions up to 24 months, the UX003 pH (b) (4) formulation stability data are not adequate to support a shelf life of (b) (4) months because the rate of aggregation is clearly different. Therefore, upon review of the stability data provided in the submission we concluded that is acceptable to establish a 24-months shelf life at long-term storage condition (5°C ± 3°C) for UX003 DP. Please update the BLA accordingly.

In response to our information request (Submission # 0042, dated August 25, 2017) the sponsor updated the BLA to reflect a 24 month shelf life at the long-term storage condition for UX003 DP.

Reviewer's comments: *The sponsor's response is acceptable.*

3.2.P.8.2 Post-Approval Stability Commitment

In response to our information request (Submission # 0040, dated August 11, 2017) the sponsor updated the UX003 DP long-term stability condition post-approval stability protocol to include visible particulate testing (Submission Table 3.2.P.8.2.2.1). In addition, the sponsor incorporated accelerated stability studies in the post-approval stability program of UX003 DP (Submission Table 3.2.P.8.2.2.2).

Reviewer's comments: *The sponsor's updated post-approval stability commitment is acceptable.*

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Ausin-Moreno

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Rukman
De Silva

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DEPARTMENT OF HEALTH AND HUMAN SERVICE Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg.51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 05 September, 2017
To: Administrative File, STN 761047/0
From: Ruth Moore, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA B1
Subject: Original BLA
US License: 2040
Applicant: Ultragenyx Pharmaceutical Inc.
Mfg Facility: Drug Substance: Rentschler Biotechnologie GmbH, Laupheim, Germany
FEI 1000291122
Drug Product: Rentschler Biotechnologie GmbH, Laupheim, Germany
FEI 1000291122
Product: UX003 (recombinant human beta-glucuronidase); Vestronidase Alfa
Dosage: 2 mg/mL for intravenous administration.
Indication: Treatment of Mucopolysaccharidosis type VII (MPS VII, Sly syndrome)
Due Date: 16 November, 2017

RECOMMENDATION: This submission is recommended for approval from a facility review perspective.

SUMMARY

The subject BLA proposes manufacture of UX003 drug substance (DS) and drug product (DP), at Rentschler Biotechnologie GmbH, Laupheim, Germany (FEI 1000291122). This facility will also manufacture and store the cell banks, and perform release and stability testing for DS and DP.

UX003 is a recombinant form of human beta-glucoronidase (GUS) produced using a genetically engineered CHO cell line. It is proposed for the treatment of patients with MPS VII (sly syndrome). UX003 drug product is manufactured as a sterile solution for intravenous administration, 2 mg/mL, provided in single-use 10 mL glass vials (b) (4). Each vial is filled to deliver a minimum extractable volume of 5 mL.

ASSESSMENT

DRUG SUBSTANCE FACILITIES

- **3.2.S.2.1 DS Manufacturers.**
  The sites proposed for UX003 DS manufacture, cell banking operations, and testing are presented below in Table 1.

TABLE 1. Proposed Sites for UX003 DS Manufacture, Cell Banking and Testing Operations

Site Name	Address	FEI Number	Responsibilities
Rentschler Biotechnologie GmbH	Erwin-Rentschler-Strasse 21 Laupheim, Germany, 88471	1000291122	UX003 (b) (4) manufacture, packaging, storage, release and stability testing; Manufacture and storage of working cell bank (WCB)
(b) (4)			Mycoplasma and viral contaminants testing (b) (4) for release of DS; Cell bank characterization
			Testing for (b) (4)
			Cell bank characterization

***Reviewer Comment 1**: The facilities for manufacture of UX003 DS are adequately described.*

- **Prior Inspection History for DS Manufacturing and Testing Sites**
  - Rentschler Biotechnologie GmbH Inc. (FEI 1000291122), UX003 DS Manufacturing and Testing Site.
    - Inspection Conducted 11/28/2016 to 12/06/2016. Inspection conducted in accordance with Compliance Program 7356.002, Drug Manufacturing Inspections, and 7356.002A, Sterile Drug Process Inspections. The inspection covered profile classes SVL (Small Volume Parenterals) and (b) (4). Profile class CBI (biotechnology derived API) was not covered during this inspection. A 1-item form 483 was issued related to a functional dead leg observed in (b) (4), and the inspection was classified VAI.
    - Inspection Conducted 06/08/2015 to 06/16/2016. Inspection conducted in accordance with Compliance Program 7356.002, Drug Manufacturing Inspections, 7356.002A Sterile Drug Process Inspections, and 7346.843, Post Approval Audit Inspections. Profile classes SVL and (b) (4) were covered. Profile class CBI was not covered during this inspection. The inspection was classified VAI.
    - Inspection Conducted 09/12/2013 to 09/20/2013. Inspection conducted in accordance with Compliance Program 7356.002A Sterile Drug Process Inspections. Profile classes SVL and (b) (4) were covered. Profile class CBI was not covered during this inspection. The inspection was classified VAI
  - (b) (4) Site for Cell Bank Characterization and In-Process Testing of DS (b) (4). The last inspection of this

facility conducted [redacted] (b) (4) was classified NAI. The site is recommended for approval based on profile and acceptable compliance status.

- [redacted] (b) (4) Testing Site for Polysorbate 20 [redacted] (b) (4). The last inspection of this facility conducted [redacted] (b) (4) was classified NAI. The site is recommended for approval based on profile and acceptable compliance status.

- [redacted] (b) (4) Testing Site for Cell Bank Characterization. The last inspection of the facility was conducted [redacted] (b) (4), and provided coverage of the Quality and Laboratory Control Systems in addition Production Systems [redacted] (b) (4). The inspection was classified VAI, and the firm's responses to the 483 observations, per the CSO's evaluation, appeared adequate. The firm is recommended for approval based on current satisfactory compliance status and acceptable CTX profile.

- **Current Prior Approval Inspection Decisions**

  Rentschler Biotechnologie GmbH Inc. (FEI 1000291122), UX003 DS Manufacturing and Testing Site. Inspection conducted 05/15/2017 to 05/23/2017 by CDER-OPF and CDER-OBP.

  A Pre-license inspection (PLI) of Rentschler Biotechnologie GmbH Inc., Laupheim, Germany was completed in support BLA 761047/0 for UX003. The inspection was conducted in accordance with CPGM 7346.832 and ICH Q7. A comprehensive review of facilities, utilities, equipment, processes and procedures was conducted to evaluate product quality, adherence to commitments in the BLA and compliance to CGMPs. A 7-item Form FDA 483 was presented to Rentschler Biotechnologie GmbH management at the conclusion of the inspection on 23 May, 2017.. The corrective actions proposed by the firm have been reviewed and deemed adequate. The final inspection classification is VAI.

  Rentschler Biotechnologie GmbH Inc. is recommended for approval for manufacture of UX003 drug substance under BLA 761047/0.

Reviewer Comment 2: *The production and testing facilities associated with the manufacture of UX003 DS are acceptable from a facilities assessment standpoint.*

3.2.S.2.2 Overview of UX003 DS Manufacturing Operations

[redacted] (b) (4)

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(b) (4)

[redacted]

- **3.2.A.1.1.2 Manufacture of Other Products**
  Rentschler is authorized by the relevant German Regulatory Authority to manufacture sterile drug products including biotechnological drug products, as well as biotechnological drug substances (recombinant proteins, monoclonal antibodies and cytokines). Steroid hormones, antibiotics such as penicillin, sulphonamides and cephalosporins or cytotoxics are not manufactured at the facility.

DRUG PRODUCT FACILITIES

- **3.2.P.3.1. DP Manufacturers.**
  The sites proposed for UX003 DP manufacture, testing, packaging, and labeling are presented below in Table 3.

TABLE 3. Sites Proposed for UX003 Drug Product Manufacture and Testing

Site Name	Address	FEI Number	Responsibilities
Rentschler Biotechnologie GmbH	Erwin-Rentschler-Strasse 21 Laupheim, Germany, 88471	1000291122	UX003 DP manufacture; release testing and stability testing, primary packaging, batch release and storage of DP
[redacted] (b) (4)			Testing for polysorbate 20 in DP
			Testing for sub-visible particles in DP
			Labeling and secondary packaging of DP

- **Prior Inspection History for DP Manufacturing and Testing Sites**
  - Rentschler Biotechnologie GmbH Inc. (FEI 1000291122) - UX003 DP Manufacturing and Testing Site. Inspections were completed 12/06/2016, 06/16/2015 and 09/20/2013. Refer to prior inspection history described above for DS Manufacturing and Testing Sites.
  - [redacted] (b) (4) Testing Site for Polysorbate 20 in Drug Product. The last inspection of this facility conducted

[redacted] was classified NAI. The site is recommended for approval based on profile and acceptable compliance status.

- [redacted] - Testing Site for Sub-visible Particles Drug Product. The last inspection of this facility conducted [redacted] was classified NAI. The site is recommended for approval based on profile and acceptable compliance status.

- [redacted] - Labeling, and Secondary Packaging of DP. Inspection conducted [redacted] was classified NAI. The site is recommended for approval based on profile and acceptable compliance status.

- **Current Prior Approval Inspection Decisions**

Rentschler GmbH, Laupheim, Germany - UX003 DP Manufacturing and Testing Site. Inspection conducted 05/15/2017 to 05/23/2017.

A Pre-license inspection (PLI) of Rentschler Biotechnologie GmbH, Laupheim, Germany was completed in support BLA 761047/0, with coverage provided for both the drug product and drug substance manufacture. The drug product fill-finish operations were done on [redacted]. The inspection focused on Quality, Facilities and Equipment, Production, Materials and Laboratory Systems, evaluation of readiness for manufacturing, data integrity, and conformance to the BLA submission. A 7-item FDA Form 483 was issued at the conclusion of the inspection. The firm committed to corrective actions that were deemed acceptable. The final inspection classification is VAI, and the firm is recommended for approval.

Reviewer Comment 12. *The production and testing facilities associated with the manufacture of UX003 DP are acceptable from a facilities assessment standpoint.*

- **3.2.P.3. Overview of UX003 Drug Product Manufacturing Operations Conducted at Rentschler Biotechnologie, Laupheim**.

[redacted]

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(b) (4)

CONCLUSION

The facilities, equipment, environmental controls, cleaning and contamination control strategy employed by Rentschler Biotechnologie GmbH Inc. (FEI 1000291122) for UX003 drug substance and drug product manufacture are adequately described, and were verified during PLI inspection. Corrections to deficiencies identified during the inspections have been deemed satisfactory. All proposed manufacturing and testing sites for BLA 761047/0 are recommended for approval from a facilities assessment standpoint.

Ruth A. Moore -S

Digitally signed by Ruth A. Moore -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruth A. Moore -S, 0.9.2342.19200300.100.1.1=2001430890
Date: 2017.09.05 16:03:28 -04'00'

Ruth Moore Ph.D.
CSO/ Quality Assessment Lead (Ag.)
OPF Division of Inspectional Assessment Branch 1

Zhihao Qiu -S

Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhihao Qiu -S, 0.9.2342.19200300.100.1.1=2000438274
Date: 2017.09.05 16:06:34 -04'00'

Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment Branch 1

Appendix B: N/A

Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Proper Name 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			x	See DMEPA review of nonproprietary name suffix.[5]
Manufacturer name, address, and license number 21 CFR 610.60			x	We consider this a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.
Lot number or other lot identification 21 CFR 610.60 21 CFR 201.18 21 CFR 201.100			x	We consider this a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.
Expiration date 21 CFR 610.60 21 CFR 201.17			x	We consider this a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.
Multiple dose containers (recommended individual dose) 21 CFR 610.60			x	Single-dose vial
Statement: "Rx	x			

[1] Per 21 CFR 1.3 (b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Abraham S. Nonproprietary name suffix memorandum. RCM # 2017-1325 BLA 761047. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 August 3. P2.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
only" 21 CFR 610.60 21 CFR 201.100				
Medication Guide 21 CFR 610.60 21 CFR 208.24			x	
No Package for container 21 CFR 610.60			x	
Partial label 21 CFR 610.60 21 CFR 201.10		x		The terms LOT and EXP are printed online during labeling. We consider this to be a partial label thus the manufacturer address and license number may be omitted to allow for other important information including storage information and preparation instructions. To conform with 21 CFR 610.60(c), revise the manufacturer information from "Manufactured for:" to read as follows: "Manufactured by: Ultragenyx Pharmaceutical Inc." *Applicant revised as requested*
No container label 21 CFR 610.60			x	
Visual inspection 21 CFR 610.60		x		Confirm there is sufficient area on the container when the label is affixed to the container to allow for visual area of inspection of the contents per 21 CFR 610.60 (e). *Applicant responded: "The label is centrally affixed to the vial via an automatic labeling machine with an electronic vision system to detect the presence of the label on the vial."* *Ultragenyx confirms there is no text on the ferrule and cap overseal of the vials.* *We find this response acceptable.*
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			We consider this a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Route of administration 21 CFR 201.5 21 CFR 201.100	x			
Preparation instructions 21 CFR 201.5		x		Revise the statement from "Do not freeze" to read "Do not freeze. Do not shake." per 21 CFR 201.5 (g) and to be consistent with section 16.2 of the prescribing information. *Applicant revised as requested*
Package type term 21 CFR 201.5		x		Revise the statement from "(b) (4)" to read as a bolded statement "Single-Dose Vial" to be consistent with the appropriate package type term per Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015. *Applicant revised as requested* Bold the statement "Discard unused portion" to increase prominence of important information. *Applicant revised as requested*
Drugs Misleading statements 21 CFR 201.6			x	
Strength 21 CFR 201.10 21CFR 201.100	x			
Drugs Prominence of required label statements 21 CFR 201.15		x		Remove the statement (b) (4)" to ensure non-required information is not competing in size and prominence with important information. *Applicant revised as requested* This is considered a partial label and this statement is not required information since this product is not expected to be prepared in a home environment.
Bar code label requirements 21 CFR 201.25 21CFR 610.67	x			

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100		x		Unbold the statement "Usual Dosage". *Applicant revised as requested*
Inactive ingredients 21 CFR 201.100				We consider this a partial label. This information must appear on the carton, PI, and IFU (if applicable).
Storage requirements				Revise the storage statement from "Store at 2°C to 8°C (36°F to 46°F)" to read "Store at 2°C to 8°C (36°F to 46°F) in original carton to protect from light" Comply with USP standards (general chapter <7>) and USP chapter <659> Packaging and Storage Requirements *Applicant responded: Ultragenyx wishes to clarify that the statement "protect from light" was removed from the recent draft US PI update (BLA 761047, eCTD sequence 0029, dated 14 July 2017); therefore, it is deemed not required for the vial container label as well.* The forced degradation studies indicated that the product is sensitive to light under the conditions used. Stability data in the BLA do not specify if the stability samples were stored protected from light. Add the "Protect from light" statement to the container label and carton labeling as previously recommended until adequate stability data are provided. "Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light" *Applicant responded: due to limited space on the vial container label, Ultragenyx proposes to keep the storage statement on the vial label as "Store at 2°C to 8°C (36°F to 46°F) in original carton".* *We find this revision acceptable since "Protect from light" statement is restored on the carton labeling and in the prescribing information.*

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Dispensing container 21 CFR 201.100			x	

Package Label[6] Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Proper name 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10				See comment for container label
Manufacturer name, address, and license number 21CFR 610.61		x		To conform with 21 CFR 610.61(b), revise the manufacturer information from "Manufactured for:" to read as follows: "Manufactured by: Ultragenyx Pharmaceutical Inc. Novato, CA 94949 U.S. License No. XXXX". Note relocation of license number to appear with the manufacturer information. *Applicant revised as requested*
Lot number or other lot identification 21CFR 610.61	x			The terms LOT and EXP are printed online during labeling.
Expiration date 21CFR 610.61 21 CFR 201.17	x			
Preservative 21CFR 610.61	x			
Number of containers 21CFR 610.61			x	
Strength/volume 21CFR 610.61		x		Revise the unit in the strength statement from "10 mg/5 ml (2 mg/ml)" to read "10 mg/5 mL (2 mg/mL)".

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				Applicant revised as requested
Storage temperature 21CFR 610.61				Revise the storage statement from "Store refrigerated at 2°C to 8°C (36°F to 46°F)" to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light" to comply with USP standards (general chapter <7>) and USP chapter <659> Packaging and Storage Requirements *Applicant revision is acceptable*
Handling: "Shake Well", "Do not Freeze" or equivalent 21CFR 610.61		x		Revise the statement from "Do not freeze" to read "Do not freeze. Do not shake." per 21 CFR 610.61(i) and to be consistent with section 16.2 of the prescribing information. *Applicant revised as requested*
Multiple dose containers (recommended individual dose) 21CFR 610.61			x	Single-dose vial
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			
Known sensitizing substances 21CFR 610.61			x	
Antibiotics added during manufacturing 21 CFR 610.61			x	
Inactive ingredients 21CFR 610.61 21 CFR 201.100		x		Revise the statement "(b) (4) " to include inactive ingredients per 21 CFR 201.100 and to read "Each ml of solution contains: 2 mg vestronidase alfa, L-histidine (3.1 mg), polysorbate 20 (0.1 mg), sodium chloride (7.88 mg) and sodium phosphate monobasic dihydrate (3.12 mg). The pH of the solution is 6.0." Inactive ingredients should appear in alphabetical order per USP <1091> Labeling of

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				Inactive Ingredients. *Applicant revised as requested*
Adjuvant, if present 21CFR 610.61			x	
Source of the product 21CFR 610.61			x	
Identity of each microorganism used in manufacturing 21CFR 610.61	x			
Minimum potency of product 21CFR 610.61 (r)	x			
Rx only 21CFR 610.61 21 CFR 201.100	x			
Divided manufacturing 21 CFR 610.63			x	Only one applicant
Distributor 21 CFR 610.64			x	
Bar code 21 CFR 610.67 21 CFR 201.25	x			
NDC numbers 21 CFR 201.2 21CFR 207.35	x			
Preparation instructions 21 CFR 201.5	x			
Package type term 21 CFR 201.5		x		Revise the statement from "(b) (4)" to read "Single-Dose Vial" to be consistent with the appropriate package type term per Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2015.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				Applicant revised as requested
Drugs Misleading statements 21 CFR 201.6	x			
Drugs Prominence of required label statements 21 CFR 201.15	x			
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	x			
Dispensing container 21 CFR 201.100			x	
Medication Guide 21 CFR 610.60 21 CFR 208.24			x	

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	x			
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	x			
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)		x		Revise from "(b) (4)" to read "0.9% Sodium Chloride Injection, USP" per

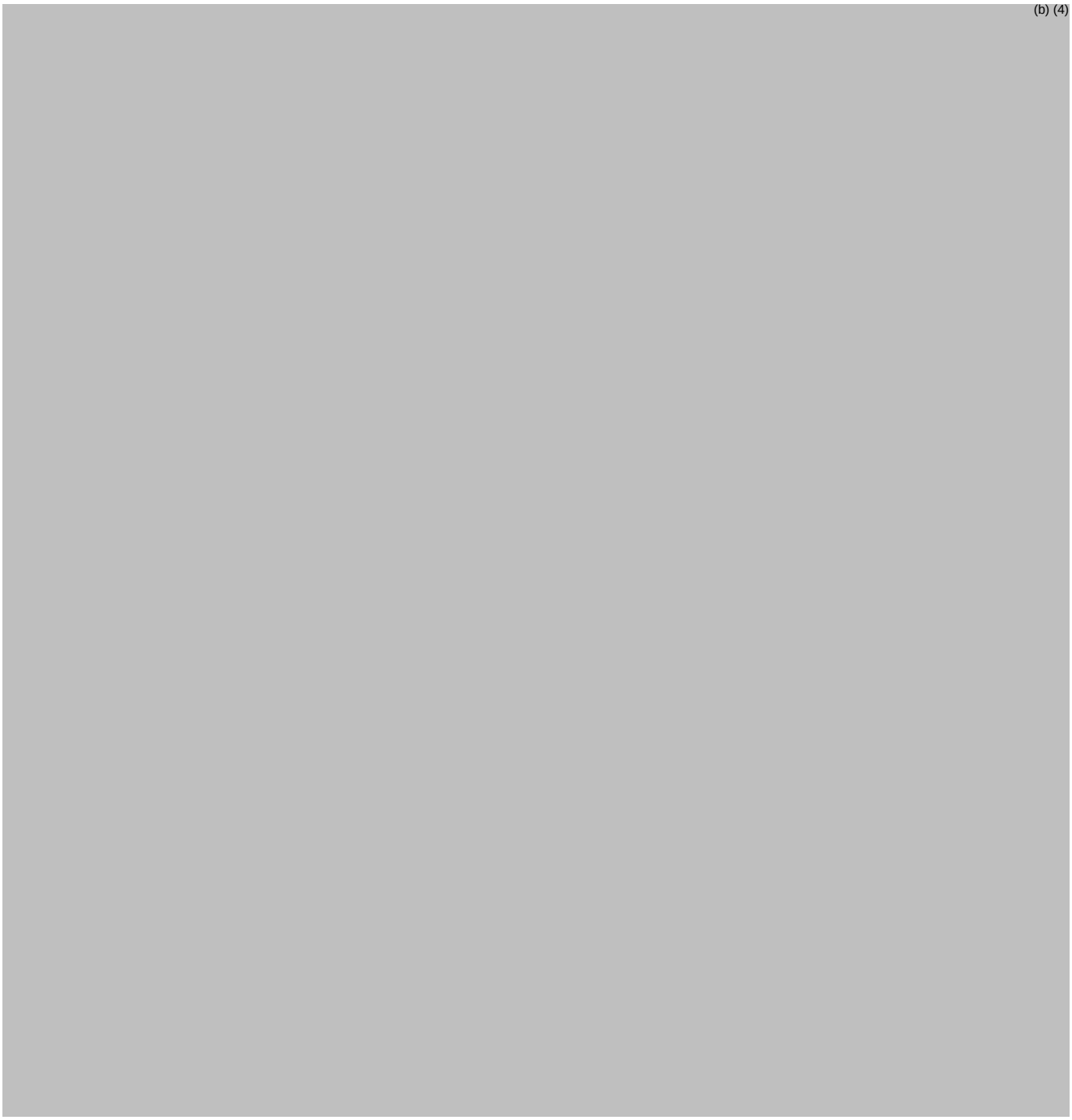
Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				appropriate USP nomenclature. *The Applicant revised as requested* Revise the statement from "If immediate use is not possible, the diluted solution may be stored up to 36 hours at 2°C to 8°C (36°F to 46°F) followed by up to (b) (4) hours at (b) (4)." to read "If immediate use is not possible, the diluted solution may be stored up to 36 hours under refrigeration at 2°C to 8°C (36°F to 46°F) followed by up to (b) (4) hours at room temperature up to a maximum of 25°C (77 °F)." *The Applicant revised as requested* The appropriate dosage form for this product is "injection". Per General Chapters: <1151> PHARMACEUTICAL DOSAGE, Concentrate is not a preferred term for human or veterinary drug products. The current use is for drug substances that are not intended for direct administration to humans or animals and the use in drug product nomenclature is being phased out (see <1121> and USP Nomenclature guidelines). *The Applicant revised as requested*
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)	x			
6.2 IMMUNOGENICITY	x			
11 DESCRIPTION 21 CFR 201.57(c)(12)		x		Add dosage form per 21 CFR 201.57(c)(12) to the paragraph that discusses the drug product "(vestronidase alfa) Injection" for intravenous infusion" *The Applicant revised as requested*
16 HOW SUPPLIED/		x		Add proper name to appear after proprietary name

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
STORAGE AND HANDLING 21 CFR 201.57(c)(17)				in the section 16.1 per OND best labeling practices. *The Applicant revised as requested*
Manufacturer information 21 CFR 610.61, 21 CFR 610.64		x		Deleted to ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h and includes a placeholder for the US license No. per 21 CFR 610.61(b) Revise the manufacturer information from "Manufactured for:" to read as follows: "Manufactured by: Ultragenyx Pharmaceutical Inc. Novato, CA 94949 U.S. License No. XXXX". *The Applicant revised as requested*
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
Title (names and dosage form)			x	
Storage and Handling			x	
Ingredients			x	
Manufacturer Information 21 CFR 610.61, 21 CFR 610.64			x	

APPENDIX D. Acceptable Labels and Labeling

Prescribing Information (submitted 22 Aug17 \\cdsesub1\evsprod\bla761047\0041\m1\us\draft-labeling-text.pdf)

Container Labels (submitted 22Aug17)



Vicky Borders-Hemphill

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Date: 8/25/2017 08:06:51AM
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Rukman De Silva

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Date: 8/25/2017 09:04:20AM
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BLA STN 761047

Mepsevii™ (vestronidase alfa-vjbk)

Manufacturer
Ultragenyx Pharmaceutical Inc.

Reviewer: Rukman De Silva, Ph.D.
Reviewer: Jacek Cieslak, Ph.D.
ATL: Cristina Ausin, Ph.D.
RC: Joel Welch, Ph.D.

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Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

OBP CMC Review Data Sheet

1. BLA#: STN 761047

2. Review Date: 08/14/2017

3. Primary Review Team:
   a. Medical Officer: Dina Zand, Katie Donohue (TL)
   b. Pharm/Tox: Yolanda Branch, Sushanta Chakder (TL)
   c. Product Quality Team: Rukman De Silva (DS/DP), Jacek Cieslak (Assay Validation, Immunogenicity); Cristina Ausin (ATL), Max Van Tassell (Micro DS), Bo Chi/Virginia Carroll (Micro DP), Dupeh Palmer (DMA QAL)
   d. Facilities: Ruth Moore (DIA, facilities), Peter Qiu (DIA TL)
   e. Clinical Pharmacology: Christine Hon, Yow-Ming Wang
   f. Statistics: Feiran Jiao, Yeh-Fong Chen, Laura Lee Johnson
   g. OBP Labeling: Vicky Border-Hemphill
   h. RBPM: Jenny Doan (OND), Truong Quach (OPPQ)

4. Major GRMP Deadlines:

   a. Filing Meeting: 04/17/2017
   b. Mid-cycle meeting: 05/17/2017
   c. Wrap-up meeting: 11/01/2017
   d. Primary review due: 08/16/2017
   f. PDUFA action date: 11/16/2017

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request #1 (manufacturing schedule)	3/22/2017
Information Request #2 (DMA)	3/28/2017
Filing Meeting	4/17/2017
Information Request #3 (DMA)	5/4/2017
Filing Communication	5/16/2017
Team Meeting	5/17/2017
Information Request #4 (OBP)	6/2/2017
Information Request #5 (DMA)	6/9/2017
Midcycle Meeting	6/12/2017
Information Request #6 (OBP)	6/15/2017
Information Request #7 (DMA)	6/22/2017
Information request to DMF (b) (4) holder	6/22/2017
Information Request #8 (DMA)	7/7/2017
Information Request #9 (OBP)	7/10/2017
Information Request #10 (DMA)	7/10/2017
Team Meeting	7/17/2017
Information Request #11 (DMA)	7/28/2017
Information Request #12 (immunogenicity assay)	8/1/2017
Information Request #13 (OBP)	8/3/2017

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761047/0001	3/16/2017	Yes
STN 761047/0011 (response to IR #3)	5/11/2017	Yes
STN 761047/0017 (response to filing communication)	6/5/2017	Yes
STN 761047/0023 (response to IR#4)	6/21/2017	Yes
STN 761047/0026 (response to IR#5 and 6)	6/28/2017	Yes
STN 761047/0031 (response to IR#9)	7/18/2017	Yes
STN 761047/0034 (response to IR#8 and Q8 in IR#9)	7/25/2017	Yes
STN 761047/0035 (response to Q2 in IR#4 and Q6 in IR#9)	7/28/2017	Yes

7. Drug Product Name/Code/Type:
   a. Proprietary Name: Mepsevii
   b. Trade Name: Mepsevii
   c. Non-Proprietary Name/USAN: vestronidase alfa-vjbk
   d. CAS Name: 1638194-78-1
   e. Common Name: UX003; Recombinant human beta-glucuronidase (rhGUS)
   f. INN Name: vestronidase alfa
   g. OBP systematic name: RPROT P08236 (BGLR_HUMAN) beta-glucuronidase [UX003]

8. Pharmacological Category: Human recombinant beta glucuronidase (lysosomal glycosaminoglycan specific enzyme)

9. Dosage Form: Solution for infusion: 10 mg/5 mL (2 mg/mL) Mepsevii solution in a single-dose vial.

10. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 2 mg/mL ((b) (4) mL/vial)
   (ii): Type of potency assay(s): Enzyme activity assay using an artificial substrate, 4 methylumbelliferyl-glucuronide (4-MUG) and cellular update bioassay to measure the kinetics of UX003 transport (internalization) into β-glucuronidase-deficient fibroblasts.

11. Route of Administration: Intravenous infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	Active
			Yes	Active
			Yes	Reviewed in support of ANDA (b) (4) and found adequate.
			Yes	Reviewed on

(b) (4)		06/14/2017 and found adequate
	Yes	Reviewed on 5/23/2015 and found adequate

13. Inspectional Activities:
Pre-approval inspection of the drug substance and drug product manufacturing facility: Rentschler Biotechnologies GmbH located in Laupheim, Germany took place on May 15-24. 2017. During the inspection, 483 observations were issued for inadequate (b) (4) for the DP filling operations. The sponsor responded to the 483 observations on June 12, 2017 and implemented necessary corrective and preventive actions to improve the facility and process to assure drug product quality and OPF recommended approval.

14. Consults Requested by OBP: None

15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation
Pending agreements on the proposed release and stability specifications, the drug product shelf-life, and the reference standard qualification protocol, the data submitted in this Biological License Application support the conclusion that the manufacture of Mepsevii™ (vestronidase alfa-vjbk) is well controlled and leads to a product that is pure and potent. Therefore, from the Chemistry, Manufacturing, and Controls perspective, it is recommended that Mepsevii™ (vestronidase alfa-vjbk) to be approved for human use (under conditions specified in the drug product label).

II. List of Deficiencies to be Communicated
None
III. List of Post-Marketing Commitments/Requirements
PMCs will be discussed in the addendum.

IV. Review of Common Technical Document- Quality Module 1
A. Environmental Assessment of Claim of Categorical Exclusion

The Sponsor claims that the BLA is categorically excluded from the requirements of environmental assessment pursuant to the provisions provided under 21 CFR 25.31(c). Thus, no environmental assessment or environmental impact needs to be performed.
The Sponsor's claim for Categorical Exclusion is acceptable.

V. Primary Container Labeling Review
Draft package labeling review provided by Vicky Border-Hemphill

VI. Review of Common Technical Document- Quality Module 3.2
Review of CTD Module 3 provided. See below.

VII. Review of Immunogenicity Assays- Module 5.3.1.4
Review of immunogenicity assays provided by Jacek Cieslak. See below

Table of Contents

Description of Drug Substance and Drug Product

Mepsevii™ (vestronidase alfa-vjbk, UX003, rhGUS) is indicated for the treatment of Mucopolysaccharidoses VII (MPS VII, Sly syndrome). MPS IV is an ultra-rare, progressively debilitating and life threatening lysosomal storage disease with estimated incidence of < 1 in 1,000,000, and < 100 living patients identified worldwide. MPS IV is caused by a deficiency in enzyme β-glucuronidase (GUS), which involved in degradation of glycosaminoglycans (GAGs) dermatan sulfate, chondroitin 6-sulfate and heparan sulfate. The deficiency in the enzyme results in GAG accumulation in various cells in multiple organ and tissue resulting in significant impaired functional capacity. MPS IV clinical symptoms may occur at birth with hydrops foetalis or later in life during adolescence or adulthood with skeletal disease and other manifestations. MPS VII symptoms include abnormal coarsened facies, pulmonary disease, cardiovascular complications, hepatosplenomegaly, joint stiffness, short stature, cognitive impairment and dysostosis multiplex. Most MPS VII patients die before the second or third decade of life. Currently there is no treatment for MPS VII, however, FDA approved enzyme replacement therapy has been used for the treatment of other forms of MPS (laronidase for MPS I, idursulfase for MPS II, elosulfase alfa for MPS IV A, and galsulfase for MPS VI). UX003 drug product (UX003 DP or DP) in single-use glass vial filled with 5 mL solution. rhGUS is the only active ingredient in the DP. The DP is a concentrate solution for infusion containing 2 mg/mL, and it is administered via intravenous infusion. (b) (4) .

S. Drug Substance

3.2.S.1 General Information

3.2.S.1.1 Nomenclature
Nomenclature of the UX003 is presented in Table S.1.1

Table S.1.1: Nomenclature

International non-proprietary name (INN)	Vestronidase alfa (pending official WHO publication)
United States adopted name (USAN)	Vestronidase alfa
Chemical name	β-Glucuronidase (synthetic human), homotetramer
Company or laboratory code	UX003
Other non-proprietary name(s)	Recombinant human beta-glucuronidase (rhGUS)
Other descriptors	Enzyme commission number: 3.2.1.31
Chemical Abstracts Service (CAS) registry number	1638194-78-1

3.2.S.1.2 Structure

UX003 is a recombinant human β-glucuronidase (rhGUS) produced in Chinese Hamster Ovary (CHO) cells. rhGUS is a glycoprotein expressed as a 651 amino acid precursor with an N-terminal signal sequence of 22 amino acids. rhGUS is post-translationally modified by glycosylation at four asparagine sites (Asp-173, Asp-272, Asp-420 and Asp 631). The glycans of rhGUS contain mannose-6-phosphate (M6P), which is required for uptake and internalization into the lysosomes by the cation independent mannose-6-phosphate receptor M6P/IGF2 (CI-MPR). The secreted mature enzyme is a homotetramer after glycosylation. Each monomer unit consists of 629 amino acids with a calculated molar mass of each non-glycosylated peptide chain of 72,562 Da. The molecular weight of each glycosylated rhGUS monomer is 79,161 Da. Each monomer unit contains four N-glycosylation sites at asparagine residues (Asp-151, Asp-250, Asp-398 and Asp-609) and five cysteine residues (Cys-16, Cys-374, Cys-385, Cys-478 and Cys-622). Cys-622 has the ability to form inter-monomer-disulfide bridge. The amino acid sequence of rhGUS and a schematic presentation of the homotetramer are shown in Figures S.1.1 and S.1.2 respectively.

Figure S.1.1: Amino acid sequence of rhGUS

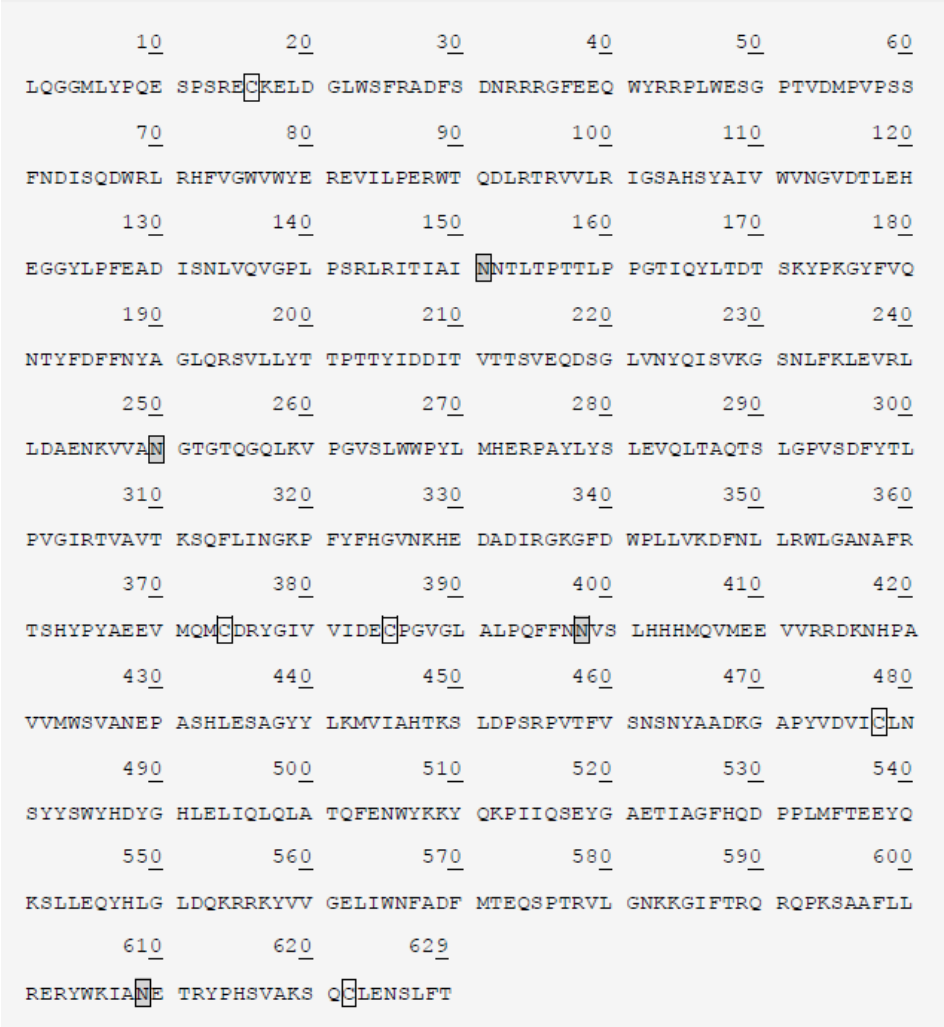
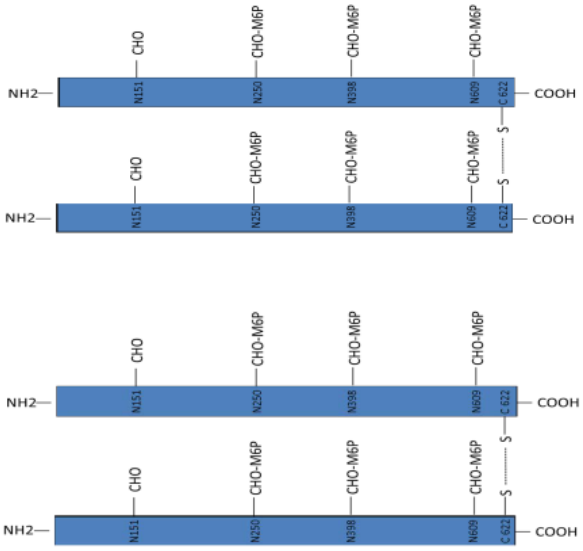


Figure S.1.2: Schematic representation of homotetramer of the rhGUS secreted proteins



CHO = *N*-glycosylated asparagine residues
CHO-M6P = *N*-glycosylated asparagine residues containing mannose-6-phosphase
-S-S- = Potential inter-monomer disulfide bridge

3.2.S.1.3 General Properties

UX003 is taken up by cells and tissues by the M6P/IGF2 receptor via the mannose-6-phosphate residues located on the enzyme's N-linked oligosaccharides and transported to the lysosome where the enzyme catalyzes the hydrolysis of β-D-glucuronic acid residues exclusively from the non-reducing end of the GAGs. The breakdown of GAG outside the lysosome is not possible. rhGUS uptake by the M6P/IGF2 receptor occurs in a large number of tissues and it is important for the maximal effectiveness of the enzyme (Sly et al. 2006, PNAS,103 (41):15172-15177). The enzyme can also be taken up by the mannose receptor (MR) due to some terminal mannose residues located on certain high mannose N-linked oligosaccharides. It is expected that intravenous treatment with rhGUS will result in cellular uptake, localization to lysosomes, and clearance of dermatan sulfate and heparan sulfate in affected tissues based on studies in MPS 7 mice (Vogler et al. 1994, Mod Pathol 7 (1):132-7), (Sly et al. 2006, PNAS,103 (41):15172-15177).

The enzymatic activity of GUS has an optimum pH between 3.5 and 4.5; however, the enzyme has low activity at pH 7 (near the pH of plasma). Therefore, the ability of GUS to degrade dermatan sulfate and heparin sulfate outside of the lysosome is limited. rhGUS is soluble at concentrations ranging from 0.5 to 3.5 mg/mL in various aqueous solutions, at salts concentrations ranging from 10 to 1000 mM, and within a pH range of 3.6 to 8.0. UX003 has a pI of 6 -7.4.

The enzymatic activity and cellular uptake of UX003 is measured using artificial enzyme substrate 4-methylumbelliferyl-glucuronide (4-MUG), which is cleaved into fluorescent 4 methylumbelliferone (4-

MU) and glucuronic acid by UX003 enzyme. The assay readout is the quantified 4-MU which corresponds to the UX003 enzyme activity.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)
Manufacturing and testing laboratories of UX003 DS are listed below in Table S.2.1

Table S.2.1: UX003 DS manufacturing and testing sites

Facility Name and Address	Facility Establishment Identifier	Responsibility
Rentschler Biotechnologie GmbH Erwin-Rentschler-Strasse 21 88471 Laupheim Germany	1000291122	• Cell bank manufacturing • Storage of cell banks • Manufacture of (b) (4) (b) (4) • Release and stability testing of drug substance • Storage of drug substance
(b) (4)		• Cell bank characterization
		• Storage of cell banks
		• Perform mycoplasma and viral contaminants testing (b) (4) for release of drug substance • Cell bank characterization
		• Testing (b) (4)

Reviewer's comment: *UX003 DS and DP are manufactured at Rentschler Biotechnologies, Germany. Rentschler Biotechnologies is a contract development and manufacturing facility (CDMO). Other products manufactured at Rentschler Biotechnologies include, sterile DP (lyophilizates, small volume parenterals), biotechnological DS and DP (recombinant proteins, monoclonal antibodies, and cytokines). The sponsor stated that steroid hormones, antibiotics such as penicillin, sulphonamides and*

cephalosporins or cyctotoxics will not be manufactured at Rentschler. In addition, the CDMO offers analytical testing, and method development services. The manufacturing activities for U.S. marketed products are mostly limited to formulation, filtration, filling, freeze dried or terminally sterile, and bulk packaging. The sponsor provided adequate information of UX003 DS Manufacturing and testing sites and their responsibilities.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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P. Drug Product

3.2.P.1 Description and Composition of the Drug Product

UX003 Drug product (DP) is a solution for infusion containing 2 mg/mL of UX003 DS. The visual appearance of the DP is clear and colorless to slightly yellow, and essentially free of visible particles.

Each vial of DP is filled to a target volume of (b) (4) mL of UX003 DS, which allows the withdrawal of 5.0 mL of deliverable volume containing 10 mg of UX003.

UX003 DP is packed in a container closure system consisting of a Type I (b) (4) glass vial with a (b) (4) rubber stopper and crimped with an aluminum flip-off cap.

The composition of UX003 DP including the function and quality of each component is provided in Table P.1.1

Table P.1.1: Composition of UX003 DP, 10 mg/vial

Component	Concentration	Composition per 5.0 mL	Function	Grade/Quality
UX003 drug substance	2 mg/mL	10 mg	Active	Manufactured to GMP[a]
Excipients				
Sodium dihydrogen phosphate dehydrate (sodium phosphate monobasic dihydrate)	20 mM	15.6 mg	(b) (4)	USP and Ph. Eur.
Sodium chloride	135 mM	39.4 mg		USP and Ph. Eur.
L-Histidine	20 mM	15.5 mg		USP and Ph. Eur.
Polysorbate 20	0.01% w/v	0.5 mg		USP and Ph. Eur.
(b) (4)				

[a] Meets the drug substance specification (see Section 3.2.S.4.1).
(b) (4)

The UX003 DP is diluted prior to administration with preservative free sterile saline for injection (0.9%). The diluent is not included in the UX003 DP packaging.

Reviewer's comment: *All excipients used in UX003 DP manufacturing are USP and Ph.Eur grade quality and the container closure system (CCS) is common to biological products. Please see the review section 3.2.P.7 for the reviewers comments related to leachable and extractable studies of DP CCS.*

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The UX003 DS is a rhGUS glycoprotein produced in CHO cells. The UX003 DS is formulated (b) (4)

(b) (4) and is filled into vials to produce the final DP. (b) (4)

Reviewer's comment: *UX003 DS and DP are manufactured at the same facility* (b) (4)

3.2.P.2.1.2 Excipients

(b) (4). A summary of compendial grade and functional of the UX003 DP excipients are listed in Table P.1.1. No excipients of human or animal origin or novel excipients are used in manufacturer of UX003 DP.

Reviewer's comment: *The information provided in the submission is adequate. During the course of product development, three manufacturing processes have been used to manufacture UX003 DS and DP. This includes the introduction of a new DS formulation* (b) (4) *to improve the DS and DP stability profile. Details of the DP formulation development and comparability study results are discussed in review section P.2.2 below.*

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

During product development, the sponsor used three formulations of UX003 DP to evaluate the DP CQA's and stability. The composition of UX003 DP formulations used in clinical and non-clinical studies are shown in Table P.2.1.

Table P.2.1: Composition of UX003 DP (b) (4) and pH 6 formulation

Name of Ingredient	Function	Concentration	Composition per vial	Concentration	Composition per vial
		(b) (4)	Formulation	pH 6.0 Formulation	
rhGUS	Active Ingredient	(b) (4)		2 mg/mL	10 mg
Excipients					
Sodium Phosphate Monobasic Dihydrate	(b) (4)			20 mM	15.6 mg
Sodium Chloride				135 mM	39.4 mg
L-Histidine				20 mM	15.5 mg
Polysorbate-20				0.01% w/v	0.5 mg
(b) (4)					

The sponsor introduced the pH 6.0 formulation because (b) (4)

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(b) (4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Manufacturing, labeling, packaging and release testing facilities and their responsibilities for UX003 DP are presented in Table P.3.1.

Table P.3.1: Manufacturing, testing, labeling, and release testing facilities for UX003 DP

Facility Name and Address	Facility Establishment Identifier	Responsibility
Rentschler Biotechnologie GmbH Erwin-Rentschler-Strasse 21 88471 Laupheim Germany	1000291122	• Manufacture of drug product • Release and stability testing • Primary packaging of drug product • Batch release of drug product • Storage of drug product
(b) (4)		• Testing for sub-visible particles
		• Testing for polysorbate 20
		• Secondary packaging • Labeling
		• Auxiliary labeling • Storage of labeled drug product
Ultragenyx Pharmaceutical Inc. 60 Leveroni Court Novato, CA 94949, USA	None	• Release of drug product to US market

Reviewer's comment: *DP and DS manufactured at the same facility: Rentschler Biotechnologies GmbH located in Laupheim, Germany. The sponsor provided adequate information of UX003 DS manufacturing and testing sites and their responsibilities. Rentschler was inspected on May 15-24. 2017. During the inspection, 483 observations were issued for inadequate* (b) (4) *for the DP filling operations. The sponsor responded to the 483 observations on June 12, 2017 and implemented necessary corrective and preventive actions to improve the facility and process to assure DP quality. I defer to DMA reviewer to evaluate the sponsor's response related to the 483 observations.*
In response to an IR (submission #0031, dated 07/18/2017), the sponsor stated that the secondary packaging and labeling site (b) (4) *has been used for the current clinical operations. The commercial DP secondary packaging and labeling will be done at* (b) (4)

3.2.P.3.2 Batch Formula

The batch formula for the proposed commercial UX003 DP is presented in the Table P.3.2. The sponsor uses (b) (4) vials of UX003 DP, respectively.

Table P 3 2: UX003 DP batch formula

(b) (4)

Reviewer's comment: *No overages are used in manufacture of the UX003 DP.*

3.2.P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The sponsor monitors the stability of UX003 DP at long-term (5°C ± 3°C), accelerated (25 °C ± 2°C /60% RH) and stressed (40 °C ± 2°C /57% RH) storage conditions. The sponsor proposed a (b) (4) months of expiry at long-term (5 °C ± 3°C) storage condition for commercial UX003 DP based on the stability data from the commercial and clinical lots representative of the commercial manufacturing process, container closure system and formulation. Stability studies were conducted using the final DP container closure system. Ongoing long-term stability studies will be continued for up to 36 months to support extension of shelf life. For long-term stability studies, the vials were stored in upright and inverted orientations. For accelerated and stress stability studies, the vials were stored in upright orientation.
In-use stability studies have been performed to support the patient use of the DP allowing storage of diluted UX003 DP in IV infusion sets at temperatures of 5°C ± 3°C for up to 36 hours and administration by infusion pump at room temperature for up to (b) (4) hours.

Summary of UX003 DP stability program are presented in Table P.8.1.

Table P.8.1: UX003 DP lots used in stability program

Stability Program	Storage Condition	Lot Number	Data Available	Stability Data
Primary Stability Batches, pH 6.0 Formulation				
Long term	5°C	1025264	24 months (of 36 months)	Table 3.2.P.8.3.2
		1032013	12 months (of 36 months)	Table 3.2.P.8.3.5
		1032014	12 months (of 36 months)	Table 3.2.P.8.3.8
		1032015	12 months (of 36 months)	Table 3.2.P.8.3.11
Accelerated	25°C / 60%RH	1025264	6 months (complete)	Table 3.2.P.8.3.3
		1032013	6 months (complete)	Table 3.2.P.8.3.6
		1032014	6 months (complete)	Table 3.2.P.8.3.9
		1032015	6 months (complete)	Table 3.2.P.8.3.12
Stress	40°C / 75% RH	1025264	6 months (complete)	Table 3.2.P.8.3.4
		1032013	6 months (complete)	Table 3.2.P.8.3.7
		1032014	6 months (complete)	Table 3.2.P.8.3.10
		1032015	6 months (complete)	Table 3.2.P.8.3.13
Clinical Stability Batches, (b) (4) Formulation				
Long term	5°C	1016656	36 months (complete)	Table 3.2.P.8.3.14
		1020202	24 months (of 36 months)	Table 3.2.P.8.3.16
Accelerated	25°C / 60%RH	1016656	6 months (complete)	Table 3.2.P.8.3.15
		1020202	6 months (complete)	Table 3.2.P.8.3.17

Reviewer's comment: *The on-going stability study includes three PPQ lots (1032013, 1032014 and 1032015) and a Phase III clinical lot (1025264). All pH 6.0 formulated lots used in stability study were representative of the commercial manufacturing process. The DP expiry should be determined by real time stability data on product representative of commercial manufacturing process. To date, the sponsor provided 24 months of long term storage (5°C ± 3°C) stability data for one lot of pH 6.0 formulated UX003 DP lot and 12 months for the three PPQ lots.*
In response to an IR (submission # 0035, dated 07/28/2017), the sponsor provided the stability data for the (b) (4) month time point for UX003 DP lot 1025264. The updated stability data are within the predefined acceptance limits. .

The sponsor proposed a (b) (4) month expiry for UX003 DP. The sponsor provided (b) (4) month stability data for only one DP lot 1025264. This is not adequate to support the proposed (b) (4) month expiry. To accept the proposed (b) (4) month long -term storage expiry, the sponsor should provide stability data representative of the commercial process for at least three DP lots for (b) (4) months. To determine an acceptable shelf life, we are considering the DP stability data corresponding to the pH (b) (4) formulation (the sponsor provided stability data at 5°C ± 3°C for up to 36 months for one lot and 24 months for a second lot and at 25°C ± 2°C / 60% RH for up to 6 months for two lots). The DP CCS is the same in both cases. During the formulation development studies the sponsor showed that the pH 6.0 formulated DP develops a lower level of aggregation than the pH (b) (4) formulated DP. To further support the shelf-life, we are also considering DS stability data from lots for lated at pH 6.0. The sponsor provided 24 months of stability data for pH 6.0 formulated DS clinical lot (1021999) and this lot shows no significant product quality changes during the 24 months. (b) (4) . In addition, the DP manufacturing process (b) (4)

is not expected to cause significant changes in product quality. Therefore, considering all the above we are granting a 24 moths shelf life for the UX003 DP.

The original submission did not have in-use stability data to demonstrate that the UX003 DP can be stored up to 36 hours at (5°C ± 3°C) followed by up to (b) (4) hours at room temperature. In response to an information request (Sequence 0026, date 06/28/2017) the sponsor provided data of diluted UX003 DP lot 1030528 in the same type of infusion bag used in the clinic and held in IV infusion set for 36 ± 1 hours at 2-8 °C, followed by 30 ± 10 minutes at room temperature, and pumped over (b) (4) hour period at room temperature. I defer to the microbiology reviewer to assess the suitability of in-u time of UX003 DP infusion solution from microbiology perspective.

3.2.P.8.2 Post-Approval Stability Commitment

The sponsor commits to continue monitoring UX003 DP lots in the current stability program according to the stability protocol. In addition, in the years when DP is manufactured, the sponsor committed to place one batch of UX003 DP in the stability program to assess the stability profile of the DP. Table P.8.2 provides information of the test methods, specifications and testing intervals to be applied during DP annual assessment of stability lots.

Table P.8.2: UX003 DP post approval annual stability protocol at long-term storage condition.

Quality Attributes	Analytical Procedures	Acceptance Criterion[a]	Time Point (Month)								
			0[a]	3	6	9	12	18	24	30	36
Clarity/opalescence	Ph. Eur. 2.2.1	(b) (4)	X	X	X	X	X	X	X	X	X
			X	X	X	X	X	X	X	X	X
Color (y-scale)	Ph. Eur. 2.2.2		X	X	X	X	X	X	X	X	X

		(b) (4)								
Sub-visible particles	Ph. Eur. 2.9.19 USP <788>		NR	NR	NR	NR	X	NR	X	X	X
			NR	NR	NR	NR	X	NR	X	X	X
			NR	NR	NR	NR	X	NR	X	X	X
Specific activity	Enzymatic assay		X	X	X	X	X	X	X	X	X
Bioassay (uptake)	Bioassay by cellular uptake		X	X	X	X	X	X	X	X	X
Purity (tetramer)	SE-HPLC		X	X	X	X	X	X	X	X	X
High-molecular weight species (HMWS)			X	X	X	X	X	X	X	X	X
Purity	RP-HPLC (reduced)		X	X	X	X	X	X	X	X	X
Total impurities			X	X	X	X	X	X	X	X	X
Purity	SDS-PAGE (reduced)		X	X	X	X	X	X	X	X	X
Sum of high-molecular weight (HMW) bands			X	X	X	X	X	X	X	X	X
Sum of low-molecular weight (LMW) bands			X	X	X	X	X	X	X	X	X
Container closure integrity	Ph.Eur.3.2.9		NR	NR	NR	NR	X	NR	X	X	X
pH	Ph. Eur. 2.2.3 USP <791>		X	X	X	X	X	X	X	X	X
Osmolality	Ph. Eur. 2.2.35 USP <785>		X	X	X	X	X	X	X	X	X

[a] To determine whether a testing result passes or fails a specification, values are rounded off to the same number of decimal places in the respective acceptance criterion per rounding rules stated in the USP General Notices and Requirements and compared to that acceptance criterion.

Reviewer's comments: *The stability indicating test methods include SE-HPLC, RP-HPLC (reduced), SDS-PAGE (reduced), specific activity and cellular uptake RP-HPLC, SEC-HPLC, SDS-PAGE, SAX-HPLC and specific activity. The proposed UX003 DP stability testing methods have been shown to be able to detect the most common degradation pathways of UX003. The sponsor was asked to implement polysorbate 20 monitoring at stability. The response to this IR will be evaluated in an addendum to this review. The stability testing methods and the frequency of sample testing are consistent with ICH guidelines. The acceptance criteria for the stability studies are reviewed in review section 3.2.P.5.1. The sponsor did not commit to place one lot per year under accelerated conditions. Please see the review comment in review section 3.2.S.7.2.*

3.2.P.8.3 Stability Data

The submission includes 24-months of long-term, 6 months accelerated and 6 months stressed storage conditions for UX003 DP lot 1025264. In addition, 12-months of long-term, 6 months accelerated and 6 months stressed storage conditions for PPQ DP lots 1032013, 1032014 and 1032015. Furthermore, the sponsor provided long-term and accelerated stability data for pH (b) (4) ormulated DP lots 1016656 and 1020202.

Reviewer's comment: *The sponsor provided stability data tables for all the on-going stability studies. I have reviewed the stability data and my summary conclusions are discussed below.*

Long-term stability condition (5°C ± 3°C):
Storage of PPQ lots at the long-term stability condition for up to 12 months showed no significant change or clear trends in quality attributes in physical appearance, protein content, potency, purity, degradation, pH, osmolality and subvisible particulates. All test results are within the predefined acceptance limits in both clinical and PPQ lots.

Reviewer's comment: *Long-term stability data for clinical lot 1025264 shows no significant degradation of critical quality attributes tested over 30 months. The most significant difference observed is for cellular uptake bio assay over the time of stability studies (~ 15% activity difference up to 30 months at long-term stability). Similar trends were observed for accelerated stability condition through 6 months' time point. However, there are no trends associated with the enzyme activities (relative, absolute and specific activities) in all stability conditions. Furthermore, no cellular uptake bio assay trends were observed for three PPQ lots through 12 months' time point at long-term storage condition. The 15% activity difference seen in cellular uptake bioassay long-term stability could be due to assay variability. Therefore, there is no safety concern due to cellular uptake bio assay activity difference seen in clinical lot 1025264. Please see the reviewer's comment regarding the DP expiry at long-term stability condition in review section 3.2.P.8.1 above.*

Accelerated stability condition (25 °C ± 2°C /60% RH):
Accelerated stability studies for the clinical and PPQ lots are performed for up to 6 months. Accelerated stability data show reduce in trends (~ 3%) of SE-HPLC tetramer and increase trends (~ 2-3%) of HMWS by SE-HPLC up to 6 months. No change for quality attributes, such as appearance, content, potency, purity by reduced SDS-PAGE and RP-HPLC, pH, osmolality and subvisible particulates.

Reviewer's comment: *UX003 DP stability results under accelerated storage conditions for PPQ lots show that there are no differences in aggregation rates among PPQ batches, and between clinical lots. SE-HPLC assay is stability indicating and the observed trends of tetramer and HMWS are acceptable.*

Stressed stability condition (40 °C ± 2°C /57% RH):
The sponsor performed stressed condition stability studies for up to 6 months to obtain additional information about the product stability. Storage of clinical and PPQ lots for up to 6 months showed no significant changes in physical appearance, protein content, potency, purity by reduced SDS-PAGE and RP-HPLC, pH, osmolality and subvisible particulates. As expected, trends were observed for % tetramer and % HMWS by SE-HPLC.

Reviewer's comment: *The stress stability study data show that the overall rates of degradation are comparable among all clinical and PPQ lots.*

In-use stability condition:
Review's comment: *The sponsor provided data for diluted UX003 DP lot 1030528 held in IV infusion set for 36 ± 1hours at 2-8 °C, followed by 30 ± 10 minutes at room temperature, and pumped over a* (b) (4) *hour period at room temperature. The stability was evaluated at the beginning (prior to the start of the infusion) and end of* (b) (4) *hour period for protein content, potency by enzyme activity, purity by SE-HPLC, reduced SDS-PAGE and reduced RP-HPLC, and subvisible particulates. The results show no*

differences in product quality attributes between the beginning and end samples. Therefore, the in-use study results demonstrate that the diluted UX003 DP is stable for 36 hours at 2-8 °C and then up to (b) (4) *hours at room temperature. I defer to the micro reviewer to assess the suitability of in-use time of UX003 DP infusion solution from microbiology perspective*

3.2.A Appendices

3.2.A.1 Facilities and Equipment

Section deferred to DMA and DIA.

3.2.A.2 Adventitious Agents Safety Evaluation

The control strategy for UX003 DS adventitious agents safety evaluation is composed of controls for raw materials, cell lines, control of manufacturing including testing of in-process materials, end production cells and an evaluation of the capacity of viral clearance by the downstream purification process.

(b) (4)

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Reviewer Comment: (b) (4)

In summary, the sponsor provided adequate viral clearance analysis to demonstrate that the process is robust with respect to its ability to remove adventitious agents.

3.2.A.3 Novel Excipients

None

3.2.R Regional Information (USA)

3.2.R.1 Executed Batch Records

A copy of the executed batch record for DS batch # 1032015 was provided in the submission. The batch record was separated into upstream and downstream sections. During the inspection I reviewed the batch GMP#7 (DS lot # 1036490).

3.2.R.2 Method Validation Package

See review sections 3.2.S.4 and 3.2.P.5

3.2.R.3 Comparability Protocols

The BLA is approved using concurrent validation for UX003 DS. The submission includes two DS PPQ batches. The sponsor will use the same protocol for the other PPQ batch and the results will be included in an AR if the batch release results are within specification or in a supplement if outside specification. .

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Immunogenicity assays validation review was performed by Jacek Cieslak.

Recommendation:

The assays to detect anti-beta-glucuronidase antibodies are suitable for use in clinical studies.

Review:

The applicant, Ultragenyx, developed an antidrug antibody (ADA) assay with a three-tiered strategy (screening, confirmatory, and titering) and a neutralizing antibody (NAb) assay to assess the

immunogenicity of beta-glucuronidase. The following documents were reviewed to determine whether assays to detect anti-beta-glucuronidase antibodies were suitable:

- Study Number: BAL-14-139-024 Validation of an Electrochemiluminescent Assay for the Detection of Anti-GUS Antibodies in Human Serum
- Study Number BAL-14-139-016 Validation of an Assay to Detect Neutralizing Antibodies to Recombinant Human β-Glucuronidase (rhGUS) by Determining the Uptake and Activity of rhGUS in a GUS-deficient Cell Line
- Method Number: BAL-15-139-MTH-001.00 Detection of Anti-UX003 (anti-GUS) Antibodies in Human Serum Samples
- Method Number: BAL-15-139-MTH-002.00 Detection of Neutralizing Antibodies to Recombinant Human β-Glucuronidase (UX003) Using a Cell-based Enzyme Uptake Assay

Antidrug Antibody (ADA) Assay

Samples, general procedure:
Positive control: mouse anti-GUS polyclonal antibody (B01P) at concentrations of 1000 ng/ml (high, HPC), 250 ng/ml (medium, MPC), and 50 ng/ml (low, LPC).

Negative control (NC): unspiked pooled human serum.

Screening assay:
The screening assay to detect anti-UX003 antibodies (ADA) in human serum uses electrochemiluminescent (ECL) technology and a bridging format. The method uses biotinylated rhGUS to capture ADA and ruthenylated rhGUS to detect antibodies which bind to the GUS enzyme (B-GUS and Ru-GUS, respectively). A Master Mix of B-GUS and Ru-GUS was prepared in assay buffer to final concentrations of 0.250 µg/mL B-GUS and 0.250 µg/mL Ru- GUS. The solution is incubated to allow for a bridge to form between ADA and capture and detection reagents. After the incubation (1 hour) the mixture is added to a streptavidin coated Meso Scale Discovery (MSD) ECL microplate (96-well plate), which captures the biotinylated reagent. The bound complexes are detected by the chemiluminescent signal generated by the ruthenylated reagent when the voltage is applied to the plate.

Reviewer comment:
ECL assay and bridging format are standard for detection of ADAs. The applicant used a tiered approach to evaluate ADAs as recommended in the FDA Draft Guidance to Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins. Samples are first tested in the screening assay. Samples that screen positive are tested in the confirmatory assay. Confirmed positive samples are titered and tested for neutralizing activity using the NAb assay. This approach is acceptable.

Confirmatory assay:
For the confirmatory assay the procedure is very similar to the screening assay; however, samples are analyzed in duplicate in the presence or absence of unlabeled GUS. The unlabeled drug competes with the biotin- and Ru- labeled drug for binding to ADA resulting in a reduced assay signal compared to samples without unlabeled competitor. Samples in which the signal drop is greater than the confirmatory cut point are considered confirmed positive.

Titering assay:
The titering assay procedure is the same as the screening assay. The positive controls are subjected to 3-fold serial dilutions until the signal fall below the cut point. The titer value is defined as the last dilution fold generating signal above the titer cut point. The minimum required dilution (MRD) is multiplied by this titer to give the final titer value.

Minimum required dilution (MRD): 1:10 (10% serum)
Minimum required dilution of 1:10 (10% serum, 10-fold) was established during assay development and confirmed during method validation.

Reviewer comment:
Based on the information provided in the original application, the selection of minimum required dilution is appropriate.

Specificity:
Per study BAL-14-139-024 the specificity acceptance criteria are: human IgG (concentrations equivalent to HPC and 5x the HPC) should not interfere with the ability of the assay to detect the surrogate positive control (SPC). The %CV should be ≤ 25% and the SPC signal should be ≥ assay cut point. Sample recoveries and %CV were within the pre-specified 25% (7.3 and 4.6%, respectively).

Reviewer comment:
The specificity acceptance criteria are suitable for ensuring that high level of human IgG will not affect the assay performance and are therefore acceptable.

Screening Cut point determination:
The screening cut point was established by analyzing 50 samples (normal adult human serum samples), using six determinations: three separate runs by two analysts. To determine the cut point data were evaluated using SAS JMP software. Four samples were identified as outliers (one technical and three biological) and removed from the cut point calculation. Data demonstrated relatively low variability (%CV of 4.3-10.4%) and normal distribution by the Shapiro Wilk test (floating cut point with correction factor adjusted for the NC should be used). The cut point was estimated based on the 95% percentile from the distribution analysis. The following formula was used to determine the cut point during the validation exercise:

Cut point correction factor = Mean cut point sample RLU + 1.645 SD – study mean NC
This calculation resulted in a cut point correction (CF) = 15.9 RLU (Relative Light Units).
Floating cut point for each plate = mean NC + 15.9 RLU.

Reviewer comment:
The study mean NC value was used to calculate the cut point correction factor. The floating cut point for the plate is established by adding 15.9 RLU to the mean of the NC samples on each assay plate.

Confirmatory assay cut point determination:

The confirmatory cut point for the validation exercise was determined by 2 analysts testing 50 samples. Results were provided in Table 5 of study BAL-14-139-024 Validation of an Electrochemiluminescent Assay for the Detection of Anti-GUS Antibodies in Human Serum (page 14). The percentage of the change from the unspiked samples was calculated for each sample.

Confirmatory Cut Point = -6.25 + 2.33 × 12.26776 = 22.3 %

The cut point was established empirically to be 22.3% for 1% false positive rate. Samples above this cut point will be considered confirmed positives during sample analysis, and will be assessed by the titer assay.

Reviewer comment:
The applicant provided the results from these analyses and outliers were appropriately determined and eliminated for the cut point factor calculation. The FDA Guidance for Industry recommends a cut point of 1% or 0.1% be used for the confirmatory assay. Based on a review of the data, the confirmatory cut point is acceptable.

Titering assay cut point determination:

The titering cut point was evaluated and the applicant determined that the screening cut point will be used in the analysis of the titer assay because no plateau effect was observed. However, if plateau effect is observed in the clinical study samples and it is necessary to establish a titer cut point, the validation report will be updated.

Reviewer comment:
Using the screening assay cut point for as a titering cut point is acceptable.
Based on the information provided in the validation protocol BAL-14-139-024, the screening, confirmatory and titering cut points are acceptable and consistent with Agency recommendations discussed in the Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products.

Pediatric population cut point:

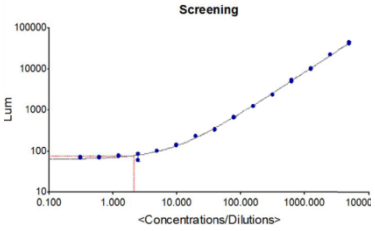
The cut points were then evaluated to determine whether they were suitable for use in analyzing pediatric samples. To confirm the relevance of the pediatric cut point, 4 pre-dose patient study samples were included in this evaluation. It was found that differences between pediatric population and adult population were minimal (data provided in appendix F of the protocol, page 43). Thus, the same cut point for both populations is used. Additionally, the relevance of the cut point was evaluated in the study population (4 post-treatment samples, refer to Table 6, page 15 of the report BAL-14-139-024) and was found that three samples were not detected but one was above the cut point and confirmed positive.

Reviewer comment:
The applicant provided the results from these analyses and outliers were appropriately determined and eliminated for the cut point factor calculation. Based on a review of the data, the pediatric cut points are acceptable.

Sensitivity:
Assay sensitivity was determined over 4 runs by 2 analysts, 2 plates per analyst. For the mouse anti-GUS polyclonal antibody (B01P) sixteen serial dilutions were tested (see Table 1).

Table 1. Sensitivity – screening assay.

Parameter	Run 9	Run 10	Run 12
A	86.2	86.2	63.9
B	1.07	1.07	1.02
C	2.82E+04	2.82E+04	5.47E+05
D	3.37E+05	3.37E+05	5.26E+06
R^2	0.999	0.999	0.998
Value at the Cut Point	1.357	1.519	2.111
Mean Sensitivity (ng/mL)		1.66	



Reviewer comment:
The sensitivity of the ECL screening assay is 1.66 ng/mL (3.66 ng/mL for confirmatory assay) and is well below the sensitivity of 250 – 500 ng/ml recommended in the Draft Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Proteins Products and is therefore acceptable. The study design was suitable for assessing assay sensitivity.

Titration Assay Linearity:
Titration assay linearity was assessed by testing three-fold dilutions of the HPC, MPC and LPC samples until the signal fell below the cut point. The titer value was defined as the last dilution fold generating signal above the titer cut point. The tested range was 1:6561 for all samples and the titer results for HPC were 1:2340, for MPC 1:270 and for the LPC 90.

Hook Effect:
Hook effect was assessed by spiking the high concentrations of positive controls into pooled neat normal human serum. The assay showed signal suppression at the highest concentration of the positive control. This was additionally confirmed using neat serum spiked with 50 µg/mL of SPC and subjected to 12 serial 2-fold dilutions. The signal was suppressed at the highest concentration; however, the signal increased at the first dilution and tittered correctly with additional dilutions.

Reviewer comment:
The results provided in Table 14 and 15 of the report demonstrate that the assay does show a hook effect only at the highest concentration of 50 µg/mL of SPC. The hook effect will not affect assay performance under normal conditions.

Drug tolerance:
The applicant evaluated the ability of the assay to detect ADA in the presence of circulating drug and established drug tolerance limits for the assay. This was assessed for HPC, MPC and LPC by performing 2-fold dilutions of UX003 starting with a concentration of 5 µg/mL. All of the samples showed signal above the cut point at all titrations indicating that the assay is tolerant to at least 5 µg/mL of free drug (see Table 13, page 20 of the validation report).

Reviewer comment:
Based on data from the PK studies, treated patients are expected to have serum levels of UX003 at ~ 0 to 28 ng/mL in the samples used to test for ADA (immunogenicity samples are to be collected prior to the drug infusion). To understand the sensitivity of the assay in the presence of drug the applicant determined the amount of drug that could be present in serum and still allow for the detection of 50 ng/mL, 250 ng/mL or 1000 ng/mL of ADA. The results presented above indicate that serum concentrations of 0 to 28 ng/mL are not expected to interfere with the detection of ADA in this assay and the assay is tolerant to at least 5 µg/mL of UX003. Therefore, assay sensitivity in the presence of on-board drug is acceptable.

Precision:
Assay precision was assessed by evaluating the frequency of false negative and false positive results from HPC, MPC, LPC and Negative QC samples. None of the positive control samples tested negative and the CV% counts ranged from 0.2 – 13.6%. None of the negative control samples tested positive and the CV% of 10.4% for screening assay.

Reviewer comment:
The assay precision was within acceptable limits of <25% for low to high positive samples and <25% for negative samples; for assays of this type these acceptance criteria are acceptable.

Intra-assay precision was assessed by analyzing six replicates of the HPC, MPC, LPC and NC by one analyst. All positive control wells had counts above the plate cut point with CV% means of 7.1 to 11.7% (Table 19 of the validation report, page 26).

Reviewer comment:
Intra-assay precision was acceptable for this type of assay and had the CV for each positive and negative control below 20%.

Inter-assay precision was assessed using HPC, MPC, LPC and NC controls run in duplicates. 21 independent runs were performed (35 plates) by 3 analysts over 10 days. The screening assay controls met the acceptance criteria with CVs ranging from 10.4 – 13.6% (Table 17, page 24). The confirmatory controls also met the acceptance criteria with CVs from 0.2 – 4.5% (Table 18, page 25).

Reviewer comment:
The inter-assay precision CVs for screening and confirmatory assays are below 25% for each control and the overall % inhibition was above the respective cut points for all positive control samples.

Selectivity:
Selectivity of the assay was assessed by spiking high and low concentrations of SPC into normal human serum samples. Unspiked samples were assessed for reference. One sample in each run had an unspiked signal above the cut point.

Reviewer comment:
At least 80% of samples tested positive or negative as appropriate and CV% means was less than 20%. The selectivity met the acceptance criteria in all runs.

Recovery:
The recovery of the assay was assessed by analyzing unspiked or spiked with 50 ng/ml UX003 (LPC) in the 0-100% hemolyzed samples from normal serum pool. Samples with more than 50% hemolysis showed a decrease in signal; however, these samples were above the assay cut point and would still be detected as positive.

Reviewer comment:
All hemolyzed samples spiked with LPC had signal above the cut point and therefore will be detected.

Stability
Short-term stability:
The stability of the NC, HPC and LPC (replicates of six) was assessed when exposed to room temperature storage for 23 hours and 3 minutes or storage in the refrigerator (47 hours and 41 minutes). The recovery results ranged from 77 – 81% with CV% counts between 4.3 – 8.4% for HPC. Recovery below 50% was observed for LPC. NC samples were not impacted by the short term-storage.

Reviewer comment:
Lower recovery was observed for all positive control samples. Recovery below 50% was observed for LPC; using degraded samples could potentially lead to the false negative results. An IR was sent to the applicant on August 1, 2017, requesting the modification of the method SOP to minimize the length of sample storage at room temperature and at 2-8°C. The applicant agreed to update the SOP of the ADA assay by September 29, 2017. This is acceptable because the method will be updated before the next sample analysis scheduled in October of 2017.
Short-term storage had no impact on NC samples.

Freeze and Thaw Stability:
The stability of the NC, HPC and LPC (replicates of six) was assessed when exposed to 6 and 9 freeze/thaw cycles (-20 °C and -80 °C, respectively).

Reviewer comment:
Lower recovery was observed for all positive control samples. Recovery below 50% was observed for the LPC. Repeated freeze and thaw cycles had no impact on NC samples. Due to the decrease of the signal for positive control samples, the number of freeze thaw cycles will be minimized. However, the applicant did not provide any additional data. An IR was sent to the applicant on August 1, 2017, requesting the modification of the method SOP to minimize the number of freeze/thaw cycles during sample analysis. The applicant agreed to update the SOP of the ADA assay by September 29, 2017. This is acceptable because the method will be updated before the next sample analysis scheduled in October of 2017.
The recovery results indicate that the high positive control samples are stable under expected conditions of use but repeated freeze thaw cycles are detrimental to all positive control samples.

Robustness:
Robustness was assessed by evaluating an impact of different streptavidin coated plates on the positive and negative control sample results. Data demonstrating an impact of other variables, such as incubation times, temperatures, reagents and instruments were not provided. An information request to the applicant was sent on June 15, 2017, to provide available validation or development data supporting the

method robustness. Additional assay parameters that were evaluated for robustness were reagents, instruments and MSD plates, incubation times and temperatures.

Reviewer comment:
None of the parameters assessed by the applicant appeared to significantly impact the assay performance. Additional robustness data submitted on July 14, 2017 as a response to the IR were evaluated and found acceptable to support the assay robustness.

Reviewer Conclusion: *The ECL assay is suitable for testing clinical samples to detect anti-GUS antibodies in human serum.*

Neutralizing Antibody (NAb) Assay

Assay Description:
The NAb assay is a modified version of the potency assay. Briefly, the assay involves treatment of GUS-deficient human fibroblasts with UX003 in the presence of 1:10 dilution of human serum, followed by measurement of the ability of UX003 to catalyze the conversion 4-methylumbelliferyl-β-D-glucuronide substrate solution (4MUG) to the fluorescent molecule, 4-methylumbilerferone. The method evaluates the potential of the antibodies to impact the uptake and/or enzymatic activity of β-glucuronidase (UX003). A neutralizing antibody to GUS, B01P, is used as a positive control for NAb activity. After exposure to GUS, cells are rinsed, lysed by freezing and the remaining GUS activity is detected by measuring the conversion of 4-methylumbelliferyl- β-D-glucuronide to 4-methylumbelliferone in a fluorescent plate reader. NAbs inhibit either cellular uptake or the enzymatic conversion of the substrate to the product resulting in a decreased signal. A sample for which the signal is decreased more than the cut point is considered NAb positive.

Reviewer comment:
The FDA Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Proteins Products recommends that NAb assays reflect the mechanism of action (MoA) of the drug and that they be either cell based bioassays or non-cell-based competitive ligand-binding assays. Because the MoA of UX003 is catalytic hydrolysis of beta-D-glucuronic acid residues from non-reducing end of the glycosaminoglycans (GAGs) following the cellular uptake to the lysosomes, the NAb assay proposed by the applicant, which is a cell based bioassay, is acceptable.

General:
Samples, general procedure:
Positive control: Mouse anti-GUS polyclonal antibody (B01P) at concentrations of 500 nM (high, HPC), 250 nM (medium, MPC), and 175 nM (low, LPC).

Negative control: unspiked pooled human serum

Minimum required dilution: 1:10 (10% serum)

Reviewer comment:

Based on the information provided in the original application and the response to the information request received on July 14, 2017, which included minimum required dilution determinations as part of the robustness evaluation, the selection of the minimum required dilution is appropriate.

NAb Assay cut point:
The NAb assay cut point was determined using serum samples from 50 drug naïve subjects (adult population). Samples were analyzed by three analysts over six runs. One technical outlier and five population outliers were identified and excluded from further calculations, no biological outliers were identified. The cut point was determined to establish a 5% false positive rate. Data were evaluated and demonstrated normal distribution (Shapiro Wilk's test).
The cut point was determined using the formula: Mean normRFU - 1.645* std dev meanRFU and is a floating cut point. The cut point on any given assay plate is defined as a factor of 0.892*mean NC RFU (relative fluorescence units).

Pediatric cut point:
The pediatric cut point was determined using serum samples from 50 drug naïve pediatric samples in a single run. Seven outliers were identified and excluded from further calculations, no biological outliers were identified. The cut point was determined to be 0.852*mean NC RFU. Pediatric and adult cut points were compared and it was concluded that pediatric cut point had a higher risk of false negatives in the assay. When the adult cut point was applied to the pediatric samples, more samples were considered positive than when the pediatric cut point was used. Therefore, the more conservative approach was used and the adult cut point with a false positive rate of 7% for the pediatric samples and a 5% false positive rate for adult samples was selected for all populations.

Reviewer comment:
The cut point will provide 7% false positive rate in the pediatric samples and therefore is acceptable.

Sensitivity:
The mean assay limit of detection (LOD) is 17.8 µg/mL. The LOD was established using eight serial dilutions. Results were obtained from two analysts over three runs.

Reviewer comment: The applicant did not achieve acceptable assay sensitivity using the polyclonal antibody preparations B01P. The sensitivity obtained using the polyclonal preparation is significantly worse than the recommended 500 ng/ml. The NAb assay sensitivity was calculated to be 17.8 µg/mL. However, because with such a poor sensitivity the assay is able to detect NAb positive samples in the study population, it is acceptable and no additional assay development studies will be required.

Dilution Linearity:
Data not provided

Reviewer comment:
It is not critical that there be dilutional linearity for this assay because the results are used qualitatively, to determine whether a subject is NAb positive or negative.

Drug tolerance:

The drug tolerance was defined as the highest concentration of drug in the positive controls resulting in a %inhibition greater than the cut point. The drug tolerance was determined to be at least 1.13 µg/ml (7.5 nM). This study was also used to establish assay specificity (at least one drug concentration of the spiked controls should be above the mean RFU of the 5 nM-spiked control; the acceptance criterion was met).

Reviewer comment:
The concentration of drug at trough levels is expected to be ~0 to 28 ng/ml and is not expected to interfere with the detection of NAbs in this assay. The assay is tolerant to at least 1.13 µg/mL of UX003. Therefore, assay sensitivity in the presence of on-board drug is acceptable.

Precision:
Inter-assay precision was assessed by evaluating the variability in the results from HPC, MPC, LPC and NC samples from nine runs by three analysts. The %CV for LPC and MPC was 9.6 and 12.5%, respectively. The %CV of the HPC was greater than the target acceptance with a value of 38.6 %. The acceptance criteria for inter-assay precision: the % CV of the normRFU for each control must be equal to or less than 30%.

Reviewer comment:
The assay had acceptable precision for the LPC and MPC samples; however, HPC samples had higher variability due to low raw signal values for RFU. This is acceptable performance for a qualitative assay.

Intra-assay precision was assessed by analyzing HPC, MPC, LPC and NC samples from three runs by two analysts. All samples demonstrated %CV values within assay acceptable criteria of % CV of the RFU for each antibody control must be equal to or less than 30%.

Reviewer comment:
All samples had %CV values <14.5%. Therefore, intra-assay precision is acceptable.

Inter-operator precision was assessed by evaluating the variability between inter- and intra-assay runs using the same acceptance criteria.

Reviewer comment:
LPC and MPC results were within the proposed acceptance criteria. However, the HPC results were greater than the target acceptance with a value of 44.5 %. The reasons for higher variability for HPC samples are discussed above (inter-assay precision). Because the assay is not a quantitative assay and is intended for qualitative evaluation of the appearance of NAbs relative to the cut point, the lack of precision at levels approaching the HPC is acceptable.

Selectivity:
Assay selectivity was assessed by evaluating spiked and unspiked normal human serum samples.
All spiked samples were positive at each level of positive control.

Reviewer comments:
The assay performed acceptably as LPC samples had RFU signal lower than unspiked samples and HPC signal was lower than in LPC samples.

Short-term stability:
The stability of the NC, HPC and LPC was assessed when exposed to room temperature storage for 3 hours 21 minutes, 10 hours 48 minutes and 21 hours 40 minutes or storage in the refrigerator (24 hours 29 minutes). The recovery results ranged from 92.8 – 112.9% with CV% counts between 2.1 – 14.5%.

Reviewer comment:
Short-term stability results demonstrate analyte stability at room temperature (17-27 °C) for up to 21 hours 40 minutes and during storage in the refrigerator (24 hours 29 minutes). Analyte short-term stability is acceptable.

Freeze and Thaw Stability:
The stability of the NC, HPC and LPC (replicates of four) was assessed when exposed to 3 and 5 freeze/thaw cycles (-80 °C).

Reviewer comment:
Repeated freeze and thaw cycles had no impact on HPC, LPC and NC samples. Analyte freeze thaw stability is acceptable.

Robustness:
Robustness was assessed for time after cell plating, incubation time and cell passage number. However, no data were provided in the application. An information request to the applicant was sent on June 15, 2017 to provide available validation or development data supporting the method robustness. According to the response, additional assay parameters that were evaluated for robustness were reagents, instruments and MSD plates, incubation times and temperatures.

Reviewer comment:
None of the parameters assessed by the applicant appeared to significantly impact the assay performance. Additional data submitted on July 14, 2017 as a response to the IR were evaluated and found acceptable to support the assay robustness.

Reviewer Conclusion: *The cell based NAb bioassay is suitable for testing clinical samples to detect neutralizing antibodies to recombinant human β-glucuronidase.*

Cristina Ausin-Moreno

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Date: 8/14/2017 11:30:02AM
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Joel Welch

Digitally signed by Joel Welch
Date: 8/14/2017 12:58:49PM
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Rukman De Silva

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Date: 8/14/2017 11:31:33AM
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Jacek Cieslak

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Date: 8/14/2017 11:32:29AM
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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761047**
From: Maxwell Van Tassell, Ph.D., DMA Branch IV
Through: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, DMA Branch IV
Subject: New 351(a) Biologics License Application (BLA)
US License: 2040
Applicant: Ultragenyx Pharmaceutical, Inc.
Product: Mepsevii (UX003, vestronidase alfa)
Indication: Treatment of Mucopolysaccharidosis type VII
Dosage: Concentrate for solution for IV infusion, 2 mg/mL
Facilities: Rentschler Biotechnologie GmbH, Erwin-Rentschler-Strasse 21, Laupheim, Germany 88471 (FEI: 1000291122)
Receipt Date: 03/16/2017
Action Date: 11/16/2017

Recommendation for Approvability: The drug substance part of BLA 761047, as amended, is recommended for approval from a product quality microbiology perspective with the following post-marketing commitment:

> To repeat the bioburden and endotoxin method qualification to include a total of three lots for the following (b) (4)

Review Summary

Ultragenyx Pharmaceutical, Inc. has submitted 351(k) BLA 761047 to obtain approval of UX003. UX003 is a recombinant human beta-glucuronidase, which facilitates the degradation of glucosaminoglycans that would otherwise accumulate and lead to multisystem tissue and organ damage in those with the rare genetic disorder Mucopolysaccharidosis Type VII.

BLA 761047 was submitted in eCTD on March 16, 2017. This review contains the assessment of the microbial quality attributes of the UX003 (b) (4) drug substance (DS) from a microbiological quality perspective. For review of drug product (DP) aspects of the application, please see review by Bo Chi, PhD.

Amendments Reviewed for Drug Substance Microbiology Quality

Document Type	eCTD Sequence	Date
Original BLA	0001	16 Mar 2017
Response to 04 May 2017 IR	0011	11 May 2017
Response to 22 Jun 2017 IR	0027	30 Jun 2017
Response to 10 Jul 2017 IR	0030	17 Jul 2017

Review Assessment

3.2.S DRUG SUBSTANCE

3.2.S.1 GENERAL INFORMATION

UX003 is a recombinant human beta-glucuronidase (rhGUS) produced in a genetically engineered stable Chinese Hamster Ovary (CHO) cell line. UX003 is a homotetrameric glycoprotein; each monomer is expressed as a 651 amino acid precursor with a 22 amino acid N-terminal signal sequence and is post-translationally glycosylated at four asparagine sites. Five cysteine residues in each monomer may facilitate intermolecular disulfide bridging.

SATISFACTORY

3.2.S.2 MANUFACTURE

3.2.S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of UX003 drug substance:

Table 1: UX003 Drug Substance Manufacturing Sites

Facility Name and Address	Facility Establishment Identifier	Responsibility
Rentschler Biotechnologie GmbH Erwin-Rentschler-Strasse 21 88471 Laupheim, Germany	1000291122	• Cell bank manufacturing and storage • Manufacture (b) (4) • Release and stability testing of drug substance • Storage of drug substance
(b) (4)		• Cell bank characterization
		• Storage of cell banks
		• Perform mycoplasma and viral contaminants testing (b) (4) for release of drug substance • Cell bank characterization
		• (b) (4)

Reviewer Comment:

The Rentschler Biotechnologie GmbH, Laupheim, Germany facility is a multiproduct contract manufacturer (b) (4). *Other drug substances and products manufactured in the facility include recombinant proteins, monoclonal antibodies, and cytokines. The facility does not produce steroid hormones, antibiotics, or cytotoxics. Refer to the cGMP status section of this review for the compliance status of the facility.*

3.2.S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

[redacted]

3.2.S.7 STABILITY

Endotoxin and bioburden testing were not incorporated into stability studies. The third PPQ lot will be placed on both long-term and accelerated stability studies, as will one commercial DS lot produced annually thereafter, using the container closure representative of the manufacturing scale system.

Reviewer's Comments:
Endotoxin and bioburden testing are not required for stability testing of drug substance.

SATISFACTORY

cGMP Status

Refer to Panorama for cGMP status of the relevant facilities.

Conclusion

I. The drug substance section of this BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval with the following post-marketing commitment that has been communicated to the sponsor:

To repeat the bioburden and endotoxin method qualification to include a total of three lots for the following (b) (4)

(b) (4)

[redacted]

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by an OBP reviewer.

III. A pre-license inspection was conducted at Rentschler Biotechnologie GmbH, Laupheim, Germany, from May 15th -19th and May 22nd - 23rd 2017 by OPF/DMA (Maria Jose Lopez-Barragan, Diane Raccasi, and Maxwell Van Tassell), OBP (Rukman De Silva and Gerald Feldman), and DIA (Ruth Moore). A seven-item Form FDA 483 was issued. Refer to Panorama for compliance status of the facilities.

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Maxwell Van Tassell

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Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 7/28/2017 09:18:18AM
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