

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761047Orig1s000

OTHER REVIEW(S)

PMR DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA #	761047
PMR Set	3271-1
Product Name:	MEPSEVII (vestronidase alfa-vjbk)
Applicant Name:	Ultragenyx Pharmaceutical Inc.
ODE/Division:	ODE III/DGIEP

SECTION B: PMR Information

1. PMR Description

Conduct a prospective, longitudinal study (Study UX003-CL401) to assess the long-term risk of immunogenicity and the risk of serious hypersensitivity reactions (including anaphylaxis) in patients with mucopolysaccharidosis type VII (MPS VII) followed for three years on MEPSEVII (vestronidase alfa-vjbk). The following information will be collected and analyzed: (1) incidence rates for serious hypersensitivity reactions, (2) incidence rates for the appearance of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against MEPSEVII (vestronidase alfa-vjbk), (3) temporal associations between ADA or Nab formation and serious hypersensitivity reactions, (4) associations between beta-glucuronidase (GUSB) genotype and serious hypersensitivity reaction risk, (5) association between intrinsic GUSB enzymatic activity and serious hypersensitivity reaction risk, and (6) assessments of the risk of immunogenicity on clinical safety outcomes. To complete these analyses, protocol UX003-CL401 will require collection of molecular genotype and intrinsic GUSB enzymatic activity (apart from any concurrent enzyme replacement). Submit annual study reports that contain results from analyses of interim data. The final study report will be based on a study population that contains at least 12 new patients (including at least six patients less than one year old) treated with MEPSEVII (vestronidase alfa-vjbk) and enrolled in Study UX003-CL401.

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

PMR Schedule Milestones^{2, 3}

Draft Protocol Submission:	12/2017
Final Protocol Submission:	04/2018
Annual Report Submission:	01/2019
Annual Report Submission:	01/2020
Annual Report Submission:	01/2021
Annual Report Submission:	01/2022
Annual Report Submission:	01/2023
Annual Report Submission:	01/2024
Annual Report Submission:	01/2025
Study Completion:	04/2025
Annual Report Submission:	01/2026
Final Report Submission:	05/2026

SECTION C: PMR Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The risk for anaphylaxis in the vestronidase alfa-vjbk development program was notable at 11% (2 of 19 subjects), higher than reported in labeling for similar enzyme replacement therapy (laronidase, idursulfase, elosulfase alfa and galsulfase). Both genotype/phenotype correlation and longer term immunogenicity studies are requested to determine any correlation that may allow infusions to occur in a non-hospital setting.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)

² Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☒ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

4. For FDAAA PMRs only [\[for PMCs skip to Q.5\]](#). Complete this entire section

a. The purpose of the study/clinical trial is to: [\[Select one, then go to Q.4.b\]](#)

- ☒ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☒ Other

The laboratory data needed to assess immunogenicity, and risk for immunogenicity, based upon genotype and biochemical phenotype contribution toward risk of the development of immunogenicity would not be available in FAERS.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

d. **The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because:** *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☒ The population(s) of interest cannot be identified in the database.
- ☒ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☒ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☒ Other

The laboratory data needed to assess immunogenicity and risk for immunogenicity based upon genotype and biochemical phenotype contribution toward risk of the development of immunogenicity would not be available in ARIA.

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** *[Select either “Yes” or “No” and provide the appropriate responses.]*

☒ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

MPS VII is an extremely rare disease, and we would anticipate that some patients who are already enrolled in extension trials of MEPSEVII (vestronidase alfa-vjbk) might be enrolled in the PMR study. As these patients will have already been exposed to MEPSEVII (vestronidase alfa-vjbk), they would not be captured in either the FAERS or ARIA system.

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?**

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☒ Other (describe) **Clinical immunogenicity study**

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR Additional Information

1. **This PMR applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

☐ For *non-PREA* pediatric studies/trials only: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☒ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

N/A

SECTION E: PMR Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

2. ☐ *(If the PMR/PMC is a randomized controlled clinical trial)* The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

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

PMR DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

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Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA #	761047
PMR Set	3271-2
Product Name:	MEPSEVII (vestronidase alfa-vjbk)
Applicant Name:	Ultragenyx Pharmaceutical Inc.
ODE/Division:	ODE 3/DGIEP

SECTION B: PMR Information

1. PMR Description

Perform a pre- and post-natal developmental study in rats to assess the effects of MEPSEVII (vestronidase alfa-vjbk) on pre- and post-natal development. The study should be designed to detect adverse effects on the pregnant/lactating female rat and on the development of conceptus and offspring from implantation through weaning. The dose levels used in the pre- and post-natal developmental study should provide adequate margins of exposure for the clinical dose.

2. PMR Schedule Milestones^{2, 3}

Draft Protocol Submission:	12/2017
Final Protocol Submission:	02/2018

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

Study/Trial Completion: 3/2019
Final Report Submission: 7/2019

SECTION C: PMR Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The pre- and post-natal development study in rats will identify any potential adverse pre- and post-natal developmental effects in humans. A pre- and post-natal development study is a standard requirement, and the Applicant agreed to conduct the study as a post-marketing requirement.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☒ Other reason (describe in text box below)

Considering the rarity of the disease and unmet medical needs, conducting the pre- and post-natal

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

development study as a PMR is justified.

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☒ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient [Explain your answer in the textbox and then go to Q.5]

☐ No, a study is not sufficient [Select all explanations that apply then go to Q.4.f]

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

- f. ☐ Because a study is not sufficient, a clinical trial is required. [Go to Q.5]

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☒ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study

TYPE OF STUDY

☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☒ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☒ Orphan or rare disease population
- ☒ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR Development Coordinator Statements⁸[Error! Reference source not found.](#)

1. The PMR is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

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

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PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA #	761047
PMC Set	3271-3
Product Name:	MEPSEVII (vestronidase alfa-vjbk)
Applicant Name:	Ultragenyx Pharmaceutical Inc.
ODE/Division:	ODE III/DGIEP

SECTION B: PMC Information

1. PMC Description

In MPS VII patients enrolled in the prospective, longitudinal Study UX003-CL401 (PMR-1), collect and analyze: (1) beta-glucuronidase (GUSB) genotype, (2) in patients without history of MESEVII (vestronidase alfa-vjbk) treatment, baseline intrinsic GUSB enzymatic activity apart from any concurrent enzyme replacement treatment, (3) a complete record of treatments with MESEVII (vestronidase alfa-vjbk) pre- and post-UX003-CL401 enrollment, and (4) results from baseline and periodic tests for MPS VII clinical outcomes to include liver and spleen size measurement, pulmonary function, motor function, and neurocognitive function.

PMC Schedule Milestones^{2, 3}

Draft Protocol Submission:	12/2017
Final Protocol Submission:	04/2018
Study Completion:	04/2032

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMC Rationale**1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.**

As less than 100 living patients have ever been diagnosed with MPS VII, the natural history of disease is based upon a limited number of patients. This registry would provide additional information to understand the long term risk and benefit for use of MEPSEVII (vestronidase alfa-vjbk) in patients with MPS VII.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☒ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?

[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

☐ Need to minimize bias and/or confounding via randomization

☐ Need for placebo control

☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).

☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest

☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

☐ Drug interaction or bioavailability studies (nonclinical only)

☐ Epidemiologic (observational) study related to safe drug use

☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Immunogenicity study (nonclinical)

☐ Meta-analysis or pooled analysis of previous observational studies

☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)

☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)

☐ Pharmacogenetic or pharmacogenomic study

☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)

☐ Quality CMC study (e.g., manufacturing, studies on impurities)

☐ Quality stability study

☒ Registry-based observational study

☐ Other (describe)

TYPE OF CLINICAL TRIAL

☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)

☐ Dose-response clinical trial

☐ Dosing trial (e.g., alternative dosing schedule)

☐ Drug interaction or bioavailability clinical trial (clinical only)

TYPE OF CLINICAL TRIAL

- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMC Additional Information

1. This PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
- ☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☒ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMC Development Coordinator Statements

1. **The PMC is clear, feasible, and appropriate because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ ***(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:***

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

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

PMC DEVELOPMENT TEMPLATE

For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

BLA # 761047
PMC Set 3271-4
Product Name: MEPSEVII (vestronidase alfa-vjbk)
Applicant Name: Ultragenyx Pharmaceutical Inc.
ODE/Division: ODE3/DGIEP

SECTION B: PMC Information

1. PMC Description

Conduct studies to address the bioanalytical method validation of the assay used to measure the pharmacodynamic marker glycosaminoglycans, the Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) method by the (b) (4). Specifically, perform incurred sample reanalysis (ISR) for samples from Study UX003-CL301, and ongoing studies UX003-CL203 and UX003-CL202. Complete the ongoing assessment of long-term sample storage stability and conduct a 2nd long-term sample storage stability assessment to cover the storage duration of all study samples from clinical trials. Use freshly prepared calibrator standards in conducting the ISR for samples from UX003-CL203 and UX003-CL202 and the 2nd long-term sample storage stability analysis.

2. PMC Schedule Milestones^{2, 3}

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

ISR for samples from UX003-CL301:

Draft Protocol Submission: 11/2017
Final Protocol Submission: 12/2017
Study Completion: 01/2018
Report Submission: 02/2018

ISR for samples from ongoing studies UX003-CL203 and UX003-CL202:

Draft Protocol Submission: 03/2018
Final Protocol Submission: 05/2018
Study Completion: 10/2018
Report Submission: 12/2018

Ongoing long-term sample storage stability study:

Study Completion: 06/2018
Report Submission: 08/2018

2nd long-term sample storage stability study:

Draft Protocol Submission: 02/2018
Final Protocol Submission: 04/2018
Study Completion: 06/2020
Final Report Submission: 08/2020

SECTION C: PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

- ISR has not been performed to demonstrate the robustness of the LC-MS/MS method. In addition, the long-term sample storage stability data of the LC-MS/MS method were insufficient to cover the storage duration for all samples from the clinical trials.
- The PMC study is to provide additional validation data to ascertain the reliability of the pharmacodynamic data from all clinical trials.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

(Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)

⁴ A “study” is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A “clinical trial” is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.”

- ☐ **PREA PMR:** Meets PREA postmarketing pediatric study *requirements* [\[Skip to Q.5\]](#)
- ☐ **FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☒ **PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☒ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

4. For FDAAA PMRs only [\[for PMCs skip to Q.5\]](#). Complete this entire section

a. The purpose of the study/clinical trial is to: [\[Select one, then go to Q.4.b \]](#)

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

- ☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

- ☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?**

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☒ Other (describe) **Bioanalytical assay validation**

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

☐ For non-PREA pediatric studies/trials only: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☐ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☒ Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMC Development Coordinator Statements

1. The PMR/PMC is clear, feasible, and appropriate because: *[Select all that apply]*

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.

- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

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

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA #	761047
Product Name:	MEPSEVII (vestronidase alfa-vjbk)
PMC 3271- 5 Description:	To conduct the bioburden and endotoxin method qualification to include a total of three lots of the following Mepsevii (vestronidase alfa-vjbk) drug substance (b) (4)
PMC Schedule Milestones:	Final Report Submission: 12/2019

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☒ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☒ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

Bioburden and endotoxin test methods have only been qualified using one lot of (b) (4) and have not been qualified using (b) (4).

2. Describe the particular review issue and the goal of the study.

Qualification of the method with three lots from these (b) (4) will provide assurance of the suitability of the methods regardless of batch to batch variability.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☒ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

The applicant will repeat the qualification of bioburden and endotoxin test methods using two additional batches of (b) (4) and three batches of (b) (4).

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA #	761047
Product Name:	MEPSEVII (vestronidase alfa-vjbk)
PMC 3271-6 Description:	To repeat the rabbit pyrogen test with three Mepsevii (vestronidase alfa-vjbk) drug product lots at the maximum human equivalent dose of 4 mg/kg. Provide summary data and study report.
Final Report Submission:	03/2018

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☒ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The sponsor discovered late in the review cycle that a miscalculation was made during the execution of the rabbit pyrogen study: the dose administered to the rabbits was 3 mg/kg, not the intended maximum human equivalent dose of 4 mg/kg. This is acceptable as a PMC because based on our recent experience, the risk of having pyrogenic substances other than bacterial endotoxin in the final DP is relatively low. The bacterial endotoxin level in DP is tested by a validated LAL test as a release test. 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.

2. Describe the particular review issue and the goal of the study.

21CFR 610.13(b) requires a rabbit pyrogen test conducted on the DP using the maximum human equivalent dose to determine if DP contains pyrogenic substances other than bacterial endotoxin. The test needs to be repeated using the correct dose to comply with the regulation.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☒ Assay

- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

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.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 761047

Product Name: MEPSEVII (vestronidase alfa-vjbk)

PMC 3271-7
Description: To re-evaluate all Mepsevii (vestronidase alfa-vjbk) drug substance 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 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.

PMC Schedule Milestones: Final Report Submission:

12/2035

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☒ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The drug substance and drug product release and stability specifications approved under the BLA are adequate to ensure the quality and safety of the initial marketed Mepsevii. However, the proposed drug substance and drug product release and stability specifications have been established from a limited number of available drug substance and drug product lots manufactured at the time of the BLA submission. Therefore, additional product manufacturing and testing experience gained during post-licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

The drug substance and drug product release and stability specifications approved under the BLA were established from drug substance and drug product lots manufactured using clinical and commercial manufacturing process. However, the number of lots used to establish the specifications is not adequate for a robust analysis of data. Therefore, all drug substance and drug product release and stability specifications should be reassessed when a statistically significant number of lots have been manufactured using the commercial manufacturing process and tested using the commercial specifications.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

Re-evaluate all Mepsevii™ 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.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 761047

Product Name: Mepsevii (vestronidase alfa-vjbk)

PMC 3271-8

Description:

To perform a leachable study to evaluate leachables in the Mepsevii (vestronidase alfa-vjbk) 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.

PMC Schedule Milestones: Final Report Submission:

01/2019

6. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

The results from the (b) (4) drug product container closure system extractable studies indicate that the identified extractables from commercial container closure system do not appear to affect the quality and safety of the initial marketed Mepsevii. However, a comprehensive leachable study to evaluate the (b) (4) 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 has not been performed.

7. Describe the particular review issue and the goal of the study.

The submission did not include comprehensive leachable studies performed 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. A complete leachable study including the evaluation of all potential volatile organic, semi-volatile organic, non-volatile organic and inorganic compounds through the (b) (4) drug product end of shelf-life should be performed under the long term and accelerated storage conditions to enable a risk evaluation of potential impact to safety and product quality.

8. [OMIT – for PMRs only]

9. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☐ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☒ Other

Describe the agreed-upon study:

Conduct a leachable study of 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 study will be performed using methods to detect identity, and quality of potential volatile organic, semi-volatile organic, non-volatile organic and inorganic compounds through the (b) (4) drug product end of shelf-life to evaluate the impact of leachables to product safety and quality.

10. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

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/s/

JENNY N DOAN
11/14/2017

CRISTINA AUSIN-MORENO
11/15/2017

KATHLEEN M DONOHUE
11/15/2017

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Template
Version: 2016-02-11**

Date: November 3, 2017

Reviewer(s): Joel L. Weissfeld, MD MPH
Division of Epidemiology 1

Deputy Director: Sukhminder K. Sandhu, PhD MPH MS
Division of Epidemiology 1

Subject: ARIA Sufficiency Memo

Drug Name(s): vestronidase alfa

Application Type/Number: BLA 761047

Applicant/sponsor: Ultragenyx Pharmaceutical Inc

OSE RCM #: 2017-1870

EXECUTIVE SUMMARY (*place "X" in appropriate boxes*)

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Ultragenyx submitted BLA 761047 for vestronidase alfa (Mepsevii®), an intravenous replacement enzyme for mucopolysaccharidosis VII (MPS VII).

1.2. Describe the Safety Concern

MPS VII is a very uncommon recessively inherited inborn error of metabolism. Patients with MPS VII inherit two defective copies of the beta-glucuronidase gene (*GUSB*). Two20 MPS VII patients in BLA 761047 experienced an anaphylactic reaction to vestronidase alfa. The clinical details about the anaphylactic reactions are not clear, including the time-to-onset, and the duration of exposure of the study drug prior to the development of the hypersensitivity reaction. However, the product will be labeled with a boxed warning stating “Anaphylaxis has occurred with MEPSEVII administration, as early as the first dose (5.1).”

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	<input checked="" type="checkbox"/>
Assess signals of serious risk	<input type="checkbox"/>
Identify unexpected serious risk when available data indicate potential for serious risk	<input type="checkbox"/>

1.4. Statement of Purpose

The Division of Gastroenterology and Inborn Error Products (DGIEP), with concurrence by OSE, requires a post-market clinical study to assess the known serious risk for anaphylaxis from vestronidase alfa. DGEIP specifically requires information about immunologic factors (i.e., anti-drug antibodies and neutralizing antibodies against vestronidase alfa) associated with anaphylaxis in patients well characterized according to *GUSB* genotype and *GUSB* function. DGIEP requires detailed information from post-market settings to inform appropriate clinical strategies for mitigating the risk for anaphylaxis from vestronidase alfa to supplement existing labeling efforts (i.e., boxed warning).

1.5. Effect Size of Interest or Estimated Sample Size Desired

DGIEP prefers prospective study of ≥ 20 patients (including ≥ 6 patients < 1 year old) who initiate treatment with vestronidase alfa.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1. Population

DGIEP requires patients with MPS VII verified by genetic tests and well characterized according to *GUSB* genotype and intrinsic *GUSB* enzymatic activity apart from any concurrent enzyme replacement treatment.

2.2. Is ARIA sufficient to assess the intended population?

No. Determinations for study eligibility (MPS VII verified by genetic testing), *GUSB* genotype, and MPS VII phenotype (intrinsic *GUSB* enzymatic activity) require results from non-standard laboratory tests not captured in administrative claims.

Moreover, although specific ICD10 codes exist for MPS types 1 (E76.0) and 2 (E76.1), there are no specific codes for MPS VII.

E76 - Disorders of glycosaminoglycan metabolism
E76 Disorders of glycosaminoglycan metabolism
E76.0 Mucopolysaccharidosis, type I
E76.1 Mucopolysaccharidosis, type II
E76.2 Other mucopolysaccharidoses
E76.3 Mucopolysaccharidosis, unspecified
E76.8 Other disorders of glucosaminoglycan metabolism
E76.9 Glucosaminoglycan metabolism disorder, unspecified

<https://icd.codes/icd10cm/chapter4/E70-E88>

3. EXPOSURES

3.1. Treatment Exposure(s)

Intravenous infusion with vestronidase alfa.

3.2. Comparator Exposure(s)

Not applicable.

3.3. Is ARIA sufficient to identify the exposure of interest?

Yes. Procedure codes in outpatient administrative claims capture physician-supervised administrations of intravenous therapeutics, such as vestronidase alfa.

4. OUTCOME(S)

4.1. Outcomes of Interest

Hypersensitivity reactions including anaphylaxis, anaphylactoid reactions, urticarial skin reactions with or without angioedema, and immune-complex-mediated illness.

4.2. Is ARIA sufficient to assess the outcome of interest?

No. Depending on the safety application, diagnostic codes in outpatient administrative claims may or may not capture with acceptable accuracy the outcomes of anaphylaxis¹ or hypersensitivity reactions other than anaphylaxis.² However, confident safety evaluations in

¹ Walsh, KE, SL Cutrona, S Foy, et al., 2013, Validation of Anaphylaxis in the Food and Drug Administration's Mini-Sentinel, *Pharmacoepidemiol Drug Saf*, 22(11), 1205-1213.

² Schneider, G, S Kachroo, N Jones, et al., 2012, A Systematic Review of Validated Methods for Identifying Hypersensitivity Reactions other than Anaphylaxis (Fever, Rash, and Lymphadenopathy), Using Administrative and Claims Data, *Pharmacoepidemiol Drug Saf*, 21(S1), 248-255.

very small patient cohorts (i.e., worldwide MPS VII patient population) demand outcomes assessed at a level of diagnostic accuracy achievable only through prospective data collection.

5. COVARIATES

5.1. Covariates of Interest

Anti-drug and neutralizing antibody titers against vestronidase alfa were deemed highly desirable by OND to help clarify clinical factors and develop mitigation strategies.

5.2. Is ARIA sufficient to assess the covariates of interest?

No. Answers to the safety concern require results from non-standard laboratory tests conducted on blood collected prospectively according to a schedule fixed by protocol.

6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1. Surveillance or Study Design

Prospective cohort.

6.2. Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. Analytic tools available in Sentinel enumerate exposures and outcomes, the information needed to assess the frequency of anaphylaxis and other outcomes of interest.

7. NEXT STEPS

The Ultragenyx post-market plan for vestronidase alfa includes Study Protocol UX003-CL401, a long-term registry study of MPS VII. FDA recommends documenting the UX003-CL401 component of the Ultragenyx post-market plan as a Post-Market Commitment (PMC) attached to BLA 761047. FDA also recommends a Post-Market Requirement (PMR), explicitly linked to Study Protocol UX003-CL401, for hypersensitivity reactions to vestronidase alfa. To communicate expectations for the PMC and PMR, OSE suggests the following language.

Post-Market Commitment: Commit to Study Protocol UX003-CL401 for a long-term registry of patients with mucopolysaccharidosis type VII (MPS VII). UX003-CL401 defines procedures for collecting data prospectively for patients with MPS VII verified by genetic tests. Critical data elements include, (1) beta-glucuronidase (*GUSB*) genotype, (2) intrinsic GUSB enzymatic activity apart from any concurrent enzyme replacement treatment, (3) complete record of pre-registry and registry treatments with vestronidase alfa, (b) (4)

(b) (4)
6) results from registry baseline and periodic tests for MPS VII clinical outcomes to include liver and spleen size, pulmonary function, motor function, and neurocognitive function.

Post-Market Requirement: Analyze hypersensitivity reactions (including anaphylaxis) in Study Protocol UX003-CL401 patients followed up to three years on vestronidase alfa. Analyses of interest include, (1) incidence rates for hypersensitivity reactions, (2) incidence rates for the



appearance of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against vestronidase alfa, (3) temporal associations between ADA or Nab formation and hypersensitivity reactions, and (4) associations between beta-glucuronidase (*GUSB*) genotype or intrinsic *GUSB* enzymatic activity and hypersensitivity reaction risk. Submit annual study reports that contain results from analyses of interim data. Base a final study report on a study population that contains at least 20 patients (including at least six patients less than one year old) who initiated vestronidase alfa treatment under Study Protocol UX003-CL401.

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/s/

JOEL L WEISSFELD
11/07/2017

SUKHMINDER K SANDHU
11/07/2017

JUDITH W ZANDER
11/07/2017

MICHAEL D NGUYEN
11/08/2017

ROBERT BALL
11/09/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 8, 2017

To: Jenny Doan, MSN, BSN, PMP, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for MEPSEVII (vestronidase alfa-vjbk)
Injection, for intravenous use

BLA: 761047

In response to Division of Gastroenterology and Inborn Errors Products' consult request dated March 29, 2017, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original BLA submission for MEPSEVII (vestronidase alfa-vjbk) Injection, for intravenous use (Mepsevii).

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI entitled, "FINAL draft-PI-labeling-Nov. 1, 2017-clean.docx" that was available in SharePoint on November 1, 2017 at 9:02am, and are provided directly on the attached marked-up copy of the labeling below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling entitled, "Final Carton Label for Mesevii Aug. 22, 2017.pdf" and "Final Vial Label for Mepsevii Aug. 22, 2017.pdf" that were available in SharePoint on November 1, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADEWALE A ADELEYE
11/08/2017

MEMORANDUM

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

DATE: September 27, 2017

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and
Inborn Errors Products (DGIEP)
Office of Drug Evaluation III (ODE III)
Office of New Drugs (OND)

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)
[REDACTED]

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection of the analytical portion of Study UX003-CL301 submitted to BLA 761047 at [REDACTED] (b) (4). This amended review provides the final classification and an additional response dated 8/31/2017.

Form FDA 483 was issued at the inspection close-out. The inspection classification is Voluntary Action Indicated (VAI).

Significant objectionable conditions were observed during this inspection that impacted the reliability of a portion of the audited study. Although the inspectional findings do not impact the reliability of all the data, significant variability can be expected in the quantified GAG concentrations using the current analytical method. Thus, I recommend that the data from Study UX003-CL301 conducted at [REDACTED] (b) (4) be accepted for Agency review for semi-quantitative purposes.

Inspected Study:**BLA 761047****Study Number:** UX003-CL301**Study Title:** "A Randomized, Placebo-Controlled, Blind-Start, Single-Crossover Phase 3 Study to Assess the Efficacy and Safety of UX003 rhGUS Enzyme Replacement Therapy in Patients with MPS 7"**Dates of Study****Conduct:** December 2, 2014 to May 4, 2016**Dates of****Sample Analysis:** November 26, 2014 to May 16, 2016 (Inclusive of sample analysis by spectrophotometric method)**Bioanalytical****Site:** [REDACTED] (b) (4)

OSIS scientist Srinivas R. Chennamaneni, Ph.D., audited the bioanalytical portion of the above study at [REDACTED] (b) (4) from [REDACTED] (b) (4).

The inspection included a thorough examination of the facilities and equipment, study records, method development and validation, including electronic records and audit trails, sample analysis, employee training records, and interviews with the firm's management and staff.

At the conclusion of the inspection, I observed objectionable findings and Form FDA 483 was issued to [REDACTED] (b) (4). The Form FDA 483 observations (**Attachment 1**), the firm's responses dated 8/3/2017 and 8/31/2017 (**Attachments 2 & 3**), and my evaluation are presented below.

OBSERVATION 1

The UPLC-MS/MS method for the determination of heparan sulfate and dermatan/chondroitin sulfate was not fully validated. Specifically, quality control samples were not used to evaluate the accuracy and precision of the method.

Firm's Response: In response to the observation, the firm stated that they used two levels of quality control samples (QCs) termed low positive control (LPC) and high positive control (HPC). During method validation, the LPC was composed of pooled biological matrix (urine or plasma) from healthy volunteers and the HPC was pooled biological matrix from healthy volunteers spiked with either heparan sulfate or chondroitin/dermatan sulfate. During sample analysis, urine or serum from healthy subjects was used instead. The LPC and HPC were subjected to the same sample extraction procedure as calibrators and subject samples. The LPCs and HPCs were included as process controls to monitor overall performance of the extraction procedure (**Attachment 2, Tables 1, 2, 3**).

Two digestion controls were prepared in water with known concentrations and were introduced into the process after the purification step. The digestion controls were specific for each heparinase digestion and chondroitinase digestion. These controls were included with every run conducted during both the validation and sample analysis of clinical study UX003-CL301 (**Attachment 4, Appendix A**).

Because the biological matrices contain endogenous GAGs, a correction factor was required to adjust the nominal concentration of GAGs and that would render samples with low concentrations of GAGs as non-quantifiable. However, a suitable GAG-free surrogate matrix was not available for spiking; thus, the calibrators were prepared in water. The calibrators were introduced into the assay after digestion with heparinases and chondroitinases and processed along with the study samples.

OSIS Evaluation: The firm didn't use quality control samples for run acceptance during the analysis of subject samples. Instead, the firm used two QCs as process controls to monitor the overall performance of the extraction procedure. The QCs were not evenly distributed within the range of the calibration curves of individual internal disaccharides (IDSCs).

The concentrations of internal disaccharides of the LPC and HPC were within the range of the calibration curves of individual Internal Disaccharides (IDSCs). Heparan sulfate IDSCs in calibration curve ranged from 0.083 to 27.666 mg/L for D0A0, 0.09 to 28.282 mg/L for D0S0, 0.09 to 28.729 mg/L for D0A6, and 0.092 to 1.086 mg/L for heparan sulfate non-reducing end (NRE) (G0A0). Chondroitin sulfate IDSCs in calibration curve ranged from 0.415 to 30.428 mg/L for D0a0, 0.507 to 30.017 mg/L for D0a4, 0.407 to 30.133 mg/L for D0a6, and 0.023 to 6.413 mg/L for chondroitin sulfate NRE (G0a0). Thus, the majority of the

subject sample concentrations were at lower end of the calibration curve around the LPC (endogenous concentrations) for most of IDSCs for heparan and chondroitin/dermatan sulfate. For heparan sulfate, the LPC IDSC G0A0 concentration was below the lower limit of quantification (**Attachment 5**).

The injection volume for calibrators was 3.0 µL, whereas the injection volume for subject samples and QCs was 6 µL. Thus, the same method was not used to analyze calibrators, QCs, and subject samples. The change in matrix (water vs. plasma/serum) and doubling the injection volume likely had an impact on ionization and mass spectrometric response.

In summary, this observation has a significant impact on the integrity of the study data. In my opinion, the data may be used for semi-quantitative assessment to monitor the baseline vs. post treatment values in subject samples.

OBSERVATION 2

The UPLC-MS/MS method validation used plasma matrix, whereas the matrix of study samples was serum. No partial validation was performed to evaluate the impact of the matrix.

Firm's Response: The firm acknowledged the observation and stated that plasma was chosen because it is commonly used in the clinical laboratory and is readily available. To demonstrate the equivalence of plasma and serum matrices, study comparing plasma and serum samples from healthy volunteers was conducted in July 2014 (not reported in the method validation report submitted to the Agency) and the concentrations of the individual IDSCs used in the quantification of heparan sulfate and chondroitin/dermatan sulfate were measured. The concentrations of IDSCs did not differ significantly between the two matrices. The results of G0A0 (heparan sulfate NRE IDSC) were below LLOQ. The firm plans to conduct a partial validation study to demonstrate comparability of assay performance between serum and plasma which will be completed by February 2018.

OSIS Evaluation: The bioanalytical method should demonstrate the accuracy and precision by using QCs prepared in the same biological matrix as study samples. During method validation, the firm used plasma to prepare the QCs. However, subject samples were in serum. In their response, the firm provided a comparison of IDSC concentrations obtained in plasma and serum matrices. The results demonstrated that the concentrations were comparable between the two matrices. Therefore, this observation

is not likely to have a significant impact on the integrity of the study data.

OBSERVATION 3

The purity of two non-reducing end standards was not available to correct the nominal concentration when preparing calibration standards.

Firm's Response: In their response, the firm stated that a purity of 100% was considered for both NRE standards during method validation and sample analysis because the certificate of analysis (**Attachment 2, Appendix 1**) containing purity information was not available. Based on the protocol, the concentration data for G0A0 and G0a0 IDSCs in study samples was used to determine the efficacy of UX003 by evaluating the percent reduction of GAG levels from the baseline measurement prior to treatment. The firm stated that adjusting the concentration of the reference standards stock solutions by applying the purity correction factor would not change the percent reduction of the GAG levels from baseline in study samples; therefore, there was no impact on the study data.

OSIS Evaluation: Although applying a purity factor would change the observed GAG concentrations, applying a correction factor would not change the percent reduction in GAG concentrations. The actual purity of NRE IDSCs standards were 98% for G0A0 and 90% for G0a0. The firm should recalculate the results by taking into account the correction factor and provide concentrations for both non-reducing end IDSCs for heparan sulfate and chondroitin/dermatan sulfate.

OBSERVATION 4

The first set of reference standards used in the UPLC-MS/MS method was tagged with ^{12}C -aniline (used as calibration standards); and the second set of reference standards was tagged with ^{13}C -aniline (used as corresponding internal standards). There is no data to support that there is no cross reaction between left over ^{12}C -aniline with the left over reference standard in aliquots tagged with ^{13}C -aniline and left over ^{13}C -aniline with the left over reference standard in aliquots tagged with ^{12}C -aniline. The aliquots from two tagging preparations were mixed before injection.

Firm's Response: In response to this observation, the firm stated that the tagging reactions used 2000-fold excess of ^{13}C -aniline over the amount of disaccharides and cited several

references in the literature. In addition, an experiment using ^{12}C -aniline tagged CS/DS disaccharide calibration standards was conducted and the results showed that the reaction is very efficient, leading to >97% tagging.

As a corrective action, the firm will conduct experiments and document the potential cross reaction for all future bioanalytical studies. The results from a study to address potential cross reaction with heparan sulfate IDSCs will be provided to the Agency by the first week of September 2017.

OSIS Evaluation: The site synthesized reference standards tagged with ^{12}C -aniline and ^{13}C -aniline in order to develop a bioanalytical method because deuterated reference standards were not commercially available. ^{12}C -aniline tagged reference was used as analyte and ^{13}C -aniline tagged reference was used as internal standard (**Attachment 6**). Although the tagged reference standards were used during sample analysis without further purification, the data provided in the response support that the tagging reaction is efficient (>97%). Thus, this observation does not impact the integrity of the study data. The firm's corrective actions are acceptable and will prevent the recurrence of the problem in future studies.

OBSERVATION 5

The Spectrophotometric method for the determination of total GAGs (Glycosaminoglycans) used calibrators prepared in water and quality control samples prepared in urine.

Firm's Response: In their response, the firm stated that due to the presence of endogenous GAGs in urine, a correction factor would be required to adjust the nominal concentration of calibrators and that would render samples with low concentrations of GAGs non-quantifiable. As no surrogate matrix without GAGs was available, the calibrators were prepared in water to achieve known concentration of IDSCs.

OSIS Evaluation: The impact of components in urine matrix on the analyte response was not evaluated. However, the firm measured the concentrations of intact GAGs (heparan sulfate, chondroitin/dermatan sulfate) for screening purposes (semi-quantitative assessment) and not a quantitative assessment. Thus, this observation does not have a significant impact on the integrity of the study data.

OBSERVATION 6

Documentation for the spectrophotometric method validation did not clearly indicate the purpose of each method validation experiment.

Firm's Response: The firm stated that for all future studies, it will include the purpose of each validation experiment and provide reference to respective raw data for traceability.

OSIS Evaluation: The firm's response is adequate. The corrective action proposed by the firm should prevent the recurrence of this observation in future studies if implemented properly. This observation does not impact the integrity of the study data.

Additional Information to Address Review Division Concerns:

All evaluations for heparan sulfate and chondroitin/dermatan sulfate are based on sum of the response of corresponding internal disaccharides used in the quantification. In addition, based on the selected internal disaccharides, the method cannot distinguish chondroitin sulfate and dermatan sulfate during sample analysis. Thus, the results for chondroitin/dermatan sulfate are combined and presented together.

For heparan sulfate, the firm quantified G0A0, D0A0, D0S0, and D0A6 IDSCs, but D0A6 was excluded from calculations. D0A2 was coeluted with D0A6 IDSC in majority of runs I evaluated during the inspection. In addition, the firm was able to quantify D2A0, D0S6, D2S0, and D2S6 IDSCs, but the data for these IDSCs were not reported.

G0A0 (heparan sulfate) and G0a0 (chondroitin sulfate) NRE IDSC concentrations are expected to be much lower in healthy volunteers compared to individuals affected with MPSVII disorder. It is not clear that how the firm was able to quantify these NREs successfully using normal matrix from healthy volunteers. The recovery of NRE IDSCs in serum and plasma was not determined.

OSIS and reviewers from the Division of Gastroenterology and Inborn Errors Products (DGIEP) met on 8/9/2017 and discussed the objectionable conditions from the inspection. My evaluations of the review division's concerns are discussed below.

- **Did the firm evaluate the impact of the different recovery in different matrices?**

OSIS Evaluation: The recovery of IDSCs varied in different matrices. In water, the recovery ranged from 34-41% for heparan sulfate and 44-51% for chondroitin sulfate. In plasma, the recovery ranged from 25-29% for heparan sulfate and 54-74% for chondroitin/dermatan sulfate (**Attachment 7**).

Although the firm used the peak area ratio of the analyte and internal standard, the variable recoveries may significantly impact the resulting concentrations. In my opinion, it is likely that the concentration of IDSCs in the study samples were underestimated because the subject samples and calibrators were in different matrices.

Conclusion:

Significant objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, there was evidence that the objectionable conditions impacted the reliability of the data from study UX003-CL301 conducted at [REDACTED] (b) (4).

I recommend that the data from study UX003-CL301 (BLA 761047) be considered for semi-quantitative purposes only. In addition, the NRE data should be corrected for the purity of the reference standards before being accepted for review by Agency. The review division should request the sponsor to provide recalculated NRE concentrations corrected for the purity of reference standards. In addition, studies using similar methods conducted at [REDACTED] (b) (4) before the end of the current Surveillance Interval should not be accepted for review by the Agency without an inspection.

Srinivas R. Chennamaneni, Ph.D.
Staff Fellow

Final Classification:

Bioanalytical Site:

VAI: [REDACTED] (b) (4)
(FEI# [REDACTED] (b) (4))

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/s/

SRINIVAS RAO N CHENNAMANENI
09/27/2017

CHARLES R BONAPACE
09/28/2017



U.S. FOOD & DRUG
ADMINISTRATION

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

LABELS AND LABELING REVIEW

Date:	August 24, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Rukman De Silva, PhD, Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761047
Product:	Mepsevii (vestronidase alfa-vjbk)
Applicant:	Ultragenyx Pharmaceutical Inc.
Submission Date(s):	March 16, 2017, June 5, 2017, August 4, 2017, and August 22, 2017

I) RECOMMENDATION

The labels and labeling for Mepsevii (vestronidase alfa-vjbk) Injection, 10 mg/5 mL single-dose vial submitted on August 22, 2017 are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted BLA 761047 on March 16, 2017 for Mepsevii (vestronidase alfa-vjbk), a recombinant human beta-glucuronidase, rhGUS, UX003, as an enzyme replacement therapy (ERT) for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

Table 1: Proposed Product Characteristics of Mepsevii (vestronidase alfa-vjbk) submitted March 16, 2017.

Proprietary Name:	Mepsevii
Nonproprietary Name:	vestronidase alfa-vjbk
Dosage Form:	Injection
Strength and Container-Closure:	10 mg/5 mL single-dose vial
Route of Administration:	Intravenous infusion
Storage and Handling:	Store MEPSEVII under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Diluted MEPSEVII should be used immediately. If immediate use is not possible, diluted MEPSEVII may be stored for 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) during administration.
Indication:	Lysosomal enzyme replacement therapy indicated for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).
Dose and Frequency:	4 mg per kg body weight administered every two weeks as an intravenous infusion over approximately 4 hours

III) MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (N/A)
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

IV) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

V) CONCLUSION

The prescribing information, container labels, and carton labeling for Mepsevii (vestronidase alfa-vjbk) Injection, 10 mg/5 mL single-dose vial were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100 and United States Pharmacopeia (USP). The labels and labeling submitted on August 22, 2017 are acceptable (see Appendix D) from a quality perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted 5June17 (<\\cdsesub1\evsprod\bla761047\0017\m1\us\draft-labeling-text-redline.pdf>))

Container Labels (submitted 16Mar17)

(b) (4)



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Appendix B: N/A

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

Table 3: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Proper Name</u> 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			x	See DMEPA review of nonproprietary name suffix. ⁵
<u>Manufacturer name, address, and license number</u> 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.
<u>Lot number or other lot identification</u> 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.
<u>Expiration date</u> 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.
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.60			x	Single-dose vial
<u>Statement: "Rx"</u>	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	
<u>only</u> 21 CFR 610.60 21 CFR 201.100				
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24			x	
<u>No Package for container</u> 21 CFR 610.60			x	
<u>Partial label</u> 21 CFR 610.60 21 CFR 201.10		x		<p>The terms LOT and EXP are printed online during labeling.</p> <p>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."</p> <p><i>Applicant revised as requested</i></p>
<u>No container label</u> 21 CFR 610.60			x	
<u>Visual inspection</u> 21 CFR 610.60		x		<p>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).</p> <p><i>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."</i></p> <p><i>Ultragenyx confirms there is no text on the ferrule and cap overseal of the vials.</i></p> <p><i>We find this response acceptable.</i></p>
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	x			<p>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.</p>

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100	x			
<u>Preparation instructions</u> 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. <i>Applicant revised as requested</i>
<u>Package type term</u> 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. <i>Applicant revised as requested</i> Bold the statement "Discard unused portion" to increase prominence of important information. <i>Applicant revised as requested</i>
<u>Drugs Misleading statements</u> 21 CFR 201.6			x	
<u>Strength</u> 21 CFR 201.10 21CFR 201.100	x			
<u>Drugs Prominence of required label statements</u> 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. <i>Applicant revised as requested</i> 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.
<u>Bar code label requirements</u> 21 CFR 201.25 21CFR 610.67	x			

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100		x		Unbold the statement "Usual Dosage". <i>Applicant revised as requested</i>
<u>Inactive ingredients</u> 21 CFR 201.100				We consider this a partial label. This information must appear on the carton, PI, and IFU (if applicable).
<u>Storage requirements</u>				<p>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</p> <p><i>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.</i></p> <p>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"</p> <p><i>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".</i></p> <p><i>We find this revision acceptable since "Protect from light" statement is restored on the carton labeling and in the prescribing information.</i></p>

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

Package Label⁶ Evaluation

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Proper name</u> 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10				See comment for container label
<u>Manufacturer name, address, and license number</u> 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. <i>Applicant revised as requested</i>
<u>Lot number or other lot identification</u> 21CFR 610.61	x			The terms LOT and EXP are printed online during labeling.
<u>Expiration date</u> 21CFR 610.61 21 CFR 201.17	x			
<u>Preservative</u> 21CFR 610.61	x			
<u>Number of containers</u> 21CFR 610.61			x	
<u>Strength/volume</u> 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	
				<i>Applicant revised as requested</i>
<u>Storage temperature</u> 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 <i>Applicant revision is acceptable</i>
<u>Handling: "Shake Well", "Do not Freeze" or equivalent</u> 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. <i>Applicant revised as requested</i>
<u>Multiple dose containers (recommended individual dose)</u> 21CFR 610.61			x	Single-dose vial
<u>Route of administration</u> 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			
<u>Known sensitizing substances</u> 21CFR 610.61			x	
<u>Antibiotics added during manufacturing</u> 21 CFR 610.61			x	
<u>Inactive ingredients</u> 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. <i>Applicant revised as requested</i>
<u>Adjuvant, if present</u> 21CFR 610.61			x	
<u>Source of the product</u> 21CFR 610.61			x	
<u>Identity of each microorganism used in manufacturing</u> 21CFR 610.61	x			
<u>Minimum potency of product</u> 21CFR 610.61 (r)	x			
<u>Rx only</u> 21CFR 610.61 21 CFR 201.100	x			
<u>Divided manufacturing</u> 21 CFR 610.63			x	Only one applicant
<u>Distributor</u> 21 CFR 610.64			x	
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25	x			
<u>NDC numbers</u> 21 CFR 201.2 21CFR 207.35	x			
<u>Preparation instructions</u> 21 CFR 201.5	x			
<u>Package type term</u> 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	
				<i>Applicant revised as requested</i>
<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6	x			
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15	x			
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	x			
<u>Dispensing container</u> 21 CFR 201.100			x	
<u>Medication Guide</u> 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	
				<p>appropriate USP nomenclature.</p> <p><i>The Applicant revised as requested</i></p> <p>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)."</p> <p><i>The Applicant revised as requested</i></p> <p>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).</p> <p><i>The Applicant revised as requested</i></p>
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		<p>Add dosage form per 21 CFR 201.57(c)(12) to the paragraph that discusses the drug product</p> <p>"(vestronidase alfa) Injection" for intravenous infusion"</p> <p><i>The Applicant revised as requested</i></p>
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. <i>The Applicant revised as requested</i>
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". <i>The Applicant revised as requested</i>
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)

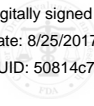
(b) (4)





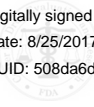
Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 8/25/2017 08:06:51AM
GUID: 50814c7000007a3d59329f660d8ddf02



Rukman
De Silva

Digitally signed by Rukman De Silva
Date: 8/25/2017 09:04:20AM
GUID: 508da6db0002668622f9d73ac81c7d27



REVIEW OF REQUEST FOR RARE PEDIATRIC DISEASE CONSULT

Date Submitted by Sponsor: March 16, 2017

Date Received by OOPD: April 13, 2017

Date Received by Reviewer: April 17, 2017

Date Consult Completed: April 20, 2017

Consult Number: RPC-2017-07

Company Code Name: UX003

Generic Name: vestronidase alfa

Sponsor: Ultragenyx Pharmaceutical Inc.

Regulatory Status: DGIEP has received a priority review application (BLA 761047) for vestronidase alfa (recombinant human beta-glucuronidase, rhGUS, UX003) as an enzyme replacement therapy (ERT) for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome). The Applicant (Ultragenyx) has requested a Rare Pediatric Disease Priority Review voucher in this BLA submission, but had not submitted a request for a “rare pediatric disease designation” prior to submitting their application.

Proposed Rare Pediatric Disease Designation: Treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

Orphan Drug Designation History: Recombinant human beta-glucuronidase received orphan drug designation for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome) (file #11-3598).

1. Background of Disease or Condition^{1,2}

Mucopolysaccharidosis type VII (MPS VII), also known as Sly Syndrome is an autosomal recessive storage disorder characterized by a deficiency of the lysosomal enzyme β -glucuronidase, which is required for the degradation of three glycosaminoglycans (GAGs): dermatan sulfate, heparan sulfate, and chondroitin sulfate. Progressive accumulation of these GAGs in lysosomes leads to increasing dysfunction in numerous tissues and organs. Symptoms of MPS VII include abnormally coarse facies, hepatosplenomegaly, pulmonary disease, cardiovascular complications (aortic and mitral valve disease), joint stiffness, trunk dwarfism, macrocephaly, cervical myelopathy, corneal clouding and deafness. In more severely affected persons developmental delay may also be present.

Currently there is no specific treatment for MPS VII. Therapy for these patients is directed toward correcting orthopedic abnormalities, respiratory support and treatment of cardiac abnormalities.

2. Population Estimate

Section 529 of the Federal Food, Drug, and Cosmetic Act as amended by the Advancing Hope Act of 2016, defines a rare pediatric disease as (1) a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents; and (2) a rare disease.

The sponsor states that greater than 50% of MPS VII patients diagnosed in the US were pediatric patients aged 0 to 18 years. This is based on what the sponsor states are its outreach efforts that identified 19 persons in the U.S. with MPS VII of these 19 patients, 18 were diagnosed prior to 18 years of age, with the majority diagnosed in infancy. All these 18 pediatric patients were diagnosed because of the presence of non-immune hydrops fetalis (NIHF), clinical symptoms or family history. The outreach efforts did not identify any asymptomatic adult patients in the U.S.

The sponsor notes that some manifestations of MPS VII continue to manifest and worsen over time. These manifestations include recurrent respiratory infections as a result of airway obstruction, cardiac dysfunction, joint stiffness and pain. However, all of these symptoms develop in childhood.

Reviewer's Comments:

The sponsor states that NIHF was present in the majority of persons with MPS VII, and was the sentinel manifestation leading to the diagnosis of MPS VII. OOPD notes that NIHF only occurs in the prenatal and neonatal periods, and that the affected person either dies or recovers during those periods. While the sponsor noted that in its outreach population the majority of MPS VII patients had had NIHF, Zielona et al.⁶ found that 45.5% of MPS VII had hydrops fetalis. The data from Zielona et al. show that NIHF affects a significant proportion of persons with MPS VII.

The median life-expectancy of MPS VII patients is 42 months⁶; based on these data the majority of deaths due to MPS VII can be estimated to occur prior to 18 years of age.

These data support the fact that the mortality burden of Sly syndrome is primarily borne by those persons who are 18 years of age and younger.

Based on the above data MPS VII is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.

The sponsor estimates that fewer than 1,300 persons in the United States have MPS VII. To calculate this target population estimate, the sponsor cites the National Organization for Rare Disorders (NORD) that estimates a prevalence rate for MPS VII of less than 1/250,000. The sponsor then applies this prevalence rate to an estimated U.S. population of 325 million to calculate a target population estimate of 1,300.

Reviewer's Comments:

The National Institutes of Health (NIH) Genetics Home Reference³ states that the estimated incidence of MPS VII is 1/250,000 newborns. Applying this annual incidence rate to an estimated 4 million live U.S. births yields an incidence of MPS VII of 16 persons with MPS VII annually. To estimate the prevalence the annual incidence is multiplied by the life expectancy. Persons with a mild form of MPS VII can live to age 50⁵, using a life expectancy of 50 years yields a target population estimate of 800. The sponsor's target population estimate of 1,300 is acceptable, and documents that MPS VII is a rare disease.

3. Scientific Rationale

Fox et al¹ have published a case report of 12 year old boy with advanced stage MPS VII who developed progressive heart valve disease, an enlarging liver and spleen, and progressively worsening pulmonary status. The authors report that the patient developed respiratory failure necessitating placement of a tracheostomy, oxygen therapy, and full-time ventilation. However, these interventions did not sufficiently support his pulmonary function and no additional medical measures could improve his pulmonary function. The patient was treated by intravenous (IV) infusions of 2 mg/kg of rhGUS administered over approximately 4 hours every 2 weeks, for 24 weeks. The authors report that at the initiation of rhGUS therapy, the patient required continuous ventilator support via his tracheostomy and the patient could not tolerate 1-hour periods off the ventilator without CO₂ levels rising to more than 80 mmHg. After 24 weeks of treatment, the patient tolerated periods of 80 minutes 2 times per day for total of 160 minutes per day off the ventilator without an increase in CO₂. Additionally, prior to treatment, the patient was aspirating food, but after 19 weeks of treatment the patient was no longer aspirating food, as assessed by barium swallow.

Reviewer's Comments:

The clinical data provided in this case report are adequate to support a medically plausible basis for the use of vestronidase alfa (rhGUS) in the treatment of MPS VII, for the purpose of rare pediatric disease designation.

4. Evaluation and Recommendations

DGIEP has received a priority review application (BLA 761047) for vestronidase alfa (recombinant human beta-glucuronidase, rhGUS, UX003) as an enzyme replacement therapy (ERT) for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome), and DGIEP has requested a consult from OOPD for assistance in reviewing of the request for a voucher to determine if the Applicant has submitted adequate data to support that their product is intended to treat a rare pediatric disease.

Section 529 of the Federal Food, Drug, and Cosmetic Act as amended by the Advancing Hope Act of 2016, defines a rare pediatric disease as (1) a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents; and (2) a rare disease.

Based on data presented in the sponsor's request for a rare pediatric disease voucher and published data MPS VII is a disease because it is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.

The sponsor has presented an adequate population estimate of 1,300.

As data have been presented that MPS VII is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents, and the target population estimate documents that MPS VII is a rare disease OOPD concurs that MPS VII qualifies as a rare pediatric disease as defined by Section 529 of the Federal Food, Drug, and Cosmetic Act as amended by the Advancing Hope Act of 2016.



John D. Milto, M.D.

Concur:  Date: 8/21/17

Henry H. Startzman III, M.D.
Director, Orphan Drug Designation Program
Office of Orphan Products Development

cc: HF-35/ Designation file RPC-2017-07
HF- 35/ Chron file
HF-35/ J. Milto

References

1. Fox, J.E., et al., First human treatment with investigational rhGUS enzyme replacement therapy in an advanced stage MPS VII patient. *Molecular Genetics and Metabolism* 2015;114(2):203-208.
2. Muenzer, J., Overview of the mucopolysaccharidoses. *Rheumatology* 2011;50:v4v12.
3. <https://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-vii#statistics>.
4. <https://www.cdc.gov/nchs/nvss/births.htm>.
5. Montañó, A.M., et al., Clinical course of Sly syndrome (mucopolysaccharidosis type VII). *Journal of Medical Genetics* 2016;53:403-418.
6. Zielonka, M., et al., Quantitative clinical characteristics of 53 patients with MPS VII: a cross-sectional analysis. *Genetics in Medicine* 2017; published online April 6, 2017.

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/s/

JENNY N DOAN

08/23/2017

on behalf of OOPD reviewer

MEMORANDUM

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

DATE: Aug 18, 2017

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III, OND

FROM: Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: [REDACTED] inspection of [REDACTED] (b) (4)
[REDACTED]

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted [REDACTED] BLA 7
(b) (4) from [REDACTED] (b) (4).

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Significant objectionable conditions were observed during this inspection that impacted the reliability of the audited studies. OSIS recommendations regarding the inspection findings are detailed in the Conclusion section below.

Inspected Study

BLA 761047: UX003, recombinant human beta-glucuronidase (rhGUS)

Study/Project #: UX003-CL301
Study Title: A Randomized, Placebo-Controlled, Blind-Start, Single-Crossover Phase 3 Study to

Assess the Efficacy and Safety of UX003
rhGUS Enzyme Replacement Therapy in
Patients with MPS 7

Sample Analysis dates: March 2016 to May 2016

CDER-OSIS reviewer Himanshu Gupta audited analytical data for heparan sulfate, dermatan sulfate and chondro-
dy UX00 (b) (4)
(b) (4) from (b) (4) The inspection included reviewing records relevant to the audited study, equipment calibration and maintenance, SOPs, and sample tracking as well as data verification against source records.

There were six Form FDA 483 observations (Attachment 1) issued at the cl out. OSIS received the email response to Form FDA 483 from (b) (4) on Aug 2, 2017 (Attachment 2).

FDA 483 observations:

Observation 1

Method validation (ULGX-GAG-01) and sample analysis (UX003-CL301) source documents were not available, including the following:

- a) weighing of reference standards for preparing stock solutions
- b) sample processing information
- c) the purity or expiration date of the reference standard for the heparan sulfate, dermatan sulfate and chondroitin sulfate analytes and internal standards
- d) dates and times for tracking sample movement in and out of freezers during method validation stability studies and sample analysis

Firm's response:

The firm acknowledged that they do not have documentation for several aspects of method validation and sample analysis because this level of documentation is not a requirement of CLIA or College of American Pathologists (CAP). The (b) (4) lab operates based on CLIA and CAP standards.

With regards to expiration dates for reference products, the firm mentioned that official expiration dates were not provided by the vendors. The firm further mentioned that following industry laboratory practices, products with no expiration dates

or retest dates can be used within 5 years of opening. For internal standard, the firm mentioned that internal standards were prepared in the (b) (4) lab itself and the firm analyzed internal standard-only blank samples to demonstrate that no unlabeled heparan sulfate, dermatan sulfate or chondroitin sulfate are present in the internal standards. However, the lab does not have the capability to evaluate the chemical purity of these internal standards. For future studies, firm mentioned that they will create SOPs for the validation of biomarker assays and sample handling.

OSIS evaluation:

Due to the lack of lab records, I could not verify:

1. The time and duration when samples were taken in and out of the freezer, which allows to confirm whether the duration the samples were out of freezer was within the evaluated stability duration.
2. The number of freeze and thaw for subject samples.
3. The amount of reference standards weighed to prepare the stock solutions and subsequent dilutions of stock solutions and associated calculations based on the purity of reference standards.

For the expiration dates, the firm did not provide any scientific documentation to support the expiration of reference standards after 5 years. For internal standards, I verified there were no unlabeled analyte peak in IS only blank.

Observation 2

For the analytical instrument software, there were no individual user accounts for accessing the instrument system for laboratory personnel and there was no audit trail information during the method validation (ULGX-GAG-01) and sample analysis (UX003-CL301).

Firm's response:

The firm mentioned that the single login and password are not shared with non-laboratory staff. The firm also mentioned that "A data audit trail was in place for the UX003-CL301 study which included both electronic and manual checks and was discussed during the inspection. The TargetLynx (LCMS data analysis program) includes an electronic audit trail, which documents changes and adjustments including any made to retention time and integration." The firm stated that the analytical values listed in the PDF output from TargetLynx were matched with those in the Excel files that were used for analyte calculations. The firm is

planning to update the TargetLynx software to allow for individual users accounts.

OSIS evaluation:

The individual account ensures that the data are processed only by the assigned user/analyst. Audit trail system captures the activities during analytical data processing. The firm mentioned in the response that the audit trail was discussed with the OSIS reviewer. However, no audit trail associated with the Masslynx/targetlynx analytical instrument's function was shown to the OSIS reviewer during the inspection. The firm was not aware of the audit trail and the full security system for the LCMS/MS instrument (Masslynx). Information on the MassLynx security features is provided in **Attachment 3**.

Observation 3

The precision and accuracy runs during method validation were not conducted using 3 QC levels with 5 replicates per QC concentration level.

Firm's response:

The firm acknowledged that precision and accuracy at 3 different QC levels with 5 replicates per QC concentration level were not performed. The firm mentioned that for future studies, a SOP will be implemented based on FDA guidance to evaluate accuracy and precision during method validation.

OSIS evaluation:

There were 2 QC levels used by the firm (25ug/ml and 250ug/mL) during validation and sample analysis. Despite the lack of 3 QC levels, overall, the precision and accuracy for the 3 analytes were acceptable for sample analysis runs based on the available data at 2 QC levels (25ug/mL and 250ug/mL).

Observation 4

Freshly prepared calibration standards and/or QCs were not used in evaluating the benchtop, freeze thaw and long term stability of the heparan sulfate, dermatan sulfate and chondroitin sulfate analytes in urine.

Firm's response:

Firm acknowledge the observation that freshly prepared calibrators were not used for stability studies. As part of the method validation, 6 month stability of the analytes was evaluated and all calibrators used during stability assessment

were made within 6 months. For future studies, they will use freshly prepared calibrators.

OSIS evaluation:

The firm prepared bulk-spiked CCs and QCs and used them throughout the method validation and study sample analyses, including the stability tests. However, there were no documents to verify when CCs, QCs, and the stability challenge samples were prepared. In addition, there were no records documenting the storage conditions from the preparation till the usage. In the absence of any records, I cannot ensure accuracy of stability data. OSIS recommends that the review division request additional data to support benchtop, freeze thaw and long term stability to cover the sample storage or handling period using freshly prepared calibrators or QCs.

Observation 5

For sample analysis (UX003-CL301), the run acceptance criteria was 20% (25% for LLOQ). If the run acceptance criteria are set at 15% and 20% for LLOQ, multiple runs would be rejected or certain concentration data would be excluded from the runs. Examples include 042516-CS-H, 042616-DS-H, 051016-CS-H, and 051216-CS-H.

Firm's response:

The firm mentioned that they did not follow the acceptance criteria of 15% and 20% (LLOQ). The firm further mentioned that during the method development, due to the complexity of the MS/MS component of the GAG assay, it was discovered that these criteria could not be reliably met and they extended the acceptability criteria for accuracy to <20% deviation (<25% for LLOQ).

OSIS evaluation:

During the inspection, the firm mentioned that the 20% (25% LLOQ) run acceptance criteria was decided based on the CAP requirement and that the firm is using the same criteria for all analysis. OSIS recommends that the review division request a complete list of accepted runs based on the 15% (20% LLOQ) acceptance criteria during method validation and sample analysis.

Observation 6

The initial concentration values between 400ug/ml (the upper limit of quantification) and 500ug/mL were not diluted into the

calibration curve range and reassayed. These initial values were reported as the final data.

Firm response:

The firm mentioned that despite that the highest calibrator used in the study was 400ug/mL, during validation 500ug/mL was validated as an upper limit of quantification (ULOQ).

OSIS evaluation:

I verified that the linearity was demonstrated up to 500ug/ml during the method validation. However, during the sample analysis, the highest concentration of the calibrators was 400ug/mL. The reported concentrations between 400-500ug/mL may not be accurate and should not be included in data analysis.

Discussion items

The following items were discussed with the firm during the closeout meeting.

- 1) Access control for the analytical instrument was not maintained. The system allows analysts to potentially delete or alter folders and files.
- 2) There was no available information for instrument qualification, calibration or maintenance for the spectrophotometer that was used for the reported UX003-CL301 creatinine concentrations.
- 3) During sample analysis, differences in IS variability should be evaluated and further investigated if necessary.
- 4) Approaches for evaluating selectivity for endogenous compounds should be explored as part of method validation.
- 5) Only two QC levels (25 and 250ug/mL) were included in the UX003-CL301 sample analysis. The current FDA recommendations states that low, medium, and high QCs should be included in sample analysis runs.
- 6) If a large number of samples require dilution, for future studies, a partial validation to modify the calibration curve range should be considered.

OSIS evaluation

The firm acknowledged these discussion items during the inspection. No further responses to the discussion items were

provided in the firm's response dated 2 Aug 2017. During the inspection, firm mentioned that they will address these discussion items in future studies. Some of these topics are also covered in the Form 483 observations as discussed above.

For discussion item 2, the firm stated that they evaluated creatinine samples that were measured by multiple laboratories, which was coordinated by CAP, and that their results were comparable with those from other labs. Therefore, I concluded that the calibration issue with the spectrophotometer will not affect the validity of the reported creatinine values.

Overall, the discussion items should not affect the data integrity of UX003-CL301.

Conclusion

Significant objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, there was evidence that the objectionable conditions impacted the reliability of the data for study UX003-CL301 (BLA 761047). The following points for the UX003-CL301 analytical data should be considered by the review division in evaluating the analytical data:

1. Due to lack of sample storage and tracking records, I cannot assure the integrity/intactness of subject samples used in the sample analysis.
2. Due to lack of the documentation on reference standard weighing, purity, and associated calculations for stock solution concentrations, I cannot assure the accuracy of reported concentrations.
3. Samples between the 400-500ug/mL concentration range should not be used in data analysis.
4. The review division should request a revised list of accepted runs using the 15% (20% LLOQ) acceptance criteria during validation and sample analysis.
5. The review division should request additional data to support benchtop, freeze/thaw, and long term stability

under the conditions consistent with the sample storage and the handling process during sample analysis.

Final Site Classification:

VAI -

(b) (4)

FEI:

(b) (4)

cc:

OSIS/Kassim/Choe/Haidar/Nkah/Fenty-Stewart/Kadavil

OSIS/DGDBE/Cho/Choi/Skelly/Au/Gupta

OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

Draft: HG 07/26/17, 08/02/17, 8/10/17, 8/14/17, 8/17/2017

Edit: SA 072617, 8/8/17, 8/10/17, SA 8/17/2017; JC 7/31/17, 8/11/17; 8/15/17, 8/17/2017, 8/18/2017

ECMS:

Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity

m/ANALYTICAL SITES/

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(recombinant human beta-glucuronidase

OSI file #:

(b) (4)

FACTS:

(b) (4)

Himanshu Gupta, Ph.D.

Division of Generic Drug Bioequivalence Evaluation

Stanley Au, Pharm.D., BCPS

Division of Generic Drug Bioequivalence Evaluation

Seongeun (Julia) Cho, Ph.D.

Division of Generic Drug Bioequivalence Evaluation

Attachments:

Attachment 1- Form FDA 483

Attachment 2- Form FDA 483 response from firm, dated 2 Aug 2017

Attachment 3- Email from firm regarding full re-installation of Masslynx for audit trails

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/s/

HIMANSHU GUPTA
08/18/2017

STANLEY AU
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SEONGEUN CHO
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Division of Pediatric and Maternal Health Review

Date: 8/14/17 **Date consulted:** 3/29/17

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: MEPSEVII (vestronidase alfa, recombinant human beta-glucuronidase, UX003)

BLA: 761047

Applicant: Ultragenyx

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of Mucopolysaccharidosis type VII (Sly syndrome)

Materials

Reviewed:

- Applicant's submitted background package and proposed labeling for BLA 761047
- DPMH consult request dated 3/29/2017, DARRTS reference ID 4077172
- DPMH review of BRINEURA (cerliponase alfa), BLA 761052, Jane Liedtka, Medical Officer, July 1, 2016.

Consult Question: "We'd like to request for your assistance with the labeling review including the Pregnancy Lactation Labeling Rule (PLLR) implementation in this product label."

INTRODUCTION

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on March 29, 2017, requesting input regarding the applicant's labeling proposal, more specifically the proposed Pregnancy and Lactation (PLLR) language (Sections 8.1/8.2).

REGULATORY HISTORY

On March 16, 2017, Ultragenyx submitted an original BLA for MEPSEVII (vestronidase alfa, recombinant human beta-glucuronidase, rhGUS, UX003). MEPSEVII is an enzyme replacement therapy for the treatment of Mucopolysaccharidosis type VII (Sly syndrome). MEPSEVII was granted Fast Track designation on July 15, 2015.

BACKGROUND

Drug Characteristics

Vestronidase alfa is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line. Vestronidase alfa provides exogenous beta-glucuronidase (GUS) enzyme for uptake into cellular lysosomes and allows for the catabolism of accumulated glycosaminoglycans (GAGs) in affected tissues. It is administered as an intravenous solution every two weeks.

- The average molecular weight is 72,562 Daltons.
- The elimination half-life is 2.5 hours.
- Serious adverse reactions include hypersensitivity reactions and anaphylaxis.

Mucopolysaccharidosis type VII (Sly syndrome) and Pregnancy

Mucopolysaccharidosis type VII (Sly syndrome) is a rare autosomal recessive lysosomal storage disorder. Epidemiologic data are scarce, but it is estimated to occur in 1:300,000 to 1:2,000,000 people worldwide.¹ Sly syndrome is characterized by deficiency of the activity of GUS, one of the enzymes involved in the degradation of three GAGs. Without GUS chondroitin sulfate, dermatan sulfate and heparin sulfate are only partially degraded, and the resulting fragments accumulate in the lysosomes of many tissues, causing cellular dysfunction.² There are a number of genetic mutations that cause Sly syndrome; as a result, the severity of symptoms can range widely. Most patients have cognitive impairment, hepatosplenomegaly, and skeletal dysplasia, however milder cases have been described with near normal intelligence. Severe cases may present as hydrops fetalis and only survive a few months. Milder cases have been described as surviving into their forties.² There are several reports regarding Sly syndrome in pregnancy as a cause of hydrops fetalis and *in utero* diagnosis of Sly syndrome in the fetus.^{3,4,5,6} However, no cases of pregnant women with Sly syndrome were found in a review of the literature.

¹ Muenzer J. Overview of mucopolysaccharidoses. *Rheumatology*. (Oxford) 2011.50(Suppl. 5):4-12.

² Montano A, et al. Clinical course of Sly syndrome (Mucopolysaccharidosis Type VII). *J Med Genet*. 2016. 53:403-418.

³ Den Hollander NS, et al. In-utero diagnosis of mucopolysaccharidosis type VII in a fetus with an enlarged nuchal translucency. *Ultrasound in Obstet and Gynecol*. 2000. 16(1):87-90.

⁴ Venkat-Raman, et al. Recurrent fetal hydrops due to mucopolysaccharidosis type VII. *Fetal Diagnosis and Therapy*. 2006. 21(3):250-254.

⁵ Frints SG, et al. Recurrent progressive non-immune hydrops foetalis: Think of mucopolysaccharidosis type VII. *Genetic Counseling*. 2010. 21(1):133-134.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁷ also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule⁸ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience

Vestronidase alfa administered intravenously to pregnant rats and rabbits during the period of organogenesis showed no maternal toxicity or effects on embryo-fetal development at doses causing serum exposures (based on AUC) up to 1.6 and 10- times, respectively, for rats and rabbits, the exposure at the recommended human dose. The reader is referred to the full Pharmacology/Toxicology review by Yolanda Branch, Ph.D.

Applicant’s Review of Literature

The applicant states, “There is no published literature or reports from our pharmacovigilance database regarding UX003 use in pregnant and lactating women.”

DPMH Review of Literature:

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex⁹ using the search terms, “vestronidase alfa and pregnancy,” “vestronidase alfa and pregnant women,” “vestronidase alfa and pregnancy and birth defects,” “vestronidase alfa and fetal malformations,” “vestronidase alfa and stillbirth,” and “vestronidase alfa and miscarriage.” No reports were found.

Summary

Human pregnancy outcome data for vestronidase alfa were not identified in the published literature, and no cases of pregnancy were identified in the applicant’s pharmacovigilance database. There are no available human data to inform a drug-associated risk of pregnancy-related outcomes. Animal reproduction studies have not shown adverse effects of vestronidase alfa on embryo-fetal development.

⁶ Platzer K, et al. Neonatal manifestation of mucopolysaccharidosis type VII (Sly syndrome) through hydrops fetalis. *Medizinische Genetik*. 2011. 23(1):198.

⁷ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁸ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

⁹ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 4/10/2017

LACTATION

Nonclinical Experience

There is no nonclinical information regarding the presence of vestronidase alfa in milk

Applicant's Review of Literature

The applicant states, "There is no published literature or reports from our pharmacovigilance database regarding UX003 use in pregnant and lactating women."

DPMH Review of Literature:

DPMH conducted a search of *Medications in Mother's Milk*, the Drugs and Lactation Database (LactMed),¹⁰ Micromedex,⁹ and of the published literature in PubMed and Embase using the search terms "vestronidase alfa and lactation," and "vestronidase alfa and breast-feeding." No reports of vestronidase alfa use during lactation were found.

Summary

There are no data on the presence of vestronidase alfa in human or animal milk, its effects on the breastfed infant or on milk production. Chemical properties of vestronidase alfa, including the molecular weight (>800 Daltons) and low oral bioavailability would decrease the possibility of infant exposure through breast milk. Therefore, DPMH recommends the following statement be added to the labeling:

There are no data on the presence of vestronidase alfa in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MEPSEVII and any potential adverse effects on the breastfed infant from MEPSEVII or from the underlying maternal condition.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Vestronidase alfa at intravenous doses up to 20 mg/kg administered weekly to rats prior to mating and after mating on gestation days 6, 9, 12, 15 and 18 (females), [approximately up to 4.5 times (male rats) and 1.6 times (female rats) the human AUC of 57.9 hr µg/mL at the 4 mg/kg dose administered once every other week] was found to have no adverse effect on fertility and reproductive performance of male and female rats. The reader is referred to the full Pharmacology/Toxicology review by Yolanda Branch, Ph.D.

Applicant's Review of Literature

The applicant did not perform a literature search.

¹⁰ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

DPMH Review of Literature:

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, “vestronidase alfa um and fertility,” “vestronidase alfa sodium and contraception,” “vestronidase alfa sodium and oral contraceptives,” and “vestronidase alfa and infertility.”

No reports were found in the published literature related to vestronidase alfa and fertility or interactions with hormonal contraception.

Review of Pharmacovigilance Database

There were no reports related to effects on fertility in the applicant’s pharmacovigilance database.

Summary

There are no human data on the effects of vestronidase alfa on either fertility or hormonal contraception. Animal studies do not indicate adverse effects of vestronidase alfa on either male or female fertility. Therefore, Section 8.3, Females and Males of Reproductive Potential, will not be included in labeling.

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of MEPSEVII labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of labeling was formatted in the PLLR format to include: “Risk Summary,” and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” subsection of labeling was formatted in the PLLR format to include: the “Risk Summary” section.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below).

DPMH discussed our labeling recommendations with the Division on August 9, 2017. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on MEPSEVII use in pregnant women to determine a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, vestronidase alfa-vjvk administered intravenously to pregnant rats and rabbits during the period of organogenesis showed no maternal toxicity or adverse developmental outcomes at doses causing serum exposures (based on AUC) up to 1.6 and 10 times respectively, for rats and rabbits, the exposure at the recommended human dose (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In animal reproduction studies, vestronidase alfa-vjbk administered intravenously to pregnant rats (once a week) and rabbits (once every three days) during the period of organogenesis showed no adverse developmental outcomes at doses up to 20 mg/kg. The 20 mg/kg dose in rats and rabbits provides approximately 1.6 and 10 times the human exposure (AUC) of 57.9 hr^{*} mcg/mL at the 4 mg/kg dose administered once every other week, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of vestronidase alfa-vjbk in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MEPSEVII and any potential adverse effects on the breastfed infant from MEPSEVII or from the underlying maternal condition.

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/s/

CATHERINE A ROCA
08/14/2017

MIRIAM C DINATALE
08/15/2017

LYNNE P YAO
08/18/2017

Addendum to Clinical Inspection Summary

Date	August 15, 2017
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB covering for Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Dina Zand, M.D., Medical Officer, DGIEP
NDA/BLA #	BLA #761047
Applicant	Ultragenyx Pharmaceutical, Inc.
Biologic	rhGUS, vestronidase alfa
NME (Yes/No)	Yes
Therapeutic Classification	Therapeutic Inborn Errors
Proposed Indication	Treatment of Mucopolysaccharidosis type VII (MPS VII, Sly syndrome)
Consultation Request Date	May 4, 2017
Summary Goal Date	August 1, 2017
Action Goal Date	November 16, 2017
PDUFA Date	November 16, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This memo is an addendum to the clinical inspection summary (CIS) for BLA #761047 that was entered into DARRTS on July 21, 2017. The conclusions of the review remain the same. The final establishment inspection reports (EIR) for the clinical sites and the sponsor were not available when the original clinical inspection summary was written, so this review provides the final classifications. The conclusions have not changed after review of the EIRs for Dr. Whitley and for Ultragenyx, the sponsor. The conclusion is that, based on the clinical site and sponsor inspections, the studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.

In addition to the on-site inspections, the review division requested that OSI verify the line listings for the BOT-2 Gross Motor Test by comparing certified source documents submitted by the sponsor to the BLA with line listings submitted for analysis. This memo contains a chart of the details of the verification process and clarifications concerning the point score discrepancies between the source documents and the line listings found during the verification process. The conclusion of the verification process also remains unchanged. As noted in the original CIS, although there were three instances of data transcription errors and unclarity concerning conduct and scoring of the BOT-2, only one of these instances (Subject (b) (6) - Red highlight in the chart on Page 5) resulted in a point scoring change. The significance of this finding is deferred to the review division.

II. BACKGROUND

The sponsor submitted this BLA for a replacement enzyme (beta-glucuronidase) for the indication of treatment of patients with Mucopolysaccharidosis (MPS) Type VII (aka MPS VII, Sly syndrome). Mucopolysaccharidosis (MPS) VII is a progressively debilitating and life-threatening disease that is caused by a deficiency of the lysosomal enzyme beta-glucuronidase. Mutations affecting enzymes involved in the degradation of complex carbohydrates known as glycosaminoglycans (GAGs) lead to chronic cellular accumulation of these substances over many years resulting in tissue damage, dysfunction, and failure of organs and systems throughout the body and ultimately death. Patients present with a phenotype of the MPS syndromes, cataracts, hepatomegaly, splenomegaly, pulmonary symptoms, and growth and cognitive delays. Development of a specific therapy for MPS VII disease has been slow because of the extreme rarity and heterogeneity of the disease. Present treatment usually consists of symptomatic care (frequent surgeries, antibiotics, and bronchodilators) and supportive care (oxygen, assistive devices, pain medications, and physical/occupational therapy).

Biologic: vestronidase alfa, aka rhGUS

Study– Protocol number and title for all studies that were inspected:

Protocol CL301 entitled “A Randomized, Placebo-Controlled, Blind-Start, Single-Crossover Phase 3 Study to Assess the Efficacy and Safety of UX003 rhGUS Enzyme Replacement Therapy in Patients with MPS 7”

Number of subjects: 12 subjects

Number of sites: 5

Number of countries where subjects were enrolled: 1 (U.S. only)

Dates that study was conducted: December 2014 to May 2016

Efficacy endpoints:

1. Urinary glycosaminoglycans (uGAG)
2. Six minute walk test (6MWT), primary clinical endpoint
3. Bruininks-Oseretsky Test of Motor Proficiency (BOT-2), secondary endpoint
 - a. Fine Motor
 - b. Gross Motor

III. RESULTS of clinical inspections (by site):

Name and type of inspected entity/Address	Protocol # /Site #/ # of Subjects	Inspection Dates	Final Classification
CI: Chester Whitley, Ph.D., M.D. University of Minnesota Children's Hospital and Clinics 2450 Riverside Avenue Minneapolis, MN 54555	UX003-CL301 Site 0151 2 Subjects	June 15, 16, 19, 20, 29, 2019	VAI
CI: Paul Harmatz, M.D. UCSF Benioff Children's Hospital Oakland 747 52nd Street Oakland, CA 94609	UX003-CL301 Site 0143 6 Subjects	June 13 to 16, 2017	VAI
Sponsor: Ultragenyx Pharmaceutical, Inc. 60 Leveroni Court Novato, CA 94949	UX003-CL301	June 13 to 20, 2017	VAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

1. Chester Whitley, Ph.D., M.D.**University of Minnesota Children's Hospital and Clinics, Minneapolis, MN 54555**

Final review of the EIR supports the classification of VAI. See CIS entered into DARRTS on July 21, 2017.

**2. Paul Harmatz, M.D., UCSF Benioff Children's Hospital Oakland
Oakland, CA 94609**

Final review of the EIR supports the classification of VAI. See CIS entered into DARRTS on July 21, 2017.

**3. Ultragenyx Pharmaceutical, Inc.
Novato, CA 94949**

Final review of the EIR supports the classification of VAI. See CIS entered into DARRTS on July 21, 2017.

Data verification conducted by the OSI Reviewer

OSI was requested to verify the BOT-2 Gross Motor scores for all 12 subjects in the clinical trial. This was requested because there appeared to be inconsistencies between three data elements: entry of N/A, entry of a blank value on the line listing, and entry of a “zero” in the raw score. Refer to original review for details of the procedure used for verification. Below are the explanations for the discrepancies found during the verification process.

Explanations

1. Red highlight- Subject (b) (6) Subtest 5 Week 24: The correct total points should be 13 but is 12 in CRF and LL. This is the only true error resulting in a point score change that was found in review of the source documents during data verification. The lower, instead of the higher, of two scores was entered into the case report form.
2. Blue highlight- Subject (b) (6) Subtest 6 Randomization: Initial examination of the source seemed to indicate that the correct total points should have been 24 but was 21 in CRF and LL because, for Items 1 and 4, the better scores were not chosen. However, during inspection a reason for the apparent error was obtained as follows:
This subject had the test at randomization performed a second time even though she did not stumble or fall. This was not noted on the source documents. During the inspection, an explanation was provided that the subject “Wanted to do her best”, so a second test was performed even though the subject did not stumble or fall. The reason for the second test was not documented in the source, so it appeared that some of the higher scores were not chosen for determination of point score. When this was clarified during the clinical site inspection of Dr. Whitley, it was determined that, appropriately, only the first trial scores were chosen.
3. Green highlight: Subject (b) (6) Subtest 6 Week 32: This item is correctly scored. The scoring rule states that the score should be N/A or left blank if one item in the subtest is not performed, and this was the correctly done for this item. However, this item was included in the review as an example to show what information may not be captured if the entire subtest is scored as N/A when one item is not performed.
4. For those rows with no highlights: These transcription errors did not result in any point changes. (Point difference LL-Source=0)

Summary Table of Data Verification: Errors, Point Differences

Error	Subject Individual Test Item	Source	CRF * and LL	Point difference LL-Source	Point * details LL/Source	Notes-See above for full explanation
X1	(b) (6) 5-5 W24	3	2	-1	2=1pt 3=2pt	Higher value “3” should have been entered
X2	(b) (6) 5-3 Rand	2.7	3.7	-1: but points in CRF are correct	3.7=2pt 2.7=1pt	
X3	(b) (6) 6-5 Rand	3	2	-1: but points in CRF are correct	2=1pt 3=2pt	
X4	(b) (6) 6-2 W16	26	26.4	0	NONE	Typo ?cause is the Q1 result “15.4
X5	(b) (6) 6-1 W16	114.7	115	0	≥16 is “0” score	Round up?
X6	(b) (6) 5-4 W40	10.5	10	0	None	Max score is 10
X7	(b) (6) 5-6 Rand	26	26		Points “1” in CRF correct	Decimal point error-26 is WAY out of range.
X8	(b) (6) 6-1 Rand	12.2	14.4	-2	14.4=1pt 12.2=3pt	See explanation above concerning unwarranted second attempt.
X9a	(b) (6) 6-2 Rand	29	28	0	NONE	
X9b	(b) (6) 6-3 Rand	18	17	0	NONE	
X9c	(b) (6) 6-4 Rand	10	7	-1	7=3pt 10=4pt	
X10a	(b) (6) 6-1 W32	11.9	blank	-4	Raw 0=0	Points CORRECTLY not entered because one item is N/A
X10b	(b) (6) 6-2 W32	30	blank	-8	Raw 0=0	
X10c	(b) (6) 6-5 W32	4	blank	-2	Raw 0=0	
X11a	(b) (6) 6-1 scren	25.2	blank	0	None	
X11b	(b) (6) 6-1 rand	23.1	blank	0	None	
X9d	(b) (6) 6-1 W16	25	84	0	Both at lowest score	Lower raw is better

*CRF: Case report Form, LL: Line listing

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Acting Branch Chief for Kassa Ayalew, M.D., M.P.H
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

cc:

Central Doc. Rm.
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Review Division /Medical Team Leader/Kathleen Donohue
Review Division /Project Manager/Jennie Doan
Review Division/Medical Officer/Dina Zand
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

SUSAN LEIBENHAUT
08/15/2017

SUSAN D THOMPSON
08/15/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Medical Team Leader
John J. Alexander, MD/MPH, Deputy Director
DPMH

BLA Number: 761,047

Sponsor: Ultragenyx

Drug: MEPSEVII [vestronidase alfa, also referred to as
recombinant human beta-glucuronidase (rhGUS)]

Indication: Treatment of Sly Syndrome

**Dosage Form and
Route of Administration:** Solution for intravenous (IV) infusion

Proposed Pediatric Regimen: 4 mg/kg every two weeks (QOW)

Division Consult Request: The Division of Gastroenterology and Inborn Error
Products (DGIEP) requests DPMH assistance with
pediatric labeling for this new biologic intended to
treat patients with Sly Syndrome.

Background

Vestronidase alfa [recombinant human beta-glucuronidase (proposed trade name MEPSEVII)] is a biologic product undergoing premarket BLA review for treatment of Sly Syndrome in pediatric and adult patients. The sponsor received orphan designation for recombinant human beta-glucuronidase for treatment Sly Syndrome on February 16, 2012. Therefore, requirements under the Pediatric Research Equity Act (PREA) do not apply to this product.

The following summary of Sly Syndrome is taken from the description located in the Online Mendelian Inheritance in Man (OMIM) data base.¹ Sly syndrome (OMIM database entry # 253,220), also known as mucopolysaccharidosis type VII (MPS VII), is an autosomal recessive inborn error of lysosomal metabolism arising from mutations in the beta-glucuronidase gene located at chromosome 7q11. Patients may present with non-immune fetal hydrops, mental retardation of variable severity, coarse facial features, visceromegaly, and dysostosis multiplex. The course is variable with diagnosis being made *in utero* (i.e., in a sibling conceptus a proband) at or near the time of birth for neonates presenting with non-immune hydrops, or in adulthood for patients presenting with mild to moderate visceromegaly (hepatomegaly and/or splenomegaly).

DPMH was consulted by DGIEP to perform a pediatric labeling review. Because the product will be labeled for use in pediatric and adult patients, pediatric labeling information will be distributed throughout labeling, and this review focuses on the Indication (section 1), Dosage and Administration (section 2), Warnings and Precautions (section 5), and Pediatric Use (section 8.4). DGIEP's review of safety (section 6, Adverse Reactions) and efficacy (section 14, Clinical Studies) is not yet complete and review of these sections is deferred to DGIEP.

The labeling recommendations in this review are based on labeling available July 18, 2017. Originally proposed text which is recommended for deletion is noted with ~~strikeout~~. Newly proposed text (by DPMH) is noted in **red bold** font.

A separate review will be performed by the Maternal Health Team to assure conformance with Pregnancy and Lactation Labeling Rule (PLLR) requirements.

1 Indication

MEPSEVII is (b) (4) indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

Reviewer comment: The proposed indication is consistent with the data summary presented by DGIEP at the midcycle meeting on July 17, 2017 and is acceptable.

¹Online Mendelian Inheritance in Man. Entry #: 253,220. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. <http://omim.org/entry/253220>. Website accessed July 10, 2017.

2 Dosage and Administration

2.1 Recommended Dosage

The recommended dosage of MEPSEVII is 4 mg/kg administered by intravenous infusion every two weeks.

(b) (4) 30 to 60 minutes prior to the start of the infusion [see *Dosage and Administration* (2.2)].

Administer the infusion over approximately 4 hours. (b) (4) **Infuse the first 2.5% of the total volume over the first hour.** After the first hour, (b) (4) increase (b) (4) **the infusion rate as tolerated in order to complete infusion over the following 3 hours,** (b) (4) according to the recommended rate guidelines in Table 1 [see *Dosage and Administration* (2.3)].

MEPSEVII (b) (4) a healthcare professional (b) (4).

2.2 Premedication

(b) (4)

- (b) (4) a non-sedating antihistamine with or without an anti-pyretic medication 30 to 60 minutes prior to the start of the infusion.
- Follow the instructions in Table 1 for the rate of infusion [see *Dosage and Administration* (2.3)].
- Observe patients closely during the infusion and following the infusion for a minimum of (b) (4) 60 min for the development of (b) (4).
- (b) (4)

2.3 Preparation Instructions

Prepare MEPSEVII according to the following steps using aseptic technique:

1. Determine the number of vials to be diluted based on the patient's weight and the recommended dose of 4 mg/kg.

(b) (4)

2. Remove the (b) (4) number of vials from the refrigerator to allow them to reach room temperature. Do not heat, microwave or shake vials.
3. (b) (4) 1:1 dilution (b) (4) 0.9% Sodium Chloride Injection, USP (b) (4)

(b) (4)

. More than 1:1 dilution may be used if patient can tolerate additional infusion volume, taking into consideration cardiac function and fluid status. (b) (4)
 at room temperature.

4. Prior to withdrawing MEPSEVII from the vial, visually inspect the solution for particulate matter and discoloration. Because this is a protein solution, slight flocculation (thin translucent fibers) may occur. The MEPSEVII solution should be colorless to slightly yellow. Discard if the solution is discolored or if there is particulate matter in the solution.
5. Slowly withdraw MEPSEVII from the appropriate number of vials using caution to avoid excessive agitation and any air or frothing. A sufficiently large needle (18 gauge) should be used to minimize bubbles in the solution.
6. Slowly add MEPSEVII to the infusion bag using care to avoid agitation, ensuring liquid to liquid contact without generating bubbles or turbulence.
7. Gently rock the infusion bag to ensure proper distribution of MEPSEVII. Do not shake the solution.

Table 1. Recommended Infusion Rate Schedule by Patient Weight for Administration of MEPSEVII at Recommended Dose of 4 mg/kg

Patient Weight Range (kg)	Total MEPSEVII Dose Range (mg)	Total MEPSEVII Volume (rounded) (ml)	(b) (4)	Total Infusion Volume (infused over 4 hours) (mL)	Infusion Rate for 1 st hour (2.5%) (ml/h)	Infusion Rate for subsequent 3 hours (97.5%/3) (ml/h)
3.5-5.9	14-23.6	10		20	0.5	6.5
6.0-8.4	24-33.6	15		30	0.8	9.8
8.5-10.9	34-43.6	20		40	1	13
11.0-13.4	44-53.6	25		50	1.3	16.3
13.5-15.9	54-63.6	30		60	1.5	19.5
16.0-18.4	64-73.6	35		70	1.8	22.8
18.5-20.9	74-83.6	40		80	2	26
21.0-23.4	84-93.6	45		90	2.3	29.3
23.5-25.9	94-103.6	50		100	2.5	32.5
26.0-28.4	104-113.6	55		110	2.8	35.8
28.5-30.9	114-123.6	60		120	3	39
31.0-33.4	124-133.6	65		130	3.3	42.3
33.5-35.9	134-143.6	70		140	3.5	45.5
36.0-38.4	144-153.6	75		150	3.8	48.8
38.5-40.9	154-163.6	80		160	4	52
41.0-43.4	164-173.6	85		170	4.3	55.3

Patient Weight Range (kg)	Total MEPSEVII Dose Range (mg)	Total MEPSEVII Volume (rounded) (ml)	(b) (4)	Total Infusion Volume (infused over 4 hours) (mL)	Infusion Rate for 1 st hour (2.5%) (ml/h)	Infusion Rate for subsequent 3 hours (97.5%/3) (ml/h)
43.5-45.9	174-183.6	90		180	4.5	58.5
46.0-48.4	184-193.6	95		190	4.8	61.8
48.5-50.9	194-203.6	100		200	5	65
51.0-53.4	204-213.6	105		210	5.3	68.3
53.5-55.9	214-223.6	110		220	5.5	71.5
56.0-58.4	224-233.6	115		230	5.8	74.8
58.5-60.9	234-243.6	120		240	6	78
61.0-63.4	244-253.6	125		250	6.3	81.3
63.5-65.9	254-263.6	130		260	6.5	84.5
66.0-68.4	264-273.6	135		270	6.8	87.8
68.5-70.9	274-283.6	140		280	7	91

Reviewer comment: DPMH would like to inquire if the formatting for Table 1 could be revised to enhance readability; for example, to have the rows alternate light shading with no shading.

2.4 Administration Instructions

(b) (4)

1. The rate of infusion (b) (4): in the first hour infuse 2.5% of the total volume, (b) (4) **and infuse** the (b) (4) **remaining volume** over the subsequent three hours (see Table 1). Any dead space in the lines should be accounted for to ensure 2.5% of the total infusion volume is delivered into the patient's bloodstream during the first hour of infusion.
2. Administer the diluted MEPSEVII solution using an infusion set equipped with an in-line, low-protein binding 0.2 micron filter.
3. Do not flush the line containing MEPSEVII to avoid a rapid bolus of infused enzyme. Due to the low infusion rate, additional saline may be added through a separate line (piggyback or Y tube) to maintain sufficient intravenous flow to prevent clotting or line blockage.
4. Do not infuse with other products in the infusion tubing. Compatibility with other products has not been evaluated.
5. Complete infusion of MEPSEVII within (b) (4) hours from the time of dilution. Discard any unused product.

5 Warnings and Precautions

5.1

(b) (4)

(b) (4)

8.4 Pediatric Use

Safety and effectiveness of MEPSEVII have been (b) (4) **established** in (b) (4) pediatric patients (b) (4)

[see Adverse Reactions (6), Clinical Studies (14)].

Summary and Recommendations

DPMH the above recommendations to DGIEP on August 4, 2017 and participated in the labeling meetings of August 8 and August 28, 2017.

The reader is referred to final negotiated labeling which may reflect additional changes.

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/s/

ETHAN D HAUSMAN

08/10/2017

HARI C SACHS

08/12/2017

I agree with these labeling recommendations

JOHN J ALEXANDER

08/14/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 3, 2017
Requesting Office or Division:	Division of Gastrointestinal and Inborn Errors Products (DGIEP)
Application Type and Number:	BLA 761047
Product Name and Strength:	Mepsevii (vestronidase alfa-vjbk) injection 2 mg/mL
Total Product Strength:	10 mg/ 5 mL
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ultragenyx Pharmaceutical Inc.
Submission Date:	March 16, 2017 June 5, 2017
OSE RCM #:	2017-556
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Mepsevii (BLA 761047), a new molecular entity (NME) BLA, submitted on March 16, 2017. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information, container label, and carton labeling for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Ultragenyx Pharmaceuticals submitted a NME BLA for Mepsevii (vestronidase alfa) for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome). DGIEP granted an orphan drug designation on February 16, 2012 and a fast track designation for this application on July 15, 2015.

We identified areas in the Prescribing Information (PI), container label, and carton labeling that can be improved to increase the clarity of information to promote the safe use of the product. Specifically, we recommend revising the dilution statement on both the container label and the carton labeling. We provide letter-ready recommendations

for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed prescribing information, container labels, and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. FULL PRESCRIBING INFORMATION: Section 2.3 Preparation Instructions

1. We recommend reorganizing the calculation of number of vials to be diluted and volume of the calculated dose in mL as the following tracked changes to increase clarity and to prevent any dosing calculation confusion.

1. Determine the number of vials to be diluted based on the patient's weight and the recommended dose of 4 mg/kg, using the following calculations (a-c):-

a. Total dose (mg) = Patient's weight (kg) x 4 mg/kg (Recommended dose)

b. Total number of vials = Total dose (mg) divided by 10 mg/vial

2. Round to the next whole vial and remove the required number of vials from the refrigerator to allow them to reach room temperature. Do not heat, microwave or shake vials.

a. Volume (mL) of calculated dose = Total dose (mg) divided by the 2 mg/mL concentration

(b) (4)

2. We recommend using the terminology "0.9% Sodium Chloride Injection, USP" instead of (b) (4) in order to comply with the USP guidelines.
3. We recommend revising Table 1 to present only critical information to avoid overlooking important information due to crowding. We recommend deleting two columns titled "(b) (4)" and Total infusion volume". For example,

4.2 RECOMMENDATIONS FOR ULTRAGENYX PHARMACEUTICALS INC

We recommend the following be implemented prior to approval of this BLA:

A. Container Label and Carton Labeling:

1. Consider revising the dilution statement from “Dilute before use” to “Must dilute before use” on the principal display panel to minimize the risk of the product being administered without dilution.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mepsevii that Ultragenyx Pharmaceuticals Inc. submitted on March 16, 2017 and June 5, 2017.

Table 2. Relevant Product Information for Mepsevii	
Initial Approval Date	N/A
Active Ingredient	vestronidase alfa-vjbk
Indication	treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome)
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	10 mg/5 mL (2 mg/mL)
Dose and Frequency	4 mg/kg every two weeks
How Supplied	Single-dose 5mL vial in a carton
Storage	For unopened vial- Store under refrigeration at 2°C to 8°C (36°F to 46°F). After dilution –If immediate use is not possible, diluted MEPSEVII may be stored for 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) during administration

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SHERLY ABRAHAM
08/03/2017

SARAH K VEE
08/03/2017

Clinical Inspection Summary

Date	July 21, 2017
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB covering for Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Dina Zand, M.D., Medical Officer, DGIEP
NDA/BLA #	BLA #761047
Applicant	Ultragenyx Pharmaceutical, Inc.
Biologic	rhGUS, vestronidase alfa
NME (Yes/No)	Yes
Therapeutic Classification	Therapeutic Inborn Errors
Proposed Indication	Treatment of Mucopolysaccharidosis type VII (MPS VII, Sly syndrome)
Consultation Request Date	May 4, 2017
Summary Goal Date	August 1, 2017
Action Goal Date	November 16, 2017
PDUFA Date	November 16, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator (CI) sites and the sponsor were inspected for this application. One CI site has the final classification of voluntary action indicated (VAI) and the other CI site has the preliminary classification of VAI. The sponsor has the preliminary classification of VAI. The inspections assessed the conduct and monitoring of the clinical trial including blinding, test article administration, adverse event reporting, six minute walk test performance and results, and blood and urine collection.

In addition to the on-site inspections, the review division requested that OSI verify the line listings for the BOT-2 Gross Motor Test by comparing certified source documents submitted by the sponsor to the BLA with line listings submitted for analysis. Result of the verification showed that there were 17 instances of transcription errors or entry of the worse of the two highest scores, which is not consistent with the protocol. Only one of these instances ((b) (6)) resulted in a point scoring change. The other instance ((b) (6)) of an apparent error was actually not an error. What appeared to be an incorrect scoring was actually correct, but the rationale for the scoring had not been recorded on the source record, a violation of Good Clinical Practices (GCP). This issue was discovered during inspection and was a verbal observation at the site. In addition to the transcription errors, there was some confusion at the sites concerning instructions for total point scoring. Discrepancies noted between source and line listings and OSI reviewer remarks resulting from difficulty with the rule for total point

scoring when any item in the subtest is determined to be N/A may be important to the review division, so they are described in the section on Data Verification.

Although the violations cited during clinical site inspection are not considered to have had an impact on data integrity, the issues identified during the verification process regarding conduct of the BOT-2 Test (e.g. lack of specific instructions in the manual concerning the need for a second test in Subtest 6), suggests that the conduct and scoring of the BOT-2 may be inherently prone to inconsistencies in performance of the test and therefore, may not be a reliable instrument. Also, a suggestion is made that, when the total point score is N/A, that the value be recalculated using the non-zero point scores. It is deferred to the review division and the Clinical Outcomes Assessment Team to assess the reliability of this secondary endpoint to be used in support of the application.

Despite that comments above concerning the BOT-2, based on the clinical site inspections, the studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.

II. BACKGROUND

The sponsor submitted this BLA for a replacement enzyme (beta-glucuronidase) for the indication of treatment of patients with Mucopolysaccharidosis (MPS) Type VII (aka MPS VII, Sly syndrome). Mucopolysaccharidosis (MPS) VII is a progressively debilitating and life-threatening disease that is caused by a deficiency of the lysosomal enzyme beta-glucuronidase. Mutations affecting enzymes involved in the degradation of complex carbohydrates known as glycosaminoglycans (GAGs) lead to chronic cellular accumulation of these substances over many years resulting in tissue damage, dysfunction, and failure of organs and systems throughout the body and ultimately death. Patients present with a phenotype of the MPS syndromes, cataracts, hepatomegaly, splenomegaly, pulmonary symptoms, and growth and cognitive delays. Development of a specific therapy for MPS VII disease has been slow because of the extreme rarity and heterogeneity of the disease. Present treatment usually consists of symptomatic care (frequent surgeries, antibiotics, and bronchodilators) and supportive care (oxygen, assistive devices, pain medications, and physical/occupational therapy).

Biologic: vestronidase alfa, aka rhGUS

Study– Protocol number and title for all studies that were inspected:

Protocol CL301 entitled “A Randomized, Placebo-Controlled, Blind-Start, Single-Crossover Phase 3 Study to Assess the Efficacy and Safety of UX003 rhGUS Enzyme Replacement Therapy in Patients with MPS 7”

Number of subjects: 12 subjects

Number of sites: 5

Number of countries where subjects were enrolled: 1 (U.S. only)

Dates that study was conducted: December 2014 to May 2016

Efficacy endpoints:

1. Urinary glycosaminoglycans (uGAG)
2. Six minute walk test (6MWT), primary clinical endpoint
3. Bruininks-Oseretsky Test of Motor Proficiency (BOT-2), secondary endpoint
 - a. Fine Motor
 - b. Gross Motor

III. RESULTS (by site):

Name and type of inspected entity/Address	Protocol # /Site #/ # of Subjects	Inspection Dates	Classification
CI: Chester Whitley, Ph.D., M.D. University of Minnesota Children's Hospital and Clinics 2450 Riverside Avenue Minneapolis, MN 54555	UX003-CL301 Site 0151 2 Subjects	June 15, 16, 19, 20, 29, 2019	Pending VAI
CI: Paul Harmatz, M.D. UCSF Benioff Children's Hospital Oakland 747 52nd Street Oakland, CA 94609	UX003-CL301 Site 0143 6 Subjects	June 13 to 16, 2017	VAI
Sponsor: Ultragenyx Pharmaceutical, Inc. 60 Leveroni Court Novato, CA 94949	UX003-CL301	June 13 to 20, 2017	Pending VAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Chester Whitley, Ph.D., M.D.**University of Minnesota Children's Hospital and Clinics, Minneapolis, MN 54555**

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator and on records and notes exchanged during these communications. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

At this site 2 subjects were screened, enrolled and completed Protocol UX003-CL301.

Study conduct, including adherence to the protocol and the details concerning conduct of the six minute walk test and the BOT-2 fine and gross motor were reviewed. Source documents were reviewed and compared to line listings from the BLA provided for eligibility criteria, adverse events, and efficacy endpoints.

At this site, Physical Therapists (PTs) were responsible for conducting the 6MWT/2MWT and BOT-2. These tests were done at an off-site physical therapy facility. During the study, the site was provided with a clinical evaluator (CE) worksheet (i.e. source documents) that included the template for the 6MWT, goniometry, and Three Minute Stair climb test. For the first year of the study (until November 5, 2015), sites would either fax or scan and e-mail the clinical evaluator worksheet, the spirometry report, and the BOT-2 forms to the Ultragenyx physical therapy team for quality review. According to the document process workflow sheet, the Ultragenyx monitor was to be copied on the return e-mail. During the monitoring visits, the monitor was to monitor the eCRF against the reviewed CE source documents.

For the BOT-2, the item was performed by the subject, and a raw score was determined and converted into a point score. Certain subtest items could be repeated under specific circumstances. The better of the two results for the item was to be converted to the point score. The raw score for each item and the total point score were entered into the eCRF. In the instruction sheet provided by the sponsor, if the test was performed a second time, the examiners were instructed to cross out the lower raw score in order to keep track of the value that should be entered into the eCRF and be used to determine the point score. For Subtest 6 the instructions were "Conduct the second trial only if the examinee stumbles or falls on the first trial." For Subtest 6, Sites were instructed to document that a subject stumbled or fell in order to explain the performance of a second trial. Subtest 6, Item #1 was the only item in the BOT-2 in which a higher value resulted in a lower point score.

The efficacy data for the 6MWT and the gross and fine motor BOT-2 scores were compared to the scoring sheets and there were no discrepancies between the source documents and the line listings. However, two instances of questionable scoring were noted and discussed with the physical therapist.

1. Concerning scoring of the BOT-2 Subtest 6 for Subject (b) (6) Randomization, it appeared that the most appropriate raw value was not consistently used to determine the highest point value.



Study staff responded that the subject did not stumble or fall during the test, but the subject wanted to do better so was allowed to perform a second trial. The examiner used the better of the raw scores from the two tests to determine the point score. After this occurred, in consultation with the sponsor representative on the same day as the conduct of the test, the examiner was instructed to use only the first trial because the subject did not stumble or fall. So the results from the first trial were scored even though items #1 and #4 had a higher value on the second test. The changes were initialed and dated on the same day as the test occurred, but do not include the reason for the change and there is no written record of the conversation.

Reviewer note: This seems to be a plausible explanation for why the values from the first test only were entered into the eCRF and scored; however, it is poor trial conduct because of the lack of documentation for the change. Also, because this was the randomization assessment, bias, even unintentional, cannot be ruled out. Given that this visit was clearly pre-treatment, it is possible that the lower score would be chosen so that improvement at a later visit would be demonstrated.

2. For Subject (b) (6) Week 32 score, the total score is N/A even though scoring of individual items would result in a 14. The examiner replied that the instructions were to score the total as N/A if any of the individual items were N/A



Reviewer note: This confusion concerning how to score total points in a subtest when one or more items is N/A was seen at the Harmatz site in scoring of a fine motor test and is discussed below in relation to Subtest 6. This subtest is actually scored correctly as total points of N/A, according to sponsor instructions provided in an information request on June 21, 2017. However, note that some information is lost in assigning a total score of N/A. This N/A is different than most of the instances of N/A which are a result of one value of zero and all others as N/A (see discussion under Data Verification section below)

With the exception of the issues with the BOT-2 noted above, the studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

No Form FDA 483 was issued,; however, the inspection was given a preliminary classification of VAI based on observations conveyed verbally, including: some evaluations were performed out of window or late; infusion rates were not always recorded by the infusion nurses; not all source records identified who was capturing data, e.g. infusion vital signs by infusion nurses; there was no documentation of final disposition for one dose that was withheld due to rash; and, the consent form lacked specific language on who to contact regarding subjects' rights and extent of confidentiality of records.

The lack of documentation of the reason for the change in scoring of the BOT-2 Subtest 6 for Subject (b) (6) Randomization noted on the previous page was also cited. This appeared to be the only observation related to this type of lapse of GCP.

**2. Paul Harmatz, M.D., UCSF Benioff Children's Hospital Oakland
Oakland, CA 94609**

For Protocol UX003-CL301 at this site, six subjects were screened, enrolled, and completed the study. The records for all subjects were reviewed in depth and compared to line listings from the BLA. The FDA field investigator covered subject protection, protocol adherence, and investigational product administration and accountability. The FDA field investigator focused on the training of study staff and conduct of the Six Minute Walk Test (6MWT) and the BOT-2. The 6MWT was conducted at the research facility and the BOT-2 was conducted by physical therapists at (b) (4) at an offsite location. One of the physical therapists was interviewed during the inspection. No supplemental oxygen or bronchodilators were needed by the subjects for the 6MWT. There was no evidence of unblinding or under-reporting of adverse events. Blood for antibody determination was drawn at appropriate time points.

During the inspection, the study coordinator stated that a checkbox of N/A in the e-CRF covered all items in the subtest. Dr. Harmatz and his team realized that, if this checkbox was used to mark all items in the subgroup as N/A, then the individual N/A items would show as blank to the sponsor and subsequently to FDA. When the items were put in individually as N/A, then they would show up as expected as N/A to sponsor and FDA.

There were discrepancies between the data in the line listings and the source documents as noted on the Form FDA 483 which was issued for inadequate and/or inaccurate records. Specifically the following discrepancies were noted:

- A. Subject # (b) (6) source document showed that the BOT-2, Week 24 Visit, test date 9/18/15, had raw scores of ≥ 21 for Subtest 1 (Fine Motor Precision) items #3 and 4. The Case Report Form presented both items in Subtest 1 as 0.

Reviewer comment: The raw scores were 72 and 21 respectively. This is a transcription error between source and CRF. The raw score is the number of errors and the point score is a rating in which no errors (zero raw score) is a point score of 7 whereas a high number of errors results in a raw score of zero. In this case, the point score of zero was entered correctly, so it did not result in a point score error.

- B. Subject # (b) (6) source document showed that the BOT-2, Screening Visit, test date 5/6/15, had raw scores of N/A for all items of Subtest 5 (Balance) and Subtest 6 (Running Speed and Agility), except item #1 of Subtest 6 was listed as 25.2. The Case Report Form presented all items of Subtests 5 and 6 as blank.
- C. Subject # (b) (6) source document showed that the BOT-2, Randomization Visit, test date 5/15/15, had raw scores of N/A for all items of Subtest 5 and 6, except item #1 of Subtest 6 was listed as 23.1. The Case Report Form presented all items of Subtests 5 and 6 as blank.
- D. Subject # (b) (6) source document showed that the BOT-2, Randomization Visit, test date 6/4/15, had raw scores of N/A, 0, 2, N/A, and 2 for Subtest 3 (Manual Dexterity) items #1-5, respectively. The Case Report Form presented all items in Subtest 3 as blank.

Reviewer comment: The site replied that Items B, C, and D were a result of a misunderstanding by the study coordinator of how data was to be recorded in the CRF when

the subject was able to complete some, but not all of the items in the subtest. In the above cases, the raw score was scored as the point score of zero and entered correctly, so it did not result in a point score error.

- E. Subject # (b) (6) source document showed that the BOT-2, Week 32 Visit, test date 1/14/16, had raw scores of 1, 2, 1, and 2 for Subtest 3 items #2-5, respectively. The Case Report Form presented the items in Subtest 3 as 0, 0, 0, and 1, respectively

Reviewer comment: The site replied that the point score instead of the raw score was recorded in the raw score field due to a transcription error. This would have changed the point score from N/A to 1 for this visit.

Dr. Harmatz responded adequately with explanations and proposed adequate corrective action in his response of June 28, 2017. Because there were no point score changes with these errors, there was no impact on efficacy.

3. Ultragenyx Pharmaceutical, Inc. Novato, CA 94949

Note: Observations below for this sponsor inspection are based on review of the Form FDA 483 and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocol UX003-CL301 including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites, and handling of adverse events and other sponsor/monitor related activities. There was no evidence of underreporting of adverse events.

Review of the sponsor documents noted the following deficiencies that were cited on the Form FDA 483:

1. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND. Specifically, for Study Site 143, the Visit log shows Interim Monitoring Visits on but not limited to the following dates: June 1-2, 2015; August 12-14, 19, 2015; September 14-15, 2015; and October 6-7, 2015 and for Site 155, the visit log shows Interim Monitoring Visits including September 14-16, 2015. However, the Sponsor was unable to provide the above reports to the FDA field investigator with the above mentioned Interim Monitoring Visit Reports for these sites on these dates.
 2. Failure to ensure proper monitoring of the study. Specifically, for Site 143, Interim Monitoring Visits have Reports for visits on February 22-23, 2016 and March 28-30, 2016, but they were not signed off by the required personnel.
- The sponsor responded in a letter on June 29, 2017 stated that they have instituted

corrective actions. They were not able to locate the missing monitoring reports for Site 143, but were able to locate the report for Site 155. However, they did not include the report in their response.

Reviewer comment: The above lack of compliance is not consistent with good clinical practices. As noted above and in the data verification section, there was confusion concerning the scoring for the BOT-2, and inadequate monitoring may have contributed to this. Other sponsor responsibilities appear to have been conducted adequately.

The studies appear to have been conducted adequately, and, with the exception of the BOT-2 scoring, the data generated by this sponsor may be used in support of the respective indication.

Data verification conducted by the OSI Reviewer

Description of the BOT-2

The BOT-2 consists of eight subtests, four of which were used in this study. The BOT-2 fine motor includes Subtest 1, Fine Motor Precision consisting of seven items and Subtest 3, Manual Dexterity consisting of 5 items. The BOT-2 Gross Motor consists of Subtest 5, Balance consisting of 9 items and Subtest 6, Running Speed and Agility consisting of 5 items. If the subject is able to follow instructions and is physically able, each of these four subtests is conducted at least once during the eight study visits (Screening, randomization, and Weeks 8, 16, 24, 32, 40 and 48). The physical therapists responsible for conducting the tests were trained by the sponsor and provided with the instruction manual. Instructions were provided for conducting a second trial. For Subtest 5 the instruction was “Conduct the second trial only if the examinee does not earn the maximum score on the first trial.” For Subtest 6 the instructions were “Conduct the second trial only if the examinee stumbles or falls on the first trial.” The sites were instructed to state explicitly on the score sheet whether the subject stumbled or fell.

Reviewer comment: The instructions for the requirement for the second test for Subtest 5 are straightforward, but for Subtest 6 appear vague. The five items in Subtest 6 are shuttle run, stepping sideways over a balance beam, one legged stationary hop, one-legged side hop, and two legged side hop. There is no definition of “stumble” in either the proprietary BOT-2 Manual or in additional instructions provided by the sponsor for conducting and scoring the test. While it may be obvious if someone falls while running, it may be difficult to determine whether someone has stumbled while hopping.

Background of request to verify BOT-2 Gross Motor

Due to inconsistencies noted at Site 143 above, OSI was requested to verify the BOT-2 Gross Motor scores for all 12 subjects in the clinical trial. This was requested because there appeared to be inconsistencies between three data elements: entry of N/A, entry of a blank value on the line listing, and entry of a “zero” in the raw score.

In the sponsor response to an information request on June 21, 2017, the sponsor responded that the differences among 0 (zero) and N/A (or NA) or a blank data field as

recorded on the source documents (e.g. the BOT-2 Record Form for BOT-2 assessments) or in the EDC as follows:

- 0 (zero): Zero represents a raw score for a test that was performed and for which the result of the test was zero. The meaning of zero is dependent upon the specifics of the test items.

- N/A (or NA) or Blank data field: These terms indicate that a specific item or subtest was either not performed by a subject or a score was not available. Both terms were used variably in the source documents and hence in the EDC and the listings.

Concerning total scores for Subtests in which any of the values are N/A, the sponsor replied that, *when a test was partially performed, the raw score was to be recorded on the source documents and entered in EDC for completed items of the subtest. However the Point Score-Total, Scale score and Age Equivalent for that subtest could not be derived since not all test items were completed in that subtest. (Italics added for emphasis).*

Reviewer comment: *The validity of this method of scoring is deferred to the review division. It is this reviewer's opinion that lack of calculation of a total score when any item in the subtest is N/A results in loss of some information about subject performance. Contrast below example for N/A that was a result of one "zero" value and all other N/As with the example of Subject (b) (6) Subtest 6 week 32 on Page 5 in which, if all scores had been used, there would have been a total score of 14.*



Verification Process and Results

For the verification process, individual points of raw data were first verified by comparing source to Line Listing 16.2.6.7.4. Next, for the discrepancies noted between the source and the line listings, the eCRF was compared with the source. This comparison confirmed that all errors originated with the eCRF entry and were carried forward into the sponsor data base and then to the line listings. There were no discrepancies noted between the eCRF and the line listings generated by the sponsor database.

For all errors made at the study site by study staff, some were transcription errors and others were errors in choice of the incorrect value if a second test had been conducted for an item. There were a total of 17 errors, only 2 of which resulted in a change in the point score as noted below.

1. Subject (b) (6) Correct total points for subtest 5 week 24 is 13 but is 12 in CRF and line listings

Reviewer note: This appears to be an error in crossing out the higher of the two scores

(b) (6)

2. Subject (b) (6): It appeared that the correct total points for Subtest 6 randomization should be 24 but is 21 in CRF and line listing.

Reviewer note: The above discrepancy is explained on Page 5 above.

Subject (b) (6) Subtest 6 Week 32 noted on Page 6 of this review was detected originally as a data transcription error, but was correctly scored as N/A according to instructions. The individual raw scores were blank in the case report form (and database) because N/A was autopopulated as noted in the inspection at Harmatz site, second paragraph Page 6.

Because additional discrepancies might exist due to errors in adding the individual item point scores or other errors in point scoring, source documents were compared with Line Listing 16.2.6.7.1 for the verification of the total points. All the data for the total point score could be verified, including the point score of N/A or ND when at least one of the items in the Subtest was designated as N/A in the source.

Reviewer note: As mentioned above, the assignment of a total score of N/A when any value in the subtest is N/A seems, to this reviewer, to result in a loss of information. Although most of the instances of N/A were a result of all N/A, blanks and zeros, some of the N/A totals would have had higher scores if the totals had been added. The validity of the use of the BOT-2 is deferred to the review division and the COA team; however, below are the subject scores that would have resulted in scores other than zero if instructions for scoring were to add the individual point scores and assign a value of zero to N/A for the item which the subject did not perform:

1. Subject (b) (6) Week 48 total score 4 for Item 2.
2. Subject (b) (6)
 - a. Subtest 6, Week 8 Item 5 was N/A, but all four other values totaled 21
 - b. Subtest 6, Week 24 Items 3-5 were N/A, but other values totaled 13
 - c. Subtest 6, Week 32, Items 3-4 were N/A, but other values totaled 14. This is noted above and was detected in the first verification because values were in the source, but were blank in the line listing
3. Subject (b) (6)

- a. *Subtest 5 Week 32 Item 1 is one*
- b. *Subtest 5 Week 40, Item 2 is four*

The appropriateness of conducting an analysis using the above point values in lieu of the N/A is deferred to the review team.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
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/s/

SUSAN LEIBENHAUT
07/21/2017

SUSAN D THOMPSON
07/21/2017

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Application: BLA 761047

Application Type: New Molecule Entity

Drug Name(s)/Dosage Form(s): Mepsevii (vestronidase alfa) Injection 10mg/5mL (2mg/mL)

Applicant: Ultragenyx

Receipt Date: March 16, 2017

Goal Date: Nov. 16, 2017

1. Regulatory History and Applicant's Main Proposals

[IND 123788](#)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 5, 2017. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS**”

Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning.***" This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment: *Phone number was not included from Applicant*

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS.”** This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment: 5.1 ICV Access Device-related Compliance- does "related" have to be capitalized?
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading **“FULL PRESCRIBING INFORMATION: CONTENTS*”** must be followed by an asterisk and the following statement must appear at the end of the TOC: **“*Sections or subsections omitted from the full prescribing information are not listed.”**
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *Applicant didn't include statement. Added in PI*

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JENNY N DOAN
05/04/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
BLA# 761047	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Mepsevii Established/Proper Name: vestronidase alfa Dosage Form: Solution for infusion Strengths: 10 mg per 5mL Route of Administration: Intravenous		
Applicant: Ultargenyx Agent for Applicant (if applicable):		
Date of Application: Mar. 16, 2017 Date of Receipt: March 16, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: Nov. 16, 2017		Action Goal Date (if different):
Filing Date: 05/15/17		Date of Filing Meeting: 04/17/17
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Cerliponase alfa is indicated for the treatment of patients with CLN2 disease, also known as tripeptidyl peptidase-1 (TPP1) deficiency.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i>		

http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .	
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Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
Review Classification: <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority (requesting for Ped Rare Dz priority voucher) <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input checked="" type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): (b) (4)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i></p>					
<p>Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</p> <p><i>If no, ask the document room staff to make the appropriate entries.</i></p>		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy		YES	NO	NA	Comment
<p>Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p> <p>If yes, explain in comment column.</p>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p>If affected by AIP, has OC been notified of the submission? If yes, date notified:</p>		<input type="checkbox"/>	<input type="checkbox"/>		
User Fees		YES	NO	NA	Comment
<p>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</p>		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i></p>		<p>Payment for this application (check daily email from UserFeeAR@fda.hhs.gov):</p> <p> <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required </p>			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i></p>		<p>Payment of other user fees:</p> <p> <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears </p>			
<p><u>User Fee Bundling Policy</u></p> <p><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</p>		<p>Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i></p> <p> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No </p>			
505(b)(2)		YES	NO	NA	Comment

(NDAs/NDA Efficacy Supplements only)																			
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>	x																
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>																	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>																	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	<input type="checkbox"/>	<input type="checkbox"/>																	
<p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>																			
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	<input type="checkbox"/>	<input type="checkbox"/>																	
<p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>				Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																			
Exclusivity	YES	NO	NA	Comment															
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																			
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																
If yes , # years requested:																			

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Claims 7 years of market exclusivity
<i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> <i>Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	No patent information has been included as this submission is not a 505(b)(2) application.
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Product has an orphan drug designation therefore exempt from PREA requirements for the current application.
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Sponsor submitted a Pharmacovigilance Plan (Non-REMS)
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels (carton and vial) <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (administration kit, UDI sticker, solution vial)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		4 mg per kg body weight administered every two weeks as an intravenous (IV) infusion, over approximately 4 hours
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No patient labeling; administered by healthcare provider via (b) (4)

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

				intracerebroventricular
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DNP, COA, OSI, OSE, OPDP, OOPD,
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): May 9	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>			None

ATTACHMENT

MEMO OF FILING MEETING

DATE: 04/17/2017

BACKGROUND: Filing Meeting for UX0003 BLA 761047

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jenny Doan	Y
	CPMS/TL:	Brian Strongin	
Cross-Discipline Team Leader (CDTL)	Kathleen Donohue		
Division Director/Deputy	Dragos Roman		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Dina Zand	Y
	TL:	Katie Donohue	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Max Van Tassell and Bo Chi	Y
	TL:		
Clinical Pharmacology	Reviewer:	Christine Hone	Y
	TL:	Yow-Ming Wang	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	Jee-Eun Lee/Nitin Mehrotra	Y
Biostatistics	Reviewer:	Feiran Jiao	Y
	TL:	Yeh-Fong Chen	Y

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Nonclinical (Pharmacology/Toxicology)	Reviewer:	Yolanda Branch	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Product Quality (CMC) Review Team:	ATL:	Cris Ausin	Y
	RBPM:	Truong Quach	Y
• Drug Substance	Reviewer:	Max Van Tassell	Y
• Drug Product	Reviewer:	Bo Chi	Y
• Process	Reviewer:	Rukman De Silva (quality) and Dpeh Palmer (DMA QAL)	Y
• Microbiology	Reviewer:		
• Facility	Reviewer:	Ruth Moore/Peter Qiu	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:	Jacek Cieslak	Y
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	N/A	
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Adewale Adeleye	
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sherly Abraham	
	TL:	Sarah Vee	
OSE/DRISK (REMS)	Reviewer:	Bob Pratt	
	TL:	Donella Fitzgerald	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Susan Leibenhaut	
	TL:	Susan Thompson	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> Clinical Assessment 	Reviewer:	Michelle Campbell	Y
	TL:	Elektra Papadopoulos	
<ul style="list-style-type: none"> Cardiorenal 		Fortunato Senatore/Martin Rose	
<ul style="list-style-type: none"> DPMH 		Pediatric – Ethan Hausman/Hari Sachs Maternal Health – Catherine Roca/Jane Liedtka	
Other attendees	Rare Disease Program- Larry Bauer		
	OOPD- John Milto		

FILING MEETING DISCUSSION:

GENERAL <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> 		<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English 		<input type="checkbox"/> YES

translation? If no, explain:	<input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments List comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments

CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 06/20/17 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

JENNY N DOAN
05/04/2017