DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
CBER, OTRR
Division of Therapeutic Proteins
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MEMORANDUM

DATE: June 17, 2002

FROM: Blair A. Fraser, Ph.D., DTP, OTRR

THROUGH: Amy Rosenberg, M.D., Director, DTP

SUBJECT: BL125058, Original Submission
Aldurazyme (recombinant human alpha-L-iduronidase) for
Mucopolysaccharidosis - I
BioMarin Pharmaceuticals, Inc.

TO: File

CC: Melanie Hartsough, Ph.D., Chair

A. INTRODUCTION

I 1. Summary

Aldurazyme (laronidase) is recombinant human alpha-L-iduronidase or rhIDU. Aldurazyme is supplied as a liquid concentrate for infusion at a dose of 100 units per kilogram of patient body weight. Each vial delivers 5 mL of Aldurazyme at a concentration of 100 units/mL. The drug substance is a purified recombinant form of the naturally occurring human glycoprotein, alpha-L-iduronidase (IDU). rhIDU is isolated from cell culture supernatant following growth of a Chinese Hamster Ovary (CHO) cell line transfected with a recombinant expression vector containing the cDNA coding region for human alpha-L-iduronidase (IDU). rhIDU is purified ----------
----------. The purified protein is formulated with polysorbate 80 in a sodium chloride and sodium phosphate buffer. The drug product is a liquid solution that is to be diluted for intravenous administration.

I 2. Review Issues and Comments

1. Please note that expiration dating will be granted at licensure, based upon real time data submitted to the application for those three final container drug product lots using the identical container closure.

2. Because there are ------ drug product manufacturers, please place one drug product lot, manufactured at each contractor, on stability at 2–8°C, annually.

3. Please provide information which confirms that the assays used for release testing of drug substance provide an assurance that all disulfide bonds have been correctly formed.

4. Please provide [

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5. Please provide ----------
Study 99TRN095, for:

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6. Please clarify the following:

a. Section 1.7.1.12, ---------- refers to Appendix IIC-89 for the SOP QCU-07-031. Appendix IIC-89 contains QCU-08-037. Table IIE-1, Drug Product Test Methods and Specifications, refers to the ----------SOP QCU-08-037.

b. Table IIC-83 and Table IIQ-4 do not compare.

c. Table IIE-3 and Table IIQ-5 do not compare.

d. In Figure 6, Appendix IIC-69, Validation Study 99TRN095, Aldurazyme [
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e. Refer to Appendix IIC-51, Method Validation Report QC-IDU-029-AVR, Figure 1. ---------- is unclearly labelled.

7. Regarding reference materials,

a. Will the reference lot, ----------, serve as the primary reference material, a working drug substance reference material, and a working reference drug product material?

b. Please clarify the distribution, storage, resupply, and accountability procedures for distributing working reference drug product materials to be used by contract drug product manufacturers.

c. As part of the reference material requalification of future working reference materials, please [
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d. Include values to consider for peptides P-3, P-35, P-64, and (Cys516 ---Cys552) in evaluation of the peptide map for requalification of future working reference materials.

8. For formulated bulk drug substance, in light of mean +/- three standard deviations, please explain and justify each of the following:

a. the upper limit specification for Polysorbate 80.
b. the limit specifications for ----------
c. the upper limit specification for ----------.
d. the upper limit specification for Chinese Hamster Ovary Cell Protein (CHOP) ----------
e. the lower limit specification for activity by ----------.

9. Forced ---------- of rhIDU causes no change in specific activity. Would a raw materials specification ---------- content in Polysorbate 80 be needed?

Review Issues that prompted requests to sponsor.

1. Regarding Drug Product Manufacturing,

a. Due to the nature of the manufacturing operation at ----------, exemption from the 21 CFR 610.12 requirement for bulk sterility testing is requested.
DMPQ needs to evaluate this request.

b. In this license application, Drug Substance Manufacturing operations will be performed at BioMarin Pharmaceuticals, Novato, CA, and Drug Product Manufacturing operations performed at Genzyme Corporation, Allston, Massachusetts 02134.

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DARP will need to determine appropriateness of this request and decide what information needs to be requested to support temporal changes in Drug Manufacturing operations.

DMPQ will need to assess the adequacy of the Genzyme drug manufacturing information provided in this submission.

DMPQ will need to assess the ---------- DMF for adequacy.

2. Updated data from the stability studies will be provided during the review of this application.

a. At time of submission, the application contains data for ------ lots of drug substance stored for up to ------ months at 2-8°C. Twelve month data will be provided as an amendment during the application review to support expiration dating of twelve months for the formulated bulk drug substance when stored at 2-8°C. (Twelve month data collection will begin by end of January, 2002; ---------- month data collection will begin by end of July, 2002.)

b. Updated data will be provided for all drug product lots stored at 2–8°C. At time of submission, data was provided for drug product lots stored at 2–8°C for between ---------- months using ----------. Expiration dating for final container drug product is requested for 24 months stored at 2–8°C.

Expiration dating will be granted at licensure, based upon real time data for the three most recently manufactured final container drug product lots using the identical container closure. Sponsor will need to submit results of ongoing stability studies for these drug product lots as they become available to support extension of the expiration date to 24 months. Data may be submitted to Annual Report with extension on license anniversary.

Stability data from a pilot manufacturing scale can be used to support the dating period for commercial product, if the pilot material was comparable (physicochemical/biological activity) and in the same container-closure system.

c. The sponsor proposes to place ----- drug product ----- on stability at 2–8°C annually

in accordance with the protocol. Vials will be stored in the ---------- only.

Because there are -----drug product manufacturers, the sponsor needs to place ----- drug product ------ manufactured at each contractor, on stability at 2–8°C, annually.

3. Characterization and Specification

a. The ---------- content of rhIDU was initially determined colorimetrically using [

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as a measure of drug substance consistency and as a measure of of product-related substances and product-related impurities. This specification should then be added to the reference material requalification.

Please modify the Certificate of Analysis for bulk drug substance to include specifications ----------per mole rhIDU.

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c. As in Figure 6, Appendix IIC-69, Validation Study 99TRN095, please provide the clearly labelled ----------

[

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4. Clarification of document,

a. Section 1.7.1.12, ----------, refers to Appendix IIC-89 for the SOP QCU-07-031. Appendix IIC-89 contains QCU-08-037. Table IIE-1, Drug Product Test Methods and Specifications, refers to the ---------- SOP QCU-08-037. *Please clarify.*

b. Table IIC-83 and Table IIQ-4 do not compare. *Please clarify*.

c. Table IIE-3 and Table IIQ-5 do not compare. *Please clarify*.

d. In Figure 6, Appendix IIC-69, Validation Study 99TRN095, Aldurazyme monomer ----------

e. Refer to Appendix IIC-51, Method Validation Report QC-IDU-029-AVR, Figure 1. ----------. *This figure needs to be labelled clearly and correctly*

5. Regarding reference materials,

a. Will the reference lot, ----------, serve as the primary reference material, a working drug substance reference material, and a working reference drug product material?

b. Please clarify the distribution, storage, resupply, and accountability procedures for distributing working reference drug product materials to be used by contract drug product manufacturers.

c. As part of the reference material requalification of future working reference materials, please include [

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d. As part of the reference material requalification of future working reference materials, please include the specification for ----------

e. Include values to consider for ---------- for requalification of future working reference material.

6. For formulated bulk drug substance, please explain and justify each of the following:

a. the upper limit specification for Polysorbate 80 exceeds the upper statistical limit of mean plus three standard deviations.
b. the specifications for ---------- lie outside the statistical limits of mean about three standard deviations.
c. the upper limit specification for ---------- exceeds the upper statistical limit of mean plus three standard deviations.
d. the upper limit specification for Chinese Hamster Ovary Cell Protein (CHOP) -------- exceeds the upper statistical limit of mean plus three standard deviations.
e. the lower limit specification for activity by ---------- exceeds the lower statistical limit of mean minus three standard deviations.

7. Forced ----------of rhIDU with the ----------, causes no changes in specific activity.

In light of this observation, is a raw materials specification for ---------- content in Polysorbate 80 warranted? Please explain.

B. BODY OF DATA

S. DRUG SUBSTANCE

S 1. General Information

S 1.1 Nomenclature

International Non-Proprietary Name (INN) Iaronidase
National Approved Name
United Stated Adopted Name (USAN): laronidase
Trivial name or chemical description Recombinant human alpha-L-iduronidase
Proposed Trade name of drug product Aldurazyme

S 1.2 Structure

Human Recombinant alpha-L-iduronidase (EC 3.2.1.76) is encoded by a human cDNA predicting a protein of ------ amino acids. After signal ---------- 628 amino acid protein with an expected molecular weight of 70,000 daltons.

Amino acid sequencing reveals ---------- at the N-terminus giving an expected protein of 628 amino acids. The protein has ---------- of the mature protein (----------), a naturally-occurring polymorphism occurring in 10% of the population.

All six potential N-glycosylation sites, asparagine residues, are modified in the recombinant protein; the ----------sites contain one or more mannose-6-phosphate residues responsible for high affinity uptake into cells. Because of the carbohydrate modifications, the recombinant protein displays an apparent molecular weight of 83,000 daltons.

Subsequent to targeted transport into the lysosome, the alpha-L-iduronidase is further processed by proteolytic cleavage between Gly 106 and Leu 107. The enzyme, spanning residues 107 through 653, remains active and has a half-life of around 9 days following uptake into fibroblasts.

S 1.3 General Properties

S 2. Manufacture

S 2.1 Manufacturer(s)

Recombinant human alpha-L-iduronidase(rhIDU) formulated bulk drug substance is manufactured by:

BioMarin Pharmaceutical Inc.
Galli Drive Facility
46 Galli Drive
Novato, CA 94949

S 2.2 Description of Manufacturing Process and Process Controls

Developmental Genetics (IIC 1.3)

- Host cells
- Gene construct
- Vector
- Final Gene Construct
- Cloning and Establishment of the Recombinant Cells lines

Cell Seed Lot System (IIC1.4)

- Master Cell Bank
- Working Cell Bank
- End of Production Cells

Cell Growth and Harvesting (IIC 1.5.1)

Purification and Downstream Processing (IIC 1.5.2)

Pooled Formulated Bulk Drug Substance (IIC 1.5.4)

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P. DRUG PRODUCT

P 1. Description and Composition of the Drug Product

Table 1: **Composition of Aldurazyme Drug Product**

Name of Ingredient	Concentration	Composition per vial	Function	Reference to Standard
rh-alpha-iduronidase	100 units/mL	2.90 mg	Active Ingredient	In-House Standard
Sodium Chloride	150 mM	43.9 mg	Tonicity Modifier	USP/EP
Sodium Phosphate, monobasic, monohydrate	92 mM	63.5 mg	Buffer	USP/EP
Sodium Phosphate, dibasic, heptahydrate	8 mM	10.7 mg	Buffer	USP/EP
Polysorbate 80	10 ug/mL	0.05 mg	Stabilizer	NF/EP
Water for Injection		5 mL	Solvent	USP/EP

P 2. Pharmaceutical Development

P 2.1 Components of the Drug Product

P 2.1.1 Drug Substance

P 2.1.2 Excipients

P 2.2 Drug Product

P 2.2.1 Formulation Development (IIA 4.3)

P 2.2.2 Overages

P 2.2.3 Physicochemical and Biological Properties

P 2.3 Manufacturing Process Development

During development, manufacturing was moved from ----------
to Galli Drive, Novato, Marin County, CA, and the scale was changed from ---- liter batch to ---------- bioreactor. Formulated drug substance batches manufactured at both sites, scales, and harvests were used to manufacture drug product lots. Representative drug product lots were compared.

Table 1: **Drug Product Testing Summary: ---liter --------- versus ------ liter Galli**

DP Lot					
Contractor					
Test	Specification				
Sterility		Pass	Pass	Pass	Pass
Volume			5.2	5.2	5.2
pH		5.5	5.5	5.6	5.5
Polysorbate 80			10	7	7

P 2.4 Container Closure System

DMPQ will review adequacy.

P 2.5 Microbiological Attributes

P 2.6 Compatibility

P 3. Manufacture

P 3.1 Manufacturer(s)

Drug product manufacturing operation are performed at Genzyme Corporation, Allston, Massachusetts 02134, and at ----------

P 3.2 Batch Formula

P 3.3 Description of Manufacturing Process and Process Controls

Genzyme performs ---------- tests as in-process tests.
---------- performs ---------- tests as in-process tests.

DMPQ will review the manufacturing process and process controls for adequacy.

P 3.4 Controls of Critical Steps and Intermediates

DMPQ will review the manufacturing process and process controls for adequacy.

It should be noted that BioMarin uses ----------
----------. DMPQ will need to evaluate the cleaning and changeover procedures and product segregation procedures at these contractors (Section 2.1 and Section 2.2) to assure adequate segregation of drug product final containers and adequacy of controls.

Drug product final containers, sealed and stored at 2-8^{o}C, are shipped from ----------
to Genzyme for final labeling and packaging.

P 3.5 Process Validation and/or Evaluation

DMPQ will review the manufacturing process and process controls for adequacy.

P 4. Control of Excipients

P 4.1 Specifications
P 4.2 Analytical Procedures
P 4.3 Validation of Analytical Procedures
P 4.4 Justification of Specifications
P 4.5 Excipients of Human or Animal Origin
P 4.6 Novel Excipients

P 5. Control of Drug Product

P 5.1 Specification(s)

Table 1: Drug Product Test Methods and Specifications

Test/Assay	Type of Measure	Specification	SOP	Method Validation Report
pH				
Polysorbate 80 (NF/EP)				
	Purity			
	Purity			
Sterility	**Safety**			

	Concentration Strength			
Volume in Container (USP/EP)	**Quality**			

P 5.2 Analytical Procedures

The analytical methods used to evaluate the quality attributes of the final container drug product are listed and are briefly described in the R 2. Method Validation Package.

P 5.3 Validation of Analytical Procedures

The analytical methods used to evaluate drug product have been validated. The validation studies included drug product samples. SeeR 2. Method Validation Package

P 5.4 Batch Analyses

----------drug product final container lots are submitted in support of the application. --------- lots were manufactured, at commercial scale, for pre-clinical and clinical development. --------lots, manufactured at commercial scale, are submitted in support of process qualification, ----------at Genzyme. Results from analyses of these lots are tabulated below, one table for pre-clinical and clinical development lots and one for process qualification lots. Ancestry of these drug product lots are included in tables as drug substance batches.

Table 1: **Drug Product Manufacturing Pre-Clinical and Clinical Development Lots**

DS Lot								
DP Lot								
Contractor								
Test	Specification							
Sterility		Pass	Pass	Pass	Pass	Pass	Pass	Pass
		3	46	2	8	6	35	4
Volume		5.2	5.2	5.2	5.4	5.2	5.3	5.2
pH		5.5	5.6	5.6	5.5	5.5	5.5	5.5
Polysorbate 80		9	8	9	9	10	8	10

Table 1: **Process Qualification Drug Product Lots**

DS Lot							
DP Lot							
Contractor							
Test	Specification						
Sterility		Pass	Pass	Pass	Pass	Pass	Pass
Volume		5.2	5.2	5.2	5.2	5.2	5.2
pH		5.5	5.6	5.5	5.5	5.6	5.6
Polysorbate 80		8	7	7	8	6	8

P 5.5 Characterisation of Impurities

P 5.6 Justification of Specification(s)

All methods used in the release of Aldurazyme were validated in accordance with ICH Guidelines Q2a and Q2b and are listed in R 2. Methods Validation Package. Specifications were established based on a minimum of three standard deviations about the mean for the determined intermediate precision of the method. The qualitative or limit-based assessments include either or both direct comparison to the reference material and/or co-mixture analysis with the reference material. For all assays used in testing of rhIDU, the specifications are equal to or tighter than those utilized for release of clinical trial supplies.

Table 1: Summary Table of Aldurazyme Drug Product Lots

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P 6. Reference Standards or Materials

A single reference material includes formulated bulk drug substance and drug product. In the ---------- (Aldurazyme) Method Validation Report QC-IDU-37-AVR (Appendix IIC-53), reference material lot ----------, is listed as a sample to be used in the analysis.

Is the reference lot, ----------, the primary reference material, a working reference material, and a working reference drug product material

P 7. Container Closure System

Suppliers of all critical manufacturing materials and services are approved through a vendor approval and qualification program. Letters of authorization to cross-reference the Drug Master Files (DMFs) for relevant components are included.

The drug product final container is a 5 cc ---------- glass vial with a 20 mm opening that meets USP/EP specifications for Type I glass. The vial is manufactured by ----------, ----------. A description of the vial manufacturing process is provided in Type III US Drug Master File ----------

The closure for the vial is a 20 mm gray butyl ---------- serum style stopper made from the

---------- rubber formulation. The stopper is manufactured by ---------- ---------- and meets UPS/EP specifications. The stoppers are siliconized (----------) for machinability prior to sterilization. Descriptions of the stopper formulation and ---------- process are provided in Type III US Drug Master Files ----------.

The stoppered vial is crimped with a 20 mm flip-off six bridge aluminum seal with a plastic button made of ----------. The aluminum seal is manufactured by ----------

The selected stopper, which meets USP/EP requirements, was chosen for compatibility with the product. The stopper is a --------butyl rubber serum stopper, which is appropriate for the high phosphate, liquid formulation in the vial. The current stopper replaced a --------butyl rubber stopper that was used during clinical development. This change was based on the vendor's recommendation for known interaction between ----------butyl stoppers and phosphate solutions. This change in stopper composition was incorporated at both fill/finish facilities starting with the first process qualification fills of formulated bulk drug substance (----------).

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P 8. Stability

P 8.1 Stability Summary and Conclusion

---------lots of drug product are currently being monitored. Included in the stability program are lots filled at both ---------- and Genzyme. These studies are intended to support expiry dating in accordance with ICH guidelines.

Real-time and accelerated stability data are provided for ----------lots of Aldurazyme drug product stored at 2–8°C, and ------- lots stored at ----------% relative humidity and at ------ stored both ----------. The stability studies at 2–8°C for these lots are ongoing through --- months while the ---°C studies are for six months and the ---°C studies are for -------- months.

The ---------- most recent drug product lots were produced from formulated bulk drug substance lots using the proposed commercial manufacturing process.

The first -------- drug product lots on stability were packaged with a ----------butyl stopper, while the next ---- lots were packaged with a ----------butyl stopper which is the proposed commercial stopper.

Lots filled at both Genzyme ---------- are included on the stability

program.

This application contains data on -------- stored at 2–8°C for ----------months, -------- for -------- months, and data on all other lots stored at 2–8°C for ---------- months. Also included are data on ------ lots stored for up to ------months at ---------- relative humidity and data on ---- lots stored at ------°C for up to ------ months. Updated data will be provided for all lots stored at 2–8°C during the application review period.

These studies are the basis for supporting the expiration-dating period of twenty-four months for drug product when stored at 2–8°C.

Stage of Production	Expiration Dating, Storage Condition
Drug Product	24 months at 2-8°C
Drug Product Shipping	7 days at 2-25°C
Infusion Bag Storage	24 hours at 2-8°C followed by up to 12 hours at room temperature

P 8.2 Post-approval Stability Protocol and Stability Commitment

The drug product 2–8°C studies will continue to thirty-six months.

Proposed by sponsor: ----- *drug product --- will be placed on stability at 2–8°C annually in accordance with the protocol. Vials will be stored in the* ---------- ----------

Proposed by Agency: *One drug product lot, manufactured at each contractor, will be placed on stability at 2–8°C annually in accordance with the protocol. Vials will be stored in the inverted orientation only.*

The intervals for testing are consistent with ICH recommendations.

Table 1: **Aldurazyme Drug Product Stability Testing Plan**

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P 8.3 Stability Data

Final Container Drug Product

These results demonstrate that the drug product lots tested met specifications when stored at 2–8°C for ---------- months, at -----°C for -----months, or at ----C for two months.

These studies will continue and updates from the 2–8°C studies, including ---------- month data on ----------, will be provided during the application review period.

At anticipated time of approval, these real time data will support an expiration

dating period of ---------- for final container drug product when stored at 2–8°C. *Collection of ---------- month data for the first qualification lot of drug product will begin April 5, 2002; for the second qualification lot of drug product will begin June 16, 2002; and for the third qualification lot of drug product will begin December 28, 2002.*

The current data support final container drug product shipping at --------C for up to ----------.

Drug Product Diluted in Infusion Bags

For administration to patients, Aldurazyme is diluted with 0.9% sodium chloride containing 0.1% human serum albumin (IND ----------) to a volume of between 100 mL and 250 mL in an infusion bag. A study was performed to examine the stability of the infusion preparation when stored at ---------- for up to ----hours, and refrigerated (2–8°C) for up to --- hours. The enzyme activity in units per milliliter remained unchanged for each scenario.

The current data support infusion bag storage of Aldurazyme for ---- hours at 2-8°C followed by up to ----------

- *Pilot scale data:*
  Real time stability data from a pilot facility or a pilot manufacturing scale can be used to support the dating period for commercial product, if the pilot material is comparable (physicochemical/biological activity) and in the ***same container-closure system****.*

- *Real time data needed on commercial process*
  The expectation is that for a new molecular entity, the manufacturer will have some stability data on the commercial product prior to approval. In most cases 3-6 months of real time data on the commercial product is requested at the time of submission of a BLA. In all cases, a commitment to collect real time stability data on the first 3 commercial lots is expected.

- *Accelerated stability data*
  Accelerated stability data are particularly useful for identifying product degradation pathways and verifying methods to be stability-indicating. Accelerated stability data may also be useful in evaluating comparability of pilot and commercial product. Accelerated data should not be used for projecting a dating period.

A. APPENDICES

A 1. Facilities and Equipment

DMPQ will evaluate the adequacy of the section of the submission.

A 2. Adventitious Agents Safety Evaluation

A 2.1 Characterization and Stability of the Cell Line

Studies were performed on cells from the Master Cell Bank (MCB) and cells from the ----------) to test for genetic identity and stability. The genomic organization of the rhIDU cDNA by ---------- was consistent with that predicted. DNA sequencing of the rhIDU coding region matched the original cDNA sequence. The gene copies per cell determined by ----------. The results of these studies confirmed the expected genetic characteristics of the cell line and the stability of the cells over the course of a production run.

Additionally, the master cell bank (MCB), working cell bank (WCB), and ---------- ---------- evaluated by: ---------- and the patterns found to be consistent with hamster; ---------- and the MCB cells were hamster; found free of bacteria, fungi, and mycoplasma.

The master cell bank (MCB), working cell bank (WCB), and ---------- ---------- were evaluated for presence of viral contaminants. *In vitro* and *in vivo* assays for the presence of viral contaminants demonstrated absence of adventitious viruses. The master cell bank tested negative for viruses in the ---------- ---------- the retrovirus-like particles, in the MCB and -----, known to exist in Chinese Hamster Ovary Cells. Additionally, the MCB and ----- tested negative for ---------- reverse transcriptase activities. *In vitro* testing of MCB and ------ for ---------- viruses and for porcine viruses was negative.

A 2.2 Biological Raw Materials

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A review of the safety data did not reveal evidence of viral contamination of the product. A total of 55 patients have received repeated infusions of Aldurazyme and have not, to date, displayed effects of viral contamination of the product.

R. REGIONAL INFORMATION

R1. Executed Batch Records (USA only)

Appendix IIC-116, Appendix IIC-117, and Appendix IIC-118 contain a BioMarin Batch Record for Drug Substance Manufacture.

Appendix IIB-3 contains a Genzyme Batch Record for Drug Product Manufacture.

Appendix IIB-4 contains a ----------Batch Record for Drug Product Manufacture.

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R3. Comparability Protocols (USA only)

None requested for Post-Marketing actions.

C. KEY LITERATURE REFERENCES