Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: September 28, 2002

To: Melanie Hartsough, BLA Committee Chair, HFM-536

From: Deborah Trout, BLA Committee Member, HFM-675

Through: Cynthia L. Kelley, Branch 1 Chief, HFM-675

Subject: Review of Biologics License Application (BLA) from BioMarin Pharmaceuticals for the manufacture, formulation, fill and packaging of Aldurazyme ; STN Number 125058/0

My review includes an evaluation of the following sections submitted in BioMarin's BLA application (reference is made to Part II: Chemistry, Manufacturing, and Controls in the electronic submission): Item IIi (sections IIi.1 - IIi.5, and IIi.8), Item IIA (sections IIA.1 and IIA.2), Item IIB (sections IIB.1 - IIB.3), Item IIC (sections IIC.1.1, IIC.1.5, IIC.1.8, IIC.1.10, IIC.2, and IIC.3), Item IIE.1, Item IIH.1, and IIQ.1 - IIQ.2.

This review memorandum is comprised of three sections. The first section are issues that can be addressed in an information request or complete review letter, the second section are issues that can be addressed in the pre-license inspection and the third section is my review narrative

Section I: Outstanding Issues that can be addressed in an Information Request or Complete Response letter.

1. Please submit safety data demonstrating that the----------, used in the storage and shipment of the Laronidase formulated bulk drug substance (rhIDU), will not leach harmful or undesirable substances into the drug substance. Safety data should include extraction/toxicological studies demonstrating that the packaging components do not adversely affect the drug substance.

2. Outstanding inspectional issues identified on the FDA Form 483's dated October 8, 2002, and November 1, 2002, issued at the conclusion of the pre-approval inspections of your Novato, California location and your contract manufacturer, Genzyme Corporation, in Allston, Massachusetts, respectively have yet to be resolved. You must satisfactorily resolve these

issues. Review of your November 21, 2002, and December 11, 2002, responses to the FDA Form 483's will be communicated in a separate letter.

Section II: Pre-license Inspection Issues

BioMarin Issues

3. Page 152, Section IIC, Table IIC-70 list a----------.. Please review Protocol N-PV-426 "Process Validation of Microbial Control in the Production Process for rhIDU" submitted in support of this bioburden specification during the pre-license inspection.

4. Page 983, Section IIC, Table 9.4.4.1. states harvest lot -------had a---------- please review the investigation associated with this contamination event.

5. The manufacture of rhIDU is a----------. Please confirm that additional incoming testing is performed as per 21CFR 211.84 (d). Supplier's Certificate of Analysis could be used provided that the supplier's test results are periodically shown to be valid by doing your own testing, which when compared to supplier's results shows agreement. Once that reliability is established then the level of testing may be reduced. In addition, ----------.

6. The BLA states that the Galli Drive Facility is designed to function as a multi-product facility. In addition, the submission indicates rhIDU is the only product manufactured at this facility. Please convey to the firm that the Galli Drive Facility will be licensed for the manufacture of rhIDU drug substance only (i.e., single product use) and that the introduction of additional products after licensure would require a prior approval supplement.

7. ----------. Please review validation data for----------. In addition, please verify that the appropriate process validation was conducted for ----------.

8. The cell culture run is completed when either the rhIDU activity in the harvest fluid is ----------

9. Please review validation data for the following intermediate holds: ----------for the harvested cell culture fluid, -------for the ----------for the ----------and -------- for the----------.

10. Throughout the drug substance manufacture, there are several ---------- operations. ------- information available for review.

11. The rhIDU drug substance from the----------. How are modules stored between uses and how are they cleaned and sanitized prior to re-use?

12. ----------. Who decides how the ------ will be stored, and are there SOPs in place for both storage procedures? ----------. Where production scale hold studies performed for each ----------?

13. Page 73, Section IIC states all of the ----------

14. Please verify all in-process sampling locations during production of the rhIDU drug substance.

15. Page 74, Section IIC, Table IIC-21 states that---------- Please verify that the rhIDU drug substance ---------- without the appropriate re-processing procedures in place.

16. The Aldurazyme filling process----------. Please review validation data ensuring the final product vials are uniform across a given lot.

17. During the pre-license inspection, the following items should be evaluated: (re)validation of the HVAC system; HEPA filter certification frequency and tests performed; environmental monitoring for both viable and non-viable particulates; monitoring of differential pressures, air temperatures, and humidity.

Genzyme Issues

18. The formulated bulk drug substance is transferred from----------. How long can the sterile bulk be held prior to filling?

19. ----------.

20. Final product vials are either labeled manually or using an automated labeling machine. Please verify there are SOPs in place for both procedures.

21. The fill/finish area is designed as a multi-product manufacturing area with only one product manufactured in the filling area at a time. In addition to Aldurazyme, multiple other Genzyme investigational and commercial products are manufactured in this area. All products are----------. Following the manufacture of each product, a series of steps including line clearance and validated cleaning procedures are performed prior to introduction of the next product. Please review cleaning and changeover procedures for all critical manufacturing areas.

22. ----------

23. Washed and pre-siliconized stoppers are received, quarantined and released prior to use. The stoppers are sterilized in a ----------using a validated cycle. They are unloaded from the autoclave and go to storage in either ----------. Please verify that the pre-washed and pre-siliconized stoppers have been assessed as to the uniformity of the silicon treatment, and the capability of the washing process to remove--------. Genzyme could rely on a supplier's Certificate of Analysis provided that the supplier's test results are periodically shown to be valid by doing their own testing, which, when compared to the supplier's data, shows agreement. Once that reliability is established, then the level of testing may be reduced.

24. Please review all media fill data for the last two years for the aseptic filling suite used in the filling of the drug product. In addition, please review related SOPs, protocols and reports associated with media fill activities.

25. Please review the following regarding equipment cleaning of the ----------
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revalidation. If the cleaning procedure is manual, the firm should have validation demonstrating reproducibility and routine testing to ensure validated process is maintained. In addition, residual limits and acceptance criteria should be achievable and verifiable. The manufacturer should be able to document by means of data that the level of residuals and acceptance criteria are scientifically sound.

26. During the pre-license inspection, the following items should be evaluated: (re)validation of the HVAC system; HEPA filter certification frequency and tests performed; environmental monitoring for both viable and non-viable particulates; monitoring of differential pressures, air temperatures, and humidity.

27. Please confirm that fluid pathways such as tubing are compatible with the drug product (i.e., do no absorb in-process materials, and do not leach unintended substances into in-process materials or the drug product).

28. Page 8, Section 7.5 of the Genzyme batch product record states the formulated bulk should be filled---------- Please review validation data associated with this time limit.

Section III: Review Narrative

Drug Substance

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, rhIDU and 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 rhIDU. 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.

Recombinant human rhIDU formulated bulk drug substance is manufactured at the following location:

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

The BioMarin Galli Drive Facility is a ----------square foot building with mammalian cell culture and protein purification capabilities. The Galli Drive Facility is designed to function as a multi-product facility. Currently rhIDU is the only product manufactured at this facility. In the future, it is expected that additional products will be manufactured in this facility. Manufacturing operations for rhIDU at 46 Galli Drive include the storage and preparation of the Master Cell Bank (MCB) and Working Cell Bank (WCB), inoculum preparation, bioreactor operations, purification and formulation of Drug Substance.

Genzyme for sterile filtration and filling operations. Genzyme Corporation performs labeling, packaging, and distribution of the final drug product.

PAGE 7 DETERMINED TO BE NOT RELEASABLE

Page 8 DETERMINED TO BE NOT RELESABLE

Drug Product

The Drug Product, Aldurazyme, is prepared by the sterile filtration and filling of the formulated bulk drug substance into vials (5 cc USP/-- Type I glass). These vials are stoppered (----------gray butyl), capped, and labeled, at which point the product is referred to as Aldurazyme. Aldurazyme is manufactured at either Genzyme Corporation (Allston Landing facility), located in Allston, Massachusetts, USA----------.

(Allston Landing)

Genzyme Corporation
Allston Landing Facility (ALF)
500 Soldiers Field Road
Allston, Massachusetts 02134
USA

The ALF facility is an ---------- square foot building with development and manufacturing capabilities. This facility is designed to function as a multi-product facility. The formulated bulk drug substance is aseptically filled in the fill finish suite at Genzyme's Allston Landing Facility. The bulk is aseptically filled into vials at a fill volume of --- mL, which allows a 5.0 mL extraction.

Each vial of Aldurazyme is single use only and delivers 5.0 mL of a solution that includes the enzyme, recombinant human Alpha-L Iduronidase, at 100 units/mL (approximately 0.58 mg/mL), 100 mM sodium phosphate, 150 mM sodium chloride, and 10µg/mL polysorbate 80, with a pH of 5.5. The final product is a solution that is clear to slightly opalescent, and colorless to pale yellow. For administration to patients, Aldurazyme is diluted with 0.9% sodium chloride containing 0.1% human serum albumin to a volume of between 100 mL and 250 mL.

The formulated bulk drug substance, ---------- satellite samples, and required documentation is shipped to the Genzyme Allston Landing Facility for final formulation and filling. After QC is notified

PAGE 10 DETERMINED TO BE NOT RELEASABLE

segregated and submitted to QA for disposition as rejected material.

Vials are labeled either manually or using an automated labeling machine. For manual labeling, all labels are pre-imprinted with a lot number and expiration date using a validated label imprinter. QA assigns the expiration date for the lot and confirms that the imprinting device is printing both the proper expiration date and lot number before the labels are imprinted. After the labels have been imprinted, the information on each individual label is verified by a fill/finish labeling operator prior to applying the label to the vial. The imprinted and verified labels are applied to the vials and each labeled vial is inspected by a fill/finish labeling operator.

Automated labeling is initiated by----------..
The labeler is fitted with rolled stock vial labels and prints the expiration date and lot number onto each label. QA assigns the expiration date for the lot. ----------. The printed labels are automatically applied to the vials as they travel down the labeling machine belt. The label stock is ----------
This allows the presence of a label on each vial to be confirmed. Labeled vials exit the machine via an off-load rotary table and may be either removed at this point for future packaging or allowed to feed the automatic cartoner. Labels are reconciled at the completion of each lot of Aldurazyme.

Labeled vials are packaged either manually or using an automated packaging machine.
For manual packaging, all cartons are pre-embossed with a lot number and expiration date using a validated carton embosser. QA assigns the expiration date for the lot and confirms that the embossing device is coding both the proper expiration date and lot number before the cartons are embossed. After the cartons have been embossed, a fill finish packaging operator verifies the information on each individual carton. Each embossed carton is filled with a labeled vial and a package insert. A fill finish packaging operator then inspects the assembled package. Following completion of the job, QA performs an AQL on the finished package.

Automated packaging is initiated by----------.
QA assigns the expiration date for the lot and confirms that the packaging machine is embossing both the proper expiration date and lot number. The cartoner is supplied with cartons and package inserts and embosses the expiration date and lot number onto each carton. ----------. A labeled vial and a package insert are automatically inserted into an embossed carton and the completed package exits the machine. The completed packages are subjected to a final AQL inspection by the QA department. The complete packaged vials are then forwarded to Genzyme Quality Assurance for quarantine at 2–8°C until final dispositioning.

The fill/finish area was designed as a multi-product manufacturing area with only one product manufactured in the filling area at a time. The fill/finish area uses dedicated equipment for all product contact surfaces with respect to Aldurazyme. In addition to Aldurazyme, multiple other

Genzyme investigational and commercial products are manufactured in this area. All products are----------. Following the manufacture of each product, a series of steps including line clearance and validated cleaning procedures are performed prior to introduction of the next product.

Vials are prepared utilizing a ----------

PAGE 13 DETERMINED NOT TO BE RELESABLE

PAGE 14 DETERMINED TO BE NOT RELEASABLE

Distribution

Storage and distribution of Aldurazyme is performed at the following Genzyme facilities:

The ----------a ---------- square foot ---------- building with material storage and distribution capabilities. This facility is designed to function as a multi-product distribution facility. The facility is designed to provide controlled storage areas and rooms at various temperatures, ambient, 2–8°C, 20°C, and 40°C. Other rooms are designed for specific containment of flammables, acids/corrosives, hazardous waste and isotopes. The ----------provides 2–8°C controlled storage areas for Aldurazyme. Materials Management coordinates the final packaging and shipment of Aldurazyme.
Other products stored at this facility include the following: ----------products and ----------. Proper procedures are in place to prevent cross contamination between different products and between products and personnel.

ENVIRONMENTAL ASSESSMENT

Claim of Categorical Exclusion
As allowed under 21 CFR 25.31(c), BioMarin claims categorical exclusion from the requirement for preparation of an environmental assessment report, as the active drug substance is a recombinant version of a naturally occurring human enzyme, which would have the same metabolites or degradation products as the non-recombinant version. In addition, the concentration or distribution of the substance itself and therefore, its metabolites and degradation products, would be significantly less than one part per billion at the point of entry into the aquatic environment. The action, therefore, would not alter significantly the concentration in the environment.