Review Memorandum for STN 125058/0

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

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To: File: STN 125058/0

From: Calvin B. Koerner, Scientific Reviewer, DMPQ/OCBQ, HFM-675

Through: Cynthia L. Kelley, Branch I Chief, DMPQ/OCBQ, HFM-675

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

Review Overview and Conclusion

The scope of this review is limited to the Division of Manufacturing and Product Quality (DMPQ) functional review for the Chemistry, Manufacturing, and Controls (CMC) section of the Aldurazyme Biological License Application (BLA) submitted by BioMarin Pharmaceutical, Inc.

Aldurazyme is a laronidase; recombinant human (a -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 (laronidase) is manufactured at BioMarin's Novato, CA facility. 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 a-L-iduronidase (IDU). ---------- 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. The drug product is sterile filtered, filled, and finished by Genzyme, Inc, Allston Landing, MA or ----------

Part II of this BLA submission is a description of the Chemistry, Manufacturing, and Controls (CMC) for rhIDU. Briefly, Sections IIA and IIB provide a description of the composition and manufacturing process (including process validation), respectively, of the drug product. Section IIC provides comprehensive information on the manufacturing, characterization, and testing of the formulated bulk drug substance. Section IIE describes the specifications and test results for the drug product. Stability data for all intermediates, formulated bulk drug substance, and drug product (including drug product diluted for infusion) are provided in Section IIF. Section IIH addresses environmental impact. Section IIQ is divided into two different subject areas: IIQ1 presents a summary of the production process history; IIQ2 presents a description of the facilities used in the manufacturing of rhIDU formulated bulk drug substance and drug product. Finally, Section IIV provides viral safety information, including assessment of adventitious agents in starting materials as well as validation of viral removal by the manufacturing process.

All information related to this submission has been reviewed and the submission is acceptable for approval pending adequate responses to the observations listed on Form FDA 483 issued to the firms.

A history of the my (CBK) review is presented in Section I. Initial review observations and corresponding resolutions are delineated in Section II. Inspectional items are delineated in Section III. Lastly, a review narrative is given in Section IV.

Section I. Review History

A comprehensive initial review of all submitted material was completed on 7 Aug 2002. The initial review resulted in 1 observation and 7 inspection items. The one observation was resolved through a discipline review letter. A Pre-Approval Inspection was conducted between 29 October – 1 November 2002 by Deborah Trout and myself (CBK). A Form FDA 483 with 8 observations was issued to the firm. With the exception of the 483 items, all inspection items were addressed and resolved during this inspection.

Section I. Initial Review Observations

Observations for BioMarin's Novato, CA facility

1. In Part IIC, Table IIC-64:----------, action limits are not calculated correctly for---------- The correct calculation is needed.

   Resolution
   This observation was added to a discipline review letter sent to the firm. See the response to this discipline review letter.

Section II. Inspection Items

The ------ manufacturing sites were scheduled for inspection. Inspectors Cynthia Kelley and Deborah Trout inspected the BioMarin Novato, CA facility. Deborah Trout and I (CBK) inspected the Genzyme Allston Landing, MA facility. Team Biologic's recent inspection of ----------facility resulted in CBER waiving this inspection. The respective findings for each inspection can be found on the issued FDA Form 483s and in their corresponding Establishment Inspection Reports (EIR). Below are the inspection items that I (CBK) identified for the BioMarin Novato, CA, facility and the Genzyme Allson Landing, MA facility during my review of the application.

Inspection Items for BioMarin's Novato, CA, facility

I forwarded the BioMarin Novato, CA, facility inspection items listed below to Cynthia Kelley and Deborah Trout prior to their departure for the inspection. These items are covered in their EIR for the BioMarin Novato, CA, facility inspection.

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In Part IIC, Section 1.5.2, Buffer Preparation, it states,----------
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Inspection Items for Genzyme's , Allston Landing, MA, facility

The inspection items for the Genzyme Allson Landing, MA, facility were covered during Deborah Trout's and mine (CBK) inspection, and are listed below with corresponding outcomes.

- In the "Performance Qualification Summary Report for ---------at the Allston Facility – Amendment 2" final report, it states, ----------
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  O*utcome*
  The sterilization information submitted in the original application is out dated. More recent validations were reviewed during the inspection. ----------
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- In the "Performance Qualification Summary Report for -------- at the Allston Facility – Amendment 3" final report, it states, ----------
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Outcome
The sterilization information submitted in the original application is out dated. More recent validations were reviewed during the inspection. ----------

- "Performance Qualification Final Report for the ----------at the Allston Landing Facility" validated ----------

Outcome
The sterilization information submitted in the original application is out dated. More recent validations were reviewed during the inspection. ----------

- In Part IIB, Section 2.1.2.7, it states, "In addition to Aldurazyme, multiple other Genzyme investigational and commercial products are manufactured in this area. All products are ---------- ----------A list of all products (clinical and licensed) manufactured at this facility is needed.

Outcome
Genzyme provided a list of "other products" in their inspection introduction package. The products currently manufactured at this facility are----------.

- In Part IIB, Section 2.2.2.2, it states, "Representative sites in the RO system are sampled and tested routinely for---------- USP XXV requires that purified water be tested for Total Organic Carbon (TOC), conductivity, and bioburden.

Outcome
The RO system is used to feed the WFI stills. RO water is not directly used in the Aldurazyme manufacturing process. Therefore, this water is not classified as purified water and does not need to be monitored according to USP specifications.

Section III Process Narrative

rhIDU is produced by transfected CHO cells ----------

---Labeling, packaging, and distribution are performed by Genzyme Corporation.

Drug Substance Process

The drug product process is broken down into --

The cells used for manufacturing are from cell line ------ a Chinese hamster ovary (CHO) cell line over-expressing recombinant human L-iduronidase (rhIDU). --

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Drug Product Process (Allston Landing)

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 5.3 mL.

The drug product process is broken down into three major steps 1) Receipt of Drug Substance 2) Sterile Filtration, Filling, & Capping, and 3) Inspection, Labeling & Packaging operations.

Receipt of Drug Substance

The formulated bulk drug substance, --- satellite samples, and the required documentation is received by the Genzyme Allston Landing Facility. After QC is notified that the formulated bulk has arrived, ----------

Sterile Filtration, Filling, & Capping

Vials are washed in ----------

Inspection, Labeling, & Packaging

Filled and capped vials are subjected to a ------visual inspection process by trained and qualified manufacturing personnel. The inspection is followed by an Acceptable Quality Level (AQL) procedure conducted by QA personnel that are also trained and qualified in inspectional procedures. All vials removed from the lot during these inspection procedures are segregated and submitted to QA for disposition as rejected material.

Labeling and packaging operations are performed according to the specified requirements in the batch records for those operations. 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 feeding the unlabeled vials onto----------. 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 labeler utilizes a ----------and expiration date are properly printed onto each label. A ----------confirms that the imprinted label is the correct revision. The printed labels are automatically applied to the vials as they travel down the labeling machine belt. The label stock is treated by the vendor with----------. This allows the presence of a label on each vial to be confirmed. Labeled vials exit the machine via ---------- 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 feeding the labeled vials to----------. 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 ----------confirms that the carton and package insert is the correct revision. 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 disposition.

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EOD: Calvin B. Koerner, Scientific Reviewer, DMPQ/OCBQ