CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

125117/0

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: February 4, 2005
Latest revision 5/25/05

To: Administrative File, **STN 125117**

From: Jianming Li, Facility/CMC Reviewer, CDER/OC/DMPQ TFRB, HFD-328 MDS for J.L.
Carolyn Renshaw, Facility/CMC Reviewer, CDER/OC/DMPQ/TRFB, HFD-328 CR 5/25/05

Through: Michael D. Smedley, Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328 MDS 5/26/05

Subject: **Review Memo: Biological License Application (BLA):** New BLA

US License 1649
Applicant Biomarin Pharmaceutical Inc.
Product Galsulfase
Indication Treatment of patients with mucopolysaccaridosis VI (MPS VI, Maroteaux Lamy Syndrome)

Due date: May 31, 2005

Recommendation: The facility/equipment information related to this application and corresponding amendments have been reviewed. Nineteen review items were noted during the review process and were subsequently resolved. The application, as amended, is recommended for approval.

Review Summary

Biomarin Pharmaceutical Inc. submitted this BLA to license Galsulfase and the associated Drug Substance and Drug Product manufacturing processes. Drug Substance manufacturing is conducted by Biomarin at their Novato, CA facility. Drug Product manufacturing is conducted by — Drug Substance and Product testing is conducted by Biomarin Pharmaceutical at its Novato, CA laboratories. For product distributed from the United States (US), labeling and packaging is performed b — and distributed by — and release testing is performed at

BioMarin. For product distributed from the European Union (EU), labeling, packaging and final qualified person (QP) release is performed at —
— and QP release testing is performed at —
—

The BLA was submitted in an electronic Common Technical Document (CTD) format. Seven Chemistry, Manufacturing and Control application amendments were submitted. The following is a list of the amendments and their corresponding contents:

Amendment BL 127117/0.002 - Proposed rhASB Manufacturing process modifications, January 13, 2005;

Amendment BL 127117/0.003 - Proposed rhASB Manufacturing process modifications – Comparability protocol, January 27, 2005;

Amendment BL 127117/0.005 - Revised sections 3.2.P.3.5 and 3.2.A.1 including requested facility diagrams and media fill information; Corrected address, February 4, 2005;

Amendment BL 127117/0.010 – Pre-license inspection follow-up: Analytical procedure standard operating procedures, March 31, 2005.

Amendment BL 127117/0.013 – Pre-license inspection follow-up: Establishment description (BLA item 15) for the distributor; Quality agreement information for —
April 8, 2005:

Amendment BL 127117/0.014 – Pre-license inspection follow-up: Process validation of the — of rhASB formulated bulk drug substance (FBDS) and addition of an in-process control test for — in FBDS, April 15, 2005; and

Amendment BL 125117.017 – galsulfase; recombinant human N-acetylgalactosamine 4-sulfatase (rhASB). Follow-up to April 28, 2005 teleconference with DMPQ/TFRB, May 10, 2005.

Amendment BL 127117/0.019 – Certificates of Analysis for FBDS and DP, May 24, 2005.

The scope of this review was limited to a TFRB functionality review for the Drug Substance's Manufacturer, Controls, Container/Closure, Facility/Equipment, and Adventitious Agents sections and the Drug Product's Pharmaceutical Development, Manufacturer, Controls, Container/Closure, Facility/Equipment, and Adventitious Agents sections and the Environmental Assessment.

An evaluation of the application for completeness and adequacy was completed on February 6, 2005. Nineteen review items were noted during this evaluation.

The firm was contacted via telephone to discuss the review items on and April 28, 2005 (See Teleconference Memo dated 4/28/05). The firm adequately resolved 12 of the review items during the teleconference. The remaining 6 review items were addressed and resolved in a

supplement amendment received by the Agency on 5/10/05 or by further discussion with the firm through e-mail. The supplement amendments were evaluated and incorporated into this memo. See the Review Narrative Section for the review items and their subsequent resolution.

Products Affected

Galsulfase

Review Narrative

Drug Substance

Manufacturer, 3.2.S.2
Sections on Manufacturers Names, Description of Manufacturing Process and Process Controls, Control of Materials, Controls of Critical Steps and Intermediates, Process Validation and/or Evaluation, Manufacturing Process Development were provided.

Manufacturers Names, 3.2.S.2.1 – This section included name, address, and responsibility of bulk substance (BS) manufacturer Biomarin Pharmaceutical Inc. and its respective production facility involved in the manufacturing and testing of the BS.

Review Comment:
This is provided for information purpose. Biomarin's Galli facility performs the formulation function. No further formulation is performed in the drug product facility,

The manufacturing sites of the bulk substance and the drug product and their functions are summarized in the following table.

Table 1. Information of rhASB manufacturing facilities

Name and Address	FEI Number	Responsibility
Biomarin Pharmaceuticals Inc. 46 Galli Drive Novato, CA 94949	FEI:3004079983 Last Inspection: November 2004	Manufacture: Formulated drug substance Control testing: Formulated bulk drug substance, drug product, and stability.
79 Digital Drive Novato, CA 94949		GMP warehouse
	FEI: Last Inspection: November, 2004	Manufacture: Drug product Control testing: Drug product

FEI: Last Inspection: May, 2004	Labeling and packaging
FEI: September, 2004	In-Process testing: •

Description of Manufacturing Process and Process Controls, 3.2.S.2.2 – This section included descriptions and flow diagrams of the drug substance manufacturing processes; batch/scale definition; cell , purification; and bulk formulation, filling, and storage.

Review Comment:
Galsulfase is the recombinant human N-acetylgalactosamine 4-sulfatase (rhASB). The firm manufactures rhASB through

and shipped to a contract manufacturer for filling operations

Lot/Scale Definition – An explanation as to what is a lot, including s, and the process volumes for each manufacturing step were provided.

Review Item 1:
Although the application explained how one FBDS lot is defined and derived from , the lot/batch numbering system is not defined and explained.

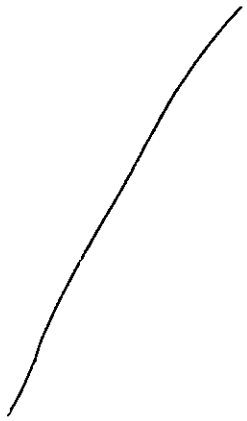
Resolution 1:
The firm was asked to explain its lot/batch numbering systems during the pre-approval inspection conducted on 2/22/-25, 2005. The purification lot number and the fill lot number are defined as following:

Table 2. Batch naming system

Position of number	Meaning	Example
1	P: purification V: fill	P for purification lot
2	Indication	6 for MPS VI
3 and 4	Year	04 for year 2004
5 and 6	Sequential lot number	03 for lot 3

t – A description of each process step in the flow diagram was

provided. The information included scale, — , major equipment, process controls, in-process tests, operational parameters, material transfer, and storage conditions. — are
—



Inspection Item 1 Resolution:

Please refer to the Establishment Inspection Report (EIR), Section XI, "Operations and Equipment, Production Processes and Validation, Cell Culture" for detailed information on

32 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

Environmental Assessment

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(c) was provided by the firm on the grounds the substances associated with this submission occurs naturally in the environment and the actions associated with this submission do not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Review Comment:
The firm claimed categorical exclusion based on both 21 CFR 25.31 (c) and (b). 21 CFR 25.31 (b) does not apply to biological product. The claim under 21 CFR 25.31 (c) is sufficient to qualify for categorical exclusion. Therefore, no amendment was requested.

cGMP Status

BioMarin Pharmaceuticals, Galli Drive, Novato, CA
A Compliance Check was completed for BioMarin Pharmaceuticals on 5/26/05. No outstanding compliance issues were identified. The following is the response from Colleen Hoyt, IPCB/DMPQ/CDER:

"The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the compliance check request for STN 125117/0. The review and final classification of the EIR for the February 2005 BioMarin preapproval inspection has determined that the inspection is acceptable and there will be no compliance actions to prevent approval of STN 125117/0."

The following facilities were compliant with GMPs as per Colleen Hoyt, IPCB/DMPQ/CDER and the inspection of these facilities was waived:

The firm was inspected in 11/2005 by Team Biologics and the decision was VAI.

According to Colleen Hoyt, OC/DMPQ/IPCB, has been NAI the last three inspections (inspected as a packager/labeler by the field) so we waived the inspection of this facility. The most recent inspection was 5/04.

Conclusion

I. The application was reviewed against existing regulations and guidelines for conformance and was found acceptable. The application, as amended, is recommended for approval. We recommend including the following PMC in the approval letter:

> We acknowledge your commitment to conduct integrity testing of the as a post-marketing commitment and your submission of the data by December 31, 2005.

II. The Drug Substance's Control of Source and Starting Materials of Biological Origin, ——, Characterization, Batch Analyses, Justification of Specifications, Reference Standards, and Stability sections and/or subsections were wholly deferred to the product office.

In addition, the Drug Product's Composition, Batch Formula, Controls of Excipients, Reference Standards, and Stability sections and/or subsections were wholly deferred to the product office.

III. Six inspection items were identified. These items were evaluated during the pre-license inspection (PLI) and are addressed in the corresponding Establishment Inspection Report (EIR).

cc: HFD-328, Smedley
FFD-328, Renshaw
HFD-328, Li
HFD-109, Needleman
HFD-122, Beaucage
HFD-122, Cherney
HFD-320, Famulare
HFD-328, TFRB Blue Files (STN 125117.0)

Revised by Smedley – 5/24/05

Archived File: S:\archive\BLAs\125117\125117.0.rev.mem.05-25-05