CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-905

MICROBIOLOGY REVIEW

Product Quality Microbiology Review

14 SEP 2006

NDA: 21-905
21-905 BC (3)

Drug Product Name
Proprietary: Valtropin™
Non-proprietary: Somatropin
Drug Product Priority Classification: S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
30-NOV-2005	01-DEC-2005	23-DEC-2005	09-JAN-2006
07-FEB-2006	08-FEB-2006	N/A	N/A
18-JUL-2006	19-JUL-2006	N/A	N/A
30-AUG-2006	06-SEP-2006	N/A	N/A

Submission History (for amendments only) – N/A

Applicant/Sponsor

Name: LG Life Sciences, Ltd.
Address: 20, Yoido-dong
Youngdungpo-gu
Seoul 150-721, Korea

Representative: Bruce Babbitt, Ph.D.
Principal Consultant (Biologics)
PAREXEL International
Telephone: (781) 434-4057
E-mail: bruce.babbitt@parexel.com

Name of Reviewer: Anastasia G. Lolas

Conclusion: Recommended for approval based on product quality microbiology

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** New Drug Application

2. **SUBMISSION PROVIDES FOR:** New drug product

3. **MANUFACTURING SITE:**
Lyophilized powder *Solvent*

b(4)

Analytical testing:

b(4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Lyophilized powder in a multiple-dose vial and 1 pre-filled syringe with 1.5 mL solvent (with antimicrobial preservative)
- Subcutaneous injection
- 5 mg/vial (15 IU), final solution: 3.33 mg/mL somatropin

5. **METHOD(S) OF STERILIZATION:** Aseptic fill

6. **PHARMACOLOGICAL CATEGORY:** Growth hormone

B. **SUPPORTING/RELATED DOCUMENTS:** OGD Microbiology Review #2 of DMF dated 11-FEB-2003 b(4)

C. **REMARKS:** The applicant submitted a BC amendment on 07-FEB-2006 to describe upgrades to the manufacturing facility. Only those upgrades that are relevant to the manufacture of this product are reviewed. b(4)

An electronic communication was sent to the US Agent on May 18, 2006 to request additional information. Another communication was sent on June 22, 2006 because 2 questions were inadvertently left out of the first information request. A BC amendment was submitted on July 18, 2006.

The US Agent was contacted again on August 7, 2006 to request additional information on questions generated during the review of the 18-JUL-2006 amendment. Another BC amendment was submitted on September 6, 2006.

file name: N021905R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval based on product quality microbiology

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug substance is sterile and manufactured using recombinant DNA technology. The drug product is aseptically filled and lyophilized. The solvent contains a preservative and is filled aseptically followed by terminal sterilization.

B. Brief Description of Microbiology Deficiencies – None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Anastasia G. Lolas

B. Endorsement Block
Bryan S. Riley, Ph.D.

C. CC Block
N/A

26 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Anastasia Lolas
5/19/2006 09:05:10 AM
MICROBIOLOGIST

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Pharmaceutical Sciences
New Drug Microbiology Staff
Bldg 21, Room 3657
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

ELECTRONIC TRANSMITTAL
From: Anastasia Lolas
Tel: (301) 796-1566
Fax: (301) 796-9737

Message To: Bruce Babbitt, Ph.D.
Principal Consultant (Biologics)
PAREXEL International
Fax Number: (978) 848-2221
Phone Number: (781) 434-4057

Date: May 18, 2006

MESSAGE: Request for additional information regarding NDA 21-905

I'm currently reviewing NDA 21-905 and I need additional information in order to complete my review. Please provide a response to the following questions and submit an official amendment to the Division of Metabolic and Endocrine Drug Products. If you have any questions, you can contact me at 301-796-1566.

Lyophilized powder

1. A description of the positive and negative controls used in the microbial ingress test, and data to demonstrate that the culture medium supported microbial growth.
2. A description of the configurations used in the of the 5 mL vials (validation data were provided for the worst-case pattern). b(4)
3. A description of the configurations used in the , where the and where in the were placed, the % recovery of and positive control values.
4. A comparison of the 2 protocols used for the initial validation and requalification studies for equipment and and SIP. Are there any differences in the validation parameters and acceptance criteria?
5. Microbial challenge studies for the TL and miscellaneous equipment maximum configurations.
6. A description of the controls in place to ensure that the seals are clean.
7. The most recent requalification data for all sterilization processes.

Solvent b(4)

1. The production were not identified.

Please call the sender directly if you have any problem with the reception of this message.

2. A description of the [redacted] patterns, methods and controls to monitor production cycles, program for requalification of [redacted] and [redacted] (if any) of the product.
3. Validation studies and methods for the [redacted] of the solvent.
4. The applicant needs to clarify the following statement from Section 3.2.P.2.5: "the process assurance of sterility is high through "parametric release" in process, together with the standard QC sterility testing at lot release". Parametric release is not acceptable for new products without a manufacturing history.
5. A description of the microbiological environmental monitoring program.
6. Validation studies for the sterility and bacterial endotoxin test methods.

b(4)

Thank you,

Anastasia Lolas
Reviewer, New Drug Microbiology Staff
OPS/CDER/FDA

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/s/

Anastasia Lolas
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MICROBIOLOGIST

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Pharmaceutical Sciences
New Drug Microbiology Staff
Bldg 21, Room 3657
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

ELECTRONIC TRANSMITTAL
From: Anastasia Lolas
Tel: (301) 796-1566
Fax: (301) 796-9737

Message To: Bruce Babbitt, Ph.D.
Principal Consultant (Biologics)
PAREXEL International
Fax Number: (978) 848-2221
Phone Number: (781) 434-4057

Date: August 7, 2006

MESSAGE: Request for additional information regarding NDA 21-905

I have reviewed the response (dated 18-Jul-2006) to the 18-May-2006 information request. However, there are still a few questions that need to be addressed. Please provide a response to the following and submit an official amendment to the Division of Metabolic and Endocrine Drug Products. If you have any questions, you can contact me at 301-796-1566.

Lyophilized powder

1. Provide the most recent data for the [redacted] of [redacted] b(4)

2. The applicant stated in the original submission that the worst-case equipment [redacted] configuration is the [redacted]. which is used for annual requalification. However, the most recent requalification run (October 2005) provided in the amendment was performed using the "miscellaneous equipment" [redacted]. Clarify which [redacted] is the worst-case based on what studies and if this has changed since the original validation. b(4)

3. Regarding the media fill procedures: All units that are [redacted] and subsequently rejected should be included in the final media fill data and report. This would be representative of what happens during production when product is inspected once and then released. The media fill procedure should be revised and a draft copy provided.

Solvent

1. Provide the sampling locations, methods, growth media and incubation conditions used in the microbiological environmental monitoring program. Provide the alert and action levels for each area classification and sampling method.

2. The Maximum Valid Dilution (MVD) for the bacterial endotoxins test has been determined based on an endotoxin limit of ——— L. However, the endotoxin limit for the product is ——— which would result in a MVD < ——— The validation of the test method is still valid but the applicant needs to be aware of this observation. b(4)

3. Provide a summary of the product-specific validation study (using pre-filled syringes) scheduled to be performed in August 2006 as soon as it is complete. (If the study and report are not complete before the PDUFA date, please let me know.)

Thank you,

Anastasia Lolas
Reviewer, New Drug Microbiology Staff
OPS/CDER/FDA

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/s/

Anastasia Lolas
8/7/2006 03:57:36 PM
MICROBIOLOGIST

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