PAREXEL International
200 West Street
Waltham, Massachusetts, 02451-1163
Phone: 781-487-9900; Fax: 781-487-0525
www.parexel.com

N-000 C

NEW CORRESP

ORIGINAL

March 10, 2006

Mary Parks, M.D.
Acting Division Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-905; Amendment 3
Somatropin (rDNA origin) for Injection: Valtropin®

Subject: Amendment to a Pending Application –request for additional information

Dear Dr. Parks,

On behalf of LG Life Sciences, Ltd. (LG), PAREXEL International (PAREXEL), acting as the US agent, is hereby submitting an amendment to New Drug Application (NDA) 21-905 for Valtropin®, which was submitted to the Division on November 30, 2005.

Valtropin®, somatropin (rDNA origin) for daily injection, is proposed for th[redacted] b(4)

PAREXEL received a filing communication dated February 1, 2006, from the Division's Regulatory Project Manager requesting additional administrative information.

In response to this notification, we herein submit the following FDA forms signed by both the foreign sponsor, LG Life Sciences, and the US Agent, PAREXEL International:

FDA Forms 356h, 3397, 3454 and 3455 (Financial Disclosure), and 3542a (Patent Information)

Amendment 3 is being submitted on one CD (approximately 3 MB). A separate instruction sheet (*revinstr.pdf*) is included (electronically only) on the CD, which contains a full description of the electronic file set-up. The instruction sheet is provided

to facilitate incorporation of the files into the Valtropin® (CTD formatted) eNDA. The CD has been scanned using Sophos Anti-Virus® software, Version 3.99, and no viruses were detected.

Should the Division have any questions regarding this submission, please do not hesitate to contact me at 781-434-4057.

Sincerely,

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

bruce.babbitt@parexel.com

cc: **LG Life Sciences**
Youn Sung Choo
Hyi-Jeong Ji

PAREXEL International (US Agent)
Hoss Dowlat
Alberto Grignolo

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

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

US Agent:
PAREXEL International
200 West Street
Waltham, MA 02451

2. TELEPHONE NUMBER *(Include Area Code)*

Sponsor: 822-3773-7803 US Agent: 781-487-9900

3. PRODUCT NAME

Valtropin®, Somatropin (rDNA origin)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-905

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

Not applicable
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

PD 3006315

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Steve Jensen for Alberto Grignolo, Ph.D.	Vice-President, Product Development	Nov. 11, 2005

FORM FDA 3397 (12/03) Alberto Grignolo, Ph.D., Corporate VP/ General Manager, PAREXEL Drug Development Consulting Feb. 22, 2006

PSC Media Arts (301) 443-1090 EF

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
LG LIFE SCIENCES LTD LG Life Sciences Ltd 20, Yoido-dong, Youngdungpo-gu Seoul 150-721 NO DATA NO DATA KR	21-905
2. TELEPHONE NUMBER 822-3773-0693	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [X] YES [ ] NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Valtropin (Somatropin)	6. USER FEE I.D. NUMBER PD3006315

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act	[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
See signature on Form FDA 3397 (previous page)		

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$767,400.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

DUNS # 68-829-8798

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
LG Life Sciences, Ltd.	November 30, 2005
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
822-3773-0693	822-785-0324
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
20, Yoido-dong Youngdungpo-gu Seoul 150-721, Korea	PAREXEL International Tel: 781-487-9900 200 West Street Fax: 781-487-0525 Waltham, MA 02451

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-905

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Somatropin	Valtropin®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Somatropin (rDNA origin)	Also known as Eutropin™

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution for Injection	5 mg (15 IU)	Subcutaneous Injection

(PROPOSED) INDICATION(S) FOR USE:

Children:

Adults:

b(4)

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug NA Holder of Approved Application NA

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: NA

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Obtain US marketing approval of Valtropin® for treatment of patients with growth hormone deficiencies.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Active Pharmaceutical Ingredient (API) Manufacturer:
LG Life Sciences, Ltd.
Iksan Plant
601 Yongje-dong, Iksan-si
Jeonbuk-do 570-350, Korea
Contact: Sunjin Koh
Tel: 82-63-830-4356

b(4)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
IND 62,376, Valtropin® (also known as Eutropin™), daily rhGH
IND 69,726. LB03002. Sustained Release Recombinant Human Growth Hormone (sr-rhGH), somatropin
DMF #
DMF #
DMF #
DMF #

b(4

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On Original

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☒	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☒	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Steven Jensen for For Alberto Grignolo, Ph.D.	Alberto Grignolo, Ph.D. Corporate VP/General Manager PAREXEL Drug Development Consulting	November 30. 2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
PAREXEL International, 200 West Street, Waltham, MA 02451	781-487-9900

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (4/03)	Signature:	Youn Sung Choo, Ph.D. Vice-President, Product Development LG Life Sciences	Date: Feb. 24, 2006

PAREXEL International
200 West Street
Waltham, Massachusetts, 02451-1163
Phone: 781-487-9900; Fax: 781-487-0525
www.parexel.com

February 7, 2006

Mary Parks, M.D.
Acting Division Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: **NDA 21-905; Amendment 2**
Somatropin (rDNA origin) for Injection: Valtropin®

Subject: **Amendment to a Pending Application – CMC Information**

Dear Dr. Parks,

On behalf of LG Life Sciences, Ltd. (LG), PAREXEL International (PAREXEL), acting as the US agent, is hereby submitting an amendment to New Drug Application (NDA) 21-905 for Valtropin®, which was submitted to the Division on December 1, 2005.

Valtropin®, somatropin (rDNA origin) for daily injection, is proposed for the ——— b(4)

This NDA amendment has two purposes. The first is to provide for facility renovations that were recently completed at the drug product contract manufacturing site ——— b(4) to upgrade the ——— manufacturing areas and specific equipment used in drug product manufacture.

The second purpose is to provide further characterization data against the newly commercially available USP somatropin to complete the extensive data already submitted in the NDA.

An overview of the content of this submission is provided following this cover letter.

Amendment 2 is being submitted on one CD (approximately 18.5 MB), as per instructions received from Kenneth Edmunds, Jr, IT Specialist, CDER, OBPS, (via e-mail dated February 3, 2006). A separate instruction sheet (*revinstr.pdf*) is included (electronically only) on the CD, which contains a full description of the electronic file set-up. The instruction sheet is provided to facilitate incorporation of the files into the Valtropin® (CTD formatted) eNDA. The CD has been scanned using Sophos Anti-Virus® software, Version 3.99, and no viruses were detected.

Should the Division have any questions regarding this submission, please do not hesitate to contact me at 781-434-4057.

Sincerely,

Bruce Babbitt

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

bruce.babbitt@parexel.com

cc: **LG Life Sciences**
Youn Sung Choo
Hyi-Jeong Ji

PAREXEL International (US Agent)
Hoss Dowlat
Alberto Grignolo

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-905

2/1/06

Parexel International
Agent for LG Life Sciences, Ltd
Attention: Alberto Grignolo, Ph.D.
200 West Street
Waltham, MA 02451-1163

Dear Dr. Grignolo:

Please refer to your November 30, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valtropin® (somatropin [rDNA origin] for Injection, 5 mg.

We also refer to your submission dated December 13, 2005.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 13, 2006, in accordance with 21 CFR 314.101(a). However, in order for us to complete our general administrative review of your submission, please submit the following information to your NDA:

> For a foreign sponsor, both the applicant and US agent must sign FDA forms 356h, 3397 (userfee@FDA.GOV), 3454 and 3455 (Financial Disclosure), and 3542a (Patent Information).

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jena Weber
2/1/2006 12:51:26 PM

Appears This Way
On Original

Weber, Jena M

From: Bruce Babbitt [redacted] b(6)
Sent: Friday, January 13, 2006 11:46 AM
To: Galliers, Enid M; Galliers, Enid M b(6)
Cc: Johnson, Kati; Lamy, Ray [redacted]
Subject: LG Life Sciences Valtropin NDA 21-905 Amendments Timetable

Dear Enid,

I hope you and your colleagues are doing well, and that things are not too hectic so early in the New Year at your Division. I am aware that Dr. Orloff has left your organization, so that you must be very busy attempting to keep your many projects moving ahead at a normal pace. The reason for this communication is that I wanted to update you regarding our plans for upcoming Amendments to LG Life Sciences' Valtropin NDA (#21-905; submitted on December 1, 2005).

A. SINGLE CMC AMENDMENT

1. Drug Product [redacted] Facility Renovations
*I was contacted by Kati Johnson on 12/5/2005, and asked to clarify when LG intends to submit data to their NDA related to facility renovations that have taken place at their drug product manufacturer [redacted] Ray Lamy returned the call to Kati on 12/6/2005 and left a voicemail message attempting to follow-up on this topic. Kati left Ray a return voicemail message on 12/12/2005, clearly indicating that we should discuss this topic directly with you. LG intends to submit the information supporting the [redacted] facility renovations at the latest by **February 8, 2006**.* b(4)

2. USP Characterization Testing
*LG has completed their drug substance characterization testing demonstrating the comparability of Valtropin to USP RS and intends to submit the data at the latest by **February 8, 2006**, along with the [redacted] facility renovation data.* b(4)

B. 1-2 CLINICAL AMENDMENTS
(the number of amendments depends upon your feedback)

1. 4-Month Safety Update
*LG plans to submit their 4-month safety update for Valtropin on **April 1, 2006**. Dr. Perlstein recommended to me during a phone call on 11/23/2005 that LG present this data by modification of the existing safety Tables (presented per indication) in the NDA.*

2. Rollover Study Data
LG has now completed two Phase III Valtropin rollover (extension) studies, BP-EU-003-RO (children with GHD) and BP-EU-002-RO (girls with TS). During the 11/23/2005 phone call with me, Dr. Perlstein recommended that LG submit the rollover study data as part of the 4-month safety update to the NDA. However, I understand from your conversation with Ray Lamy on 12/8/2005 that this approach for submitting the rollover data might not be appropriate (dependent upon the type of data to be submitted), and that a separate NDA Amendment distinct from the 4-month safety update might be required.

Per your request to Ray Lamy, below is a brief description of the composition of the rollover/extension study data planned for submission to the NDA:

***Study BP-EU-003-RO** : children with GHD; ITT = 122; follow-up to BP-EU-003 study; safety and efficacy of Valtropin for an additional 12 months of therapy; long-term safety and efficacy data to be submitted.*

Study BP-EU-002-RO *: girls with TS; ITT = 29; follow-up to BP-EU-002 study; safety and efficacy of Valtropin for an additional 12 months of therapy; long-term safety and efficacy data to be submitted.*

Please let me know if LG's rollover/extension study data can be submitted with the NDA 4-month safety update, as suggested by Dr. Perlstein. If so, our target submission date for this information is ***April 1, 2006****. If you do suggest separate submissions, we could also accommodate an April 2006 submission of the rollover study data (we could also submit this data at a later time, if that would be more convenient for the review team).*

Additionally, I am aware that during your conversation with Ray Lamy you requested that PAREXEL establish a secure e-mail connection to your Division, as soon as possible. Ray is currently working with our service provider, VeriSign, to get this task completed. We expect that this connection will be up and running in ***approximately one week*** *(I just received a PIN number, password and installation instructions today), and I will provide you with the relevant information for using this connection at that time.*

Thank you for your time and attention to this message, and please feel free to call me if you want to talk about any of the information included in this communication.

Regards,

Bruce Babbitt, Ph.D.
PAREXEL International
US Agent for LG Life Sciences

phone : 781-434-4057

Appears This Way
On Original

Division of Metabolic and Endocrine Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 21-905

Name of Drug: Valtropin (somatropin [rDNA] for Injection)

Sponsor: L.G. Life Sciences, LTD

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Electronic/Paper (1.1)

Submission Date: November 30, 2005 **Receipt Date:** December 1, 2005

Filing Date: January 30, 2006 **User-fee Goal Date: October 1, 2006**

Proposed Indication: For the [redacted] b(4)

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Vol. 1
2. Form FDA 356h (original signature)	X		Vol. 1
Establishment information (facilities ready for inspection?)	X		
b. Reference to DMF(s) & Other Applications	X		Electronic
3. User Fee FDA Form 3397	X		Vol. 1
4. Patent information & certification	X		Vol. 1
5. Debarment certification (Note: Must	X		Vol. 1

have a definitive statement)			
6. Field Copy Certification	X		Vol. 1
7. Financial Disclosure	X		Vol. 1
8. Comprehensive Index	X		Vol. 1
9. Pagination	X		Where applicable
10. Summary Volume	X		Electronic
11. Review Volumes	X		Electronic & Vol. 1
12. Labeling (PI, container, & carton labels, & pre-filled syringe).	X		Electronic
a. unannotated PI	X		Electronic
b. annotated PI	X		Electronic
c. immediate container	X		Electronic
d. carton	X		Electronic
e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Electronic
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Electronic

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Electronic
2. Foreign Marketing History		✔	N/A
3. Summary of Each Technical Section	X		Electronic, where applicable
a. Chemistry, Manufacturing, & Controls (CMC)	X		Electronic
b. Nonclinical Pharmacology/Toxicology	X		Electronic
c. Human Pharmacokinetic & Bioavailability	X		Electronic
d. Microbiology	X		Electronic
e. Clinical Data & Results of Statistical Analysis	X		Electronic
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Electronic
5. Summary of Safety	X		Electronic
6. Summary of Efficacy	X		Electronic

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	X		Electronic

2. Controlled Clinical Studies	X		Electronic
a. Table of all studies	X		Electronic
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Electronic
c. Optional overall summary & evaluation of data from controlled clinical studies	X		Electronic
3. Integrated Summary of Efficacy (ISE)	X		Electronic
4. Integrated Summary of Safety (ISS)	X		Electronic
5. Drug Abuse & Overdosage Information			Electronic, labeling
6. Integrated Summary of Benefits & Risks of the Drug	X		Electronic
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	X		Electronic (labeling)

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	X		Electronic, indication(s) are for peds population
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		X	

a. Proposed unannotated labeling in MS WORD	X		Electronic
b. Stability data in SAS data set format (only if paper submission)		X	
c. Efficacy data in SAS data set format (only if paper submission)		X	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	
3. Exclusivity Statement (optional)		X	

Y=Yes (Present), N=No (Absent)

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/s/

Jena Weber
1/31/2006 10:50:48 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPS, Attention: David Hussong, Ph.D.
HFD-805

FROM: DEMP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT: NDA	DATE OF DOCUMENT
12/23/05		21-905		11/30/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Valtropin (somatropin rDNA origin) for Injection	S	Growth Hormone	7/15/06

NAME OF FIRM: LG Life Sciences, Ltd.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review and comment on microbiology controls proposed for the drug substance, drug product, and diluent; sterilization and aseptic processing validation for the drug product and diluent; antimicrobial effectiveness in the reconstituted multi-dose product. The NDA is electronic and in CTD format. The sections for Microbiology's review are found throughout the CMC folder.

PDUFA DATE: 10/1/06

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)		
Jena Weber, 301-796-1306	☒ DFS ONLY	☐ MAIL	☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER		

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/s/

David Hussong
12/28/2005 10:27:48 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Division/Office):
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420

FROM: DEMP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/23/05		21-905	Tradename Proposal	11/30/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Valtropin (somatropin rDNA origin) for Injection	S	Growth Hormone	7/15/06

NAME OF FIRM: LG Life Sciences, Ltd.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Review and comment on proposed tradename:

PDUFA DATE: 10/1/06
Package Insert, Container, Vial, and Carton Labels – available via EDR

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jena Weber
12/23/2005 12:38:06 PM

Weber, Jena M

From: Nguyen, Quynh M
Sent: Friday, December 23, 2005 12:56 PM
Benedetto, Shannon
Weber, Jena M
Subject: FW: DFS Email - N 021905 N 000 30-Nov-2005 - Forms

Attachments: 09001464805dbaa1.pdf

09001464805dbaa1
.pdf (18 KB)

Hi Sharon,

This consult was DFSed inadvertently to ODS, but it is meant for DDMAC, so I'm forwarding it to you.

Thanks,
Quynh Nguyen
Project manager
ODS/DDRE

-----Original Message-----
From: CDER DocAdmin, DFS
Sent: Friday, December 23, 2005 12:57 PM
To: CDER ODS CONSULTS; CDER DDR510 Public Folder
Subject: DFS Email - N 021905 N 000 30-Nov-2005 - Forms

:ument room update the following:

		Decision Date	Decision Code
N 021905 N 000	30-Nov-2005	23-Dec-2005	:
N 021905 N 000 BM	13-Dec-2005	23-Dec-2005	:

Document Type: Forms
Form Group: CONSULT
Form Name: ODS Consult (Except Tradename Reviews)
Submission Description: DDMAC consult request

Author(s)/Discipline(s)
---
1. Jena Weber, CSO

Signer(s)
---
1. Jena Weber
23-Dec-2005

Supervisory Signer(s)
---
1. Jena Weber
23-Dec-2005

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Division/Office)*: DDMAC; attention: Shannon Benedetto			FROM: Jena Weber, PM Division of Metabolism & Endocrinology Products	
DATE: 12/23/05		NDA 21-905	TYPE OF DOCUMENT: PI, carton, vial & container labels	DATE OF DOCUMENT:11/30/05
NAME OF DRUG: Valtropin (somatropin rDNA) for Injection	PRIORITY CONSIDERATION: NO		CLASSIFICATION OF DRUG: Growth Hormone	DESIRED COMPLETION DATE: **7/15/06**
NAME OF FIRM: L.G. Life Sciences, Ltd.				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE–NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	X LABELING
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

Comments: Original NDA Submission. Please review and comment prn on all proposed LBL. Each section (PI, carton, vial & container) is available via EDR. **User Fee Goal Date: 10/1/06.**

SIGNATURE OF REQUESTER: Jena Weber, PM 301-796-1306	METHOD OF DELIVERY: DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jena Weber
12/23/2005 12:56:20 PM

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PAREXEL International

PAREXEL

10182 Telesis Court
San Diego, California 92121
+1 858 452 2345 Fax: +1 858 452 6543
www.parexel.com

December 13, 2005

David G. Orloff, M.D.
Division Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-905; Amendment 1
Somatropin (rDNA origin) for Injection: Valtropin®

Subject: Amendment to a Pending Application – Resubmission of Electronic Files

Dear Dr. Orloff,

On behalf of LG Life Sciences, Ltd. (LG), PAREXEL International (PAREXEL), acting as the US agent, is hereby submitting an amendment to New Drug Application (NDA) 21-905 for Valtropin®, which was submitted to the Division on November 30, 2005.

Valtropin®, somatropin (rDNA origin) for daily injection, is proposed for the [redacted] b(4)

PAREXEL received a facsimile dated December 9, 2005, from the CDER Electronic Document Room Staff indicating that some files within the folder *crf/BP-EU-003* of the Valtropin® NDA could not be copied from the CD-ROM provided.

In response to this notification, we herein submit all files contained within this folder to replace those provided in the original eNDA submission.

Amendment 1 is being submitted on one CD (approximately 44 MB) following the instructions provided in the December 9, 2005 facsimile. The CD has been scanned using Sophos Anti-Virus® software, Version 3.99, and no viruses were detected.

Should the Division have any further problems copying any of the files contained in this submission, please do not hesitate to contact me at 781-434-4057.

Sincerely,

Christie Hamel on behalf of

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

bruce.babbitt@parexel.com

cc: **LG Life Sciences**
Youn Sung Choo
Hyi-Jeong Ji

PAREXEL International (US Agent)
Hoss Dowlat
Alberto Grignolo

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-905

NDA ACKNOWLEDGMENT

12/6/05

Parexel International
Agent for LG Life Sciences, Ltd
Attention: Alberto Grignolo, Ph.D.
200 West Street
Waltham, MA 02451-1163

Dear Dr. Grignolo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Valtropin® (somatropin [rDNA origin] for Injection, 5 mg.
Review Priority Classification:	Standard
Date of Application:	November 30, 2005
Date of Receipt:	December 1, 2005
Our Reference Number:	NDA 21-905

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 30, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **October 1, 2006.**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
12/6/2005 09:32:40 AM

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PAREXEL International
200 West Street
Waltham, Massachusetts, 02451-1163
Tel : 781-487-9900; Fax : 781-487-0525
www.parexel.com

PAREXEL.

ORIGINAL

November 30, 2005

David G. Orloff, M.D.
Division Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 21-905
Somatropin (rDNA origin) for Injection: Valtropin®

Subject: NDA - Original Application

Dear Dr. Orloff,

On behalf of LG Life Sciences, Ltd. (LG), PAREXEL International (PAREXEL), acting as the US agent, is hereby submitting a New Drug Application (NDA) for Valtropin® (registered in October 2005, but described as Valtropin® throughout the dossier), a new drug for human use, in accordance with the regulations set forth in 21 CFR 314.50. Valtropin®, somatropin (rDNA origin) for daily injection, is proposed for the [redacted] b(4)

Eutropin™ INJ (a 1.33 mg / 4 IU formulation of somatropin initially approved for marketing in Korea) has gained regulatory approval in 12 countries worldwide (Brazil, Chile, Colombia, Egypt, India, Indonesia, Iraq, Korea, Pakistan, Syria, Thailand, and Venezuela) and is marketed in all of them. From 1992-2004, an estimate [redacted] vials b(4) have been sold, providing approximately 12 years of human exposure.

The Applicant has previously discussed structure, format, and requirements for paper/electronic copies for this NDA directly with the Division at a pre-NDA meeting held on December 1, 2004, and during subsequent phone calls with Enid Galliers, Regulatory Project Manager for NDA 21-905, held on April 22, 2005 and April 25, 2005.

Based upon these discussions, it was agreed that the entire NDA would be formatted per the ICH Common Technical Document (CTD) structure, and would be submitted electronically per the following Guidances for Industry: *Providing Regulatory Submissions in Electronic Format - General Considerations (January 1999) and Providing Regulatory Submissions in Electronic Format NDAs (January 1999).*

An eNDA folder structure is used for the electronic submission as opposed to an eCTD folder structure. Therefore, all modules of the NDA are submitted electronically as PDF files and include internal (within each document) and external (from the overall Table of Contents to other documents) bookmarks and hyperlinks. Clinical data is supplied as SAS transport files. It was also agreed with Ms. Galliers that any information that might be needed during the review as paper copy would be provided only upon receiving a formal request for such information from the Division.

As requested by Ms. Galliers, Module 1 has been provided as paper copy (as well as electronically) in an NDA Archival copy jacket. The electronic submission is being submitted on 3 CD-ROMs (approximately 1.5 GB), sent in a separate binder along with the paper copy of Module 1 to 5901-B Ammendale Road, Beltsville, MD 20705, as per the instructions on CDER's Electronic Regulatory Submissions and Review (ERSR) web page. The CD-ROMs have been scanned using Sophos Anti-Virus® software, Version 3.99, and no viruses were detected. The user fee of $767,400 (User Fee ID: PD3006315) was paid by LG as an electronic transfer of funds to the Mellon Bank, Pittsburgh, initiated on November 17, 2005. PAREXEL has verified FDA's receipt of the user fee, via an e-mail received on November 23, 2005 from Beverly Friedman, Office of Regulatory Policy, CDER.

This NDA includes clinical data from the following five completed clinical studies involving approximately 284 patients (189 children, 95 adults) and 24 healthy males to support the proposed labeling for Valtropin®:

- **Study No. BP-EU-003**; a randomized, controlled, double-blind, 12-month, multi-center (Europe), Phase III clinical study of Eutropin™ (now filed under the trade name Valtropin®) against an active control in 149 treatment-naive children with GHD (149 patients [99 versus 50] randomized; 147 patients [98 versus 49] safety population; 129 patients [88 versus 41] full analysis set),

- **Study No. HGCL-001**; a randomized, placebo-controlled, double-blind, multi-center (Korea), Phase III clinical study of Eutropin™ INJ administered over a duration of 3-6 months in 95 adults with GHD (95 patients randomized; 92 patients treated, ITT population, safety population),

- **Study No. BP-EU-002**; an uncontrolled, open, single-center (Moscow) 12-month Phase III clinical study of Eutropin™/Eutropin™ INJ (now filed under the trade name Valtropin®) in 30 girls with Turner Syndrome (30 patients full analysis set, safety analysis set),

- **Study No. TS-KOR-06102005**; an uncontrolled, open, multi-center (Korea) 12-month Phase III clinical study of Eutropin™/Eutropin™ INJ in 60 girls with Turner Syndrome (60 patients enrolled and analyzed for safety; 50 patients analyzed for efficacy), and

- **Study No. BP-EU-001**; a randomized, controlled, double-blind, cross-over, single-dose Phase I bioavailability study of Eutropin™ (now filed under the trade name Valtropin®) in 24 male, healthy volunteers, against a comparator product.

In addition to the completed clinical studies listed above, the following two extension studies have been performed by LG:

- **Study No. BP-EU-003-RO**; a Phase III, open, rollover study to assess the safety of children with GHD continuing 12 months of further treatment with Eutropin™ (now filed under the trade name Valtropin®), or switching from their previous investigational treatment to 12 months of new treatment with Eutropin™, and

- **Study No. BP-EU-002-RO**; a 12-month extension phase of Study BP-EU-002 in girls with Turner Syndrome.

The results of these two studies will be submitted as Amendments to NDA 21-905 in approximately two months. The Applicant believes that the additional data derived from these two extension studies will not negatively impact the pivotal safety and efficacy data included in this submission.

LG plans to submit a comprehensive Pharmacovigilance Plan for Valtropin® during the NDA review process, once the Division has conducted its risk management assessment in the targeted patient populations and provided its recommendations to the Applicant.

Regarding pharmaceutical matters, the data of a sixth characterization campaign of studies on Valtropin® against the newly commercially available somatropin, USP, will be submitted as an NDA amendment, complementing the body of evidence substantiating the authenticity of somatropin manufactured by LG.

Finally, there have been recent facility renovations at LG's drug product manufacturer, _____, that are considered by the Applicant to be minor (i.e., would be classified as a notifiable supplement post approval) and without any potential effect on the quality of the Valtropin® drug product. All relevant documentation supporting these facility changes will be submitted as a formal amendment to NDA 21-905, when it becomes available. b(4)

LG and PAREXEL look forward to the Division's review of this application. Should the reviewers need assistance regarding any aspect of this NDA, or need any hard copies of any CTD modules, please do not hesitate to contact me at 781-434-4057.

Sincerely,

Bruce Babbitt

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

bruce.babbitt@parexel.com

cc: **LG Life Sciences**
Youn Sung Choo
Hyi-Jeong Ji

PAREXEL International (US Agent)
Hoss Dowlat
Alberto Grignolo

LG Life Sciences

LG Life Sciences, Ltd.

Risk Assessment

Guidance for industry on risk management activities for drug and biological products was one of the goals of the Prescription Drug User Fee Act (PDUFA III, June 12, 2002). Specifically, FDA issued three concept papers (March 2005), each focusing on one aspect of risk management:

1. *Premarketing Risk Assessment (Premarketing Guidance)*
2. *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*
3. *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*

Many of the recommendations presented in the above guidances focus on situations in which a product may pose a clinically important and unusual type or level of risk.

The Sponsor believes that Valtropin®, somatropin (rDNA origin), a once-daily formulation of recombinant human growth hormone, has an acceptable risk to benefit ratio and behaves as would be expected for any other somatropin product intended for daily subcutaneous injection, and currently approved and marketed in the US.

Since the Sponsor has performed and will continue to perform, the routine risk assessment and risk minimization activities required for products by the Federal Food, Drug, and Cosmetic Act (FDCA) and pertinent FDA implementing regulations (e.g., FDA requirements for professional labeling and adverse event monitoring and reporting) during Valtropin®'s development and marketing, it is the Sponsor's opinion that an additional RiskMAP is not necessary for this product.

Date: NOV. 11, 2005

Youn Sung Choo, PhD
Vice-President, Product Development
LG Life Sciences, Ltd
20, Yoido-dong
Youngdungpo-gu
Seoul 150-721, Korea
Phone: +82 2 3773 0693
Fax: +82 2 785 0324
E-mail: yschoo@lgls.co.kr

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LG Life Sciences

LG Life Sciences, Ltd.

Environmental Assessment

"Per *21 CFR §25, Environmental impact considerations,* LG Life Sciences, Ltd. claims a categorical exclusion per *21 CFR § 25.31(a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety,* for the subject NDA for Valtropin®. To the knowledge of LG Life Sciences, Ltd. no extraordinary circumstances exist."

Date: Nov. 11, 2005

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 1, 2004

TIME: 2:00-3:00 p.m.

LOCATION: Parklawn 3rd Floor, Chesapeake Room

APPLICATION: IND 62,376

DRUG NAME: Valtropin (somatropin [rDNA origin] for injection)
TYPE OF MEETING: Pre-NDA

MEETING CHAIR: David G. Orloff, M.D.

MEETING RECORDER: Monika Johnson, Pharm.D.

FDA ATTENDEES:

Division of Metabolic and Endocrine Drug Products
David G. Orloff, M.D./Director
Robert Perlstein, M.D./Medical Reviewer
Jim Wei, M.D., Ph.D./Biopharmaceutics Reviewer, DPE II, OCPB
Hae Young Ahn, Ph.D./Biopharmaceutics Team Leader, DPE II, OCPB
Enid Galliers/Project Management Chief
Jeri El Hage, Ph.D./Pharmacology and Toxicology Team Leader
Herman Rhee, Ph.D./Pharmacology and Toxicology Reviewer
J. Todd Sahlroot, Ph.D./Biostatistics Team Leader, DB II, OB, OPSS
Cynthia Liu, Ph.D./Biostatistics Reviewer, DB II, OB, OPSS

Division of New Drug Chemistry II, Office of New Drug Chemistry
Janice Brown, M.S./Chemistry Reviewer
Stephen K. Moore, Ph.D./Chemistry Team Leader
Blair Fraser, Ph.D./Deputy Director
Eric Duffy, Ph.D./Director

EXTERNAL CONSTITUENT ATTENDEES:

LG Life Sciences

Soon-Jae Park, Ph.D.	Vice-President, Product Development
Hyi-Jeong Ji, Ph.D.	Senior Manager, Regulatory Affairs and Product Development
Young-Phil Lee, Ph.D.	Principal Scientist
Hyun-Jeong Koh	Project Manager

PAREXEL International (U.S. agent)

Hoss Dowlat, Ph.D.	Director, Regulatory Affairs
Bruce Babbitt, Ph.D.	Principal Consultant
Rick Schwen, Ph.D.	Principal Consultant

Consultants

b(4)

BACKGROUND: Valtropin (formerly known as Eutropin) is a recombinant human growth hormone product. The Agency has had the following meetings regarding Eutropin development:

November 5, 1998- Sponsor—LG Chemical and Merck KGaA, Pre-NDA meeting

September 27, 2000- Sponsor-BioPartners GmbH, End of Phase II meeting

August 6, 2003- Sponsor BioPartners, Guidance Meeting

Sponsorship was transferred from BioPartners GmbH to LG Life Sciences, Ltd. with PAREXEL, International as their US Agent.

The LG Life Sciences is proposing the following indications: b(4)

The sponsor originally was interested in the 505(b)(2) route of submission, but, given the current absence of Agency guidance for 505(b)(2) submissions for "follow-on protein products", the sponsor now wishes to proceed via the 505(b)(1) route of submission.

MEETING OBJECTIVES:

- Provide feedback to the sponsor regarding an acceptable regulatory pathway for Eutropin
- Advise the sponsor regarding the structure and content of the planned CTD-formatted NDA submission
- Provide feedback to the sponsor regarding appropriate labeling for the drug product

DISCUSSION POINTS:

Following introductions, Dr. Orloff stated the following regarding 505(b)(2) applications:

At this time, a policy/guidance regarding 505(b)(2) application requirements for recombinant human growth hormone products has not been completed.

The Agency then proceeded to provide responses (**bold font**) to the questions submitted by the sponsor (underlined). *Italics text* indicated discussion that took place at the meeting.

Regulatory Pathway

1) The applicant is aware that FDA is actively seeking input from representatives of the biopharmaceutical industry regarding how best to define and characterize so-called "follow-on protein products". Once this activity is completed, it is expected that FDA will be better positioned to establish draft guidelines regarding the scope of pre-clinical and clinical data that will be needed to sufficiently demonstrate safety and efficacy for these products. The applicant is also aware that there are many legal issues that remain to be resolved as FDA attempts to create some type of abbreviated approval pathway for follow-on biologics similar to the ANDA or 505(b)(2) application process. Given these factors, the applicant believes that an alternative NDA submission to the 505(b)(2) for Eutropin™ should be considered.

   Does the Division agree?

   FDA response: The Division agrees. Given the current lack of clarity regarding the requirements for a 505(b)(2) submission for "follow-on protein products" such as recombinant human growth hormone products, the Division recommends a 505(b)(1) submission.

2) In the core CTD, the applicant has presented head-to-head comparisons of non-clinical and clinical data for Eutropin™ against several marketed human growth hormone products, including Humatrope®. The data for the marketed products has been derived from both Summary Basis of Approval (SBA) documents and published articles.

   Does the Division agree that data accessed through FOI may be used for comparative purposes?

   FDA response: Yes.

   Is the comparative data necessary in light of the Division's response to Question 1?

   FDA response: Non-clinical comparative data are not essential. Clinical comparative data obtained from published literature may be helpful in our overall assessment of the information from the sponsor's trials for the Turner and adult GHD proposed indications. The sponsor plans to submit 3-month placebo controlled data in support of an indication for adult GHD. Comparative information from published literature may be helpful in our evaluation of the extent to which 3 month data reflect data after longer durations of therapy.

   Reliance by the FDA on unpublished data submitted in support of the approval of other rhGH products for its determination of the efficacy and safety of your product will render this application a 505(b)(2) application. However, the division believes

that the inclusion of data from the published literature in order to provide context for consideration of your findings in children with Turner syndrome and adults with growth hormone deficiency is acceptable under 505(b)(1). Final decision on whether all proposed indications can be considered under 505(b)(1) must await submission and regulatory review.

NDA Format and Content

3) The applicant filed an MAA in CTD format to the EMEA in June 2004, seeking marketing approval for Eutropin™ in the European Union. The applicant has provided selected CTD modules in this briefing package for reference and review by the Division. Included in the reference documents are Module 2.7, Clinical Summary, Module 2.4, Non-Clinical Overview, and Module 2.3, Quality Overall Summary.

   Does the Division agree that the format and content of the sample modules from the core CTD dossier meet FDA requirements for an NDA submission?

   FDA response: Yes, pending review.

4) The core CTD dossier, identical with that recently filed in Europe, consists of 45 volumes. In addition, there will be additional volumes of clinical case report forms. Since most modules are currently available as WORD and PDF documents on CD, the applicant proposes to submit a paper CTD (with modules 1, 2 and 3 provided electronically in their present form) for marketing approval.

   Does the Division agree with this approach?

   FDA response: Yes, but with the following additional comments/requests. The Division's Clinical Reviewer requested that, in addition to the clinical summaries contained in Module 2, the clinical study reports in Module 5 should be submitted electronically as PDF documents. Also, the document room will not accept any MS Word files with the exception of labeling. All documents must be submitted in PDF (for review using Adobe Acrobat), including labeling. The Division requests that MS Word versions of labeling also should be submitted. Datasets must be submitted in SAS transport files.

5) The are two studies which were conducted in Korea for which clinical summaries are available in the CTD:

   - an uncontrolled clinical study of Eutropin™ in girls with Turner syndrome
   - a randomized, double-blind, placebo-controlled, clinical study of Eutropin™ in adults with GHD

   Does the Division require that the study reports for these two studies be translated into English, and is there a requirement for electronic datasets for these studies?

   FDA response: Yes, these study reports must be translated into English. Yes, electronic datasets should be submitted for these studies.

Product Labeling

6) The applicant is preparing a preliminary package insert (PI) to represent what we believe to be an acceptable class label for a somatropin product in the U.S. The clinical indications, the dosage recommendations, and the route of administration sought in the labeling are all supported by clinical data derived from both controlled and uncontrolled clinical trials of Eutropin™. The applicant used Lilly's Humatrope® Summary of Product Characteristics (SPC) as a model for preparing the product label for Europe. In the U.S., however, the corresponding U.S. PI is very different, in particular with regard to the adverse reactions section. For example, ADEs are described in the Humatrope® U.S. PI and not ADRs as in the Humatrope® E.U. SPC. Additionally, the U.S. PI separates ADEs by indication, while the E.U. SPC describes ADRs across all treatment areas. We have noted that the U.S. PI for Nutropin AQ® more closely resembles the E.U. SPC for Humatrope®. Consequently, the applicant is proposing to follow the U.S. PI based on Nutropin AQ®.

Does the Division agree that this approach in developing labeling for Eutropin™ meets current standards?

FDA response: No. Adverse events should be separated by indication, as in the Humatrope U.S. package insert. In addition, 1) brief clinical summaries should be provided in the CLINICAL STUDIES section of the package insert for *all* label-enabling studies, including the study conducted in children with growth hormone deficiency (data comparing the growth response after Valtropin to the growth response after Humatrope may or may not need to be included), and 2) the PRECAUTIONS, WARNINGS, and CONTRAINDICATIONS sections of the package insert should be as comprehensive and *current* as possible. In this regard, the *most recent* package inserts for the other FDA-approved somatropin products should be used as models.

Statistical Analysis Plan

7) For the reference-controlled study claiming non-inferiority of Eutropin™ versus Humatrope®, statistical analysis of the primary target variable height velocity at 12 months was performed by the one-sided t-test for two independent samples. Confidence interval estimation was based on the ANCOVA model. The confirmatory analysis of the primary efficacy variable was to be clearly distinguished from supporting exploratory analyses of the primary and secondary variables. For each parameter, standard descriptive summary statistics were displayed. All p-values and confidence levels of additional inferential statistical methods were to be interpreted in the exploratory sense.

Detailed information is given in:

- CSR BP-EU-003, page 43-46 (see tab following questions)
- CSR BP-EU-002, page 35-37 (see tab following questions)

Does the Division agree that this represents the best way to present this data for statistical review?

FDA response: Yes, however, we consider the ITT analysis as primary. During the review of other active control studies, we have not found a consistent pattern with respect to the conservativeness of the ITT analysis. In some studies, the ITT analysis was more conservative than other analyses, in some studies it was not. In the absence of compelling evidence either way, it seems important to emphasize the analysis (ITT) that best preserves the randomization. We would also like to see a completers analysis to examine the consistency of this result with the ITT approach.

Also, please provide height and associated dates for all data collected prior to entering the study so that height velocity at baseline can be verified.

Clinical Development

8) The applicant has completed five clinical trials of Eutropin™ spanning both patients (children and adults with GHD) and healthy volunteers. These studies include a) a controlled clinical trial in children with GHD of Eutropin™ (15 IU) against Humatrope®, b) a controlled clinical trial in adults with GHD of Eutropin™ (4 IU) against placebo, c) two uncontrolled clinical studies in girls with Turner syndrome, and d) a bioequivalence study in healthy volunteers comparing Eutropin™ against Humatrope®. The applicant believes that these studies, taken together, are sufficient to support the proposed labeling claims and marketing approval for Eutropin™.

   Does the Division agree, given the regulatory pathway recommended by the Division in response to Question 1?

   FDA response: Yes, pending review. As indicated in the response to Question 2 above, we believe that the submission of published literature in support of your findings in children with Turner syndrome and adults with growth hormone deficiency is acceptable under 505(b)(1).

9) The applicant believes that Eutropin™ safety data presented in Section 2.7.4 of the core CTD dossier, taken together with Eutropin™ efficacy data presented in Section 2.7.3, is sufficient to meet FDA requirements. No integrated data analyses are planned due to the variability in disease populations. Instead of integrated summaries, a side-by-side comparison of Eutropin™ and Humatrope® study data is provided.

   Does the Division agree that side-by-side summaries are sufficient and that no formal ISS or ISE analyses are required in the NDA submission?

   FDA response: Yes, with the following request. The safety data for patients with pediatric growth hormone deficiency, Turner syndrome and adult growth hormone deficiency should be presented and discussed separately.

Non-Clinical Development

10) The applicant believes that the non-clinical CTD package (module 2.4), which consists of data derived from studies performed by the applicant together with tabulations of comparative data derived from Summary Basis of Approval (SBA) documents and NDA

review summaries (accessed by the applicant through FOI), is sufficient to qualify impurities and support the safety of Eutropin™. In addition, the applicant believes that the overall non-clinical profile associated with the proposed product is comparable to that of other marketed somatropins.

Does the Division agree that the non-clinical data included in CTD module 2.4 supports the safety of the proposed product, and is acceptable for filing a marketing application?

FDA response: Yes.

Chemistry, Manufacturing, and Controls (CMC)

11) CMC CTD modules submitted to the EMEA for review were designed for both the EU and the US, and will be included in the US NDA. Some additional certificates of analysis and batch records, as well as new updated stability data, will be added to these modules in order to meet current US requirements. There will be stability data derived from at least [redacted] commercial lot sizes of drug product, including at least one year of standard shelf life (2°-8°C) stability data for each lot following ICH guidelines included in the CMC section of the NDA. b(4)

Does the Division agree that the planned format and content of the CMC section of the CTD is sufficient for the NDA?

FDA response: Yes, your proposed format is acceptable; however, we are unable to comment on the content until a review of your submission is complete. We have the following additional recommendations:

a. For a 505(b)(1) application, the CMC section should not include comparative analysis with Humatrope (or any other approved growth hormone product).

b. Include bioidentity testing in the drug substance or drug product specifications.

c. All impurities should be characterized. You should also determine whether these are process- or product- related (see ICH Q6B). In particular, the IEF gels indicate the presence of a minor band that may be the result of [redacted] yeast. b(4)

d. If you plan to label your product "USP", you should follow the USP somatropin monographs including correlation of bioassay results with HPLC Assay. This may be submitted in an amendment if not available at time of filing the NDA.

The Sponsor indicated they have no evidence of glycosylation of the rhGH. The Agency inquired if the protein was fully sequenced. The Sponsor replied affirmatively, however there were some ambiquities.

12) The quality overall summary (CTD module 2.3) and drug product formulation development (CTD module 3.2.P.2.2.1) are provided as part of the supporting documents in the Briefing Package.

Does the Division agree that these CTD CMC modules meet FDA's requirements and that the necessary information is provided to support a marketing application?

FDA response: Yes.

Additional comments/requests by the Division:

1. Please express all laboratory results in "American" units.

2. Were patients with overt diabetes mellitus excluded from the 4 pivotal studies?

3. With regard to the placebo controlled study conducted in adults with growth hormone deficiency, a) include the methodology utilized to measure total body fat and lean body mass (DEXA vs. BIA); b) include the paradigm utilized to titrate the starting dose of Valtropin as per serum IGF-I levels and adverse events; c) compare the efficacy results and mean final doses of Valtropin in men vs. women receiving estrogen replacement therapy; d) attempt to correlate the changes in body composition and serum IGF-I levels; e) include fasting blood glucose shift tables and narrative summaries for patients who manifested abnormal glucose tolerance on-study (sustained and transient); f) express serum IGF-I results as both absolute values and standard deviation scores (means and distribution of effect).

DECISIONS (AGREEMENTS) REACHED:

See discussion questions.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None.

ACTION ITEMS:

None.

ATTACHMENTS/HANDOUTS:

None.

Signed by Meeting Chair: December 17, 2004 /s/ (date)
David Orloff, Director, DMEDP

Recorded by : December 17, 2004 /s/ (date)
Monika Johnson, RPM, DMEDP

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/s/

Monika Johnson
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MEMORANDUM OF TELECON

DATE: August 6, 2003

APPLICATION NUMBER: IND 62,376, Eutropin (somatropin for injection)

BETWEEN:

Name: [redacted] b(4)

Hyi-Jeong Ji, Principal Scientist
Conrad Savoy, Head, Pharma Development, hGH Project, BioPartners
Young-Phil Lee, Senior Scientist

Phone: 202-728-1400

Representing: SRA International, Inc., US Agent for BioPartners

AND

Name:

Division of Metabolic and Endocrine Drug Products, HFD-510
Monika Johnson, PharmD, Regulatory Project Manager
Enid Galliers, Chief Project Management Staff
Duu Gong Wu, PhD, Deputy Director, DNDCII
Janice Brown, MS, Chemistry Reviewer

SUBJECT: Eutropin Development [505(b)(2)] non-AB rating

BACKGROUND

On May 8, 2003, the sponsor requested a meeting to discuss developmental issues and provide clarification of the requirements for testing for host cell protein (HCP) impurities in Eutropin. The meeting was originally granted as a face-to-face but mutually changed to a teleconference.

There have been ongoing communications (November 1998- November 2002) between the Agency (FDA) and SRA International, Inc., regarding development of this product.

On July 30, 2003, our team (clinical, chemistry, and biopharmaceutics), with David Orloff, Division Director, discussed the questions outlined in the May 8, 2003 submission. After this meeting, it was confirmed by the pharmacology/toxicology (pharm/tox) supervisors, Drs. Jeri El Hage and Karen Davis-Bruno that the pharm/tox studies presented in the IND and reviewed (Aug 23, 2002) by Dr. Herman Rhee were adequate to qualify HCP.

The sponsor submitted a proposal (Attachment III) for characterizing the manufacturing process-related impurities on July 24, 2003. FDA stated that with the exception of the process related

substances, the approach was acceptable. There should be comparative analysis of the process related substances with the listed drug or levels published in peer reviewed literature.

DISCSUSSION

Following introductions, FDA stated that the completed pharm/tox studies submitted to the IND qualify the HCP if the construct is the same and the genetic background has not changed. The sponsor confirmed understanding, but stated that they may not use the pharm/tox studies because there were some formulation changes in the drug product but the drug substance was identical to that used in the animal studies. The sponsor wanted to discuss alternate development options if the pharm/tox studies were not used for HCP qualification which include comparing the HCP levels in their product with published levels of other biotech products. Dr. Wu stated that the Agency discourages discussion of hypothetical scenarios because actual animal studies have already been performed which qualify the HCP levels in the drug substance. Subsequently, the sponsor declared that the stand behind the studies submitted.

The sponsor asked if the submitted (emailed August 6, 2003 agenda item) Immuno-ligand assay (completed threshold detection assay) was reviewed and found acceptable. FDA replied that it is a 'review issue' because there was not enough detail of the method to perform a meaningful review. We also recommended that the ELISA demonstrate a broad specificity against a wide range of the host cell proteins.

CONCLUSIONS

The sponsor was told that Somatropin 505(b)(2) guidance document is evolving and that the Agency's authority to approval a 505(b)(2) application is being challenged. Although we cannot predict the future, the Division felt obliged to inform the sponsor.

The sponsor requested to reserve a meeting for early October 2003, in the event that other issues may arise. FDA declined this request because we addressed all outstanding issues. We recommended that another meeting request be submitted if new issues arise.

Monika Johnson
Regulatory Project Manager

/s/ August 20, 2003
Duu Gong Wu, PhD
Deputy Director, DNDCII

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/s/

Monika Johnson
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Meeting Minutes

IND # and Drug Name:	Pre-IND Eutropin (somatropin [rDNA origin])
Meeting Date:	September 27, 2000
Time:	11:00 am
Location:	Parklawn "Chesapeake" Conference Room
Indication:	Growth Hormone Deficiency in Children & Adults; Turner's Syndrome
Sponsor:	BioPartners GmbH
Type of Meeting:	EOP2
Sponsor Contact:	Bruce Bernard @ 202-728-1400 x16
Regulatory Project Manager:	Crystal King @ 301-827-6423
FDA Participants:	John Jenkins, M.D., Office Director David Orloff, M.D., Division Director Saul Malozowski, M.D., Ph.D., Medical Team Leader Robert Perlstein, M.D., Medical Reviewer Stephen Moore, Ph.D., Chemistry Team Leader Janice Brown, Ph.D., Chemistry Reviewer Jeri El-Hage, Ph.D., Pharmacology Supervisor Dave Hertig, M.S., Pharmacology Reviewer Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader Jim Wei, M.D., Ph.D., Biopharmaceutics Reviewer Joy Mele, M.S., Biometrics Reviewer Crystal King, P.D., M.G.A., Regulatory Project Manager
Sponsor Participants:	Cornelius Sobel, Ph.D., Director & VP, BioPartners Bruce Bernard, Ph.D., President, SRA International

b(4)

Young-Phil Lee, Ph.D., Senior Research Scientist, Life Science R&D

BioPartners
September 27, 2000

Meeting Objective: To clarify submission issues for an IND and subsequent 505(b)(2) NDA for Eutropin.

Background: BioPartners is the new sponsor for Eutropin. LG Chemical Ltd. is the manufacturer and marketer of Eutropin in several Asian countries since 1993. Refer to pre-IND meeting minutes of November 5, 1998.

A meeting package was submitted to the Division on July 29, 2000, and is appended as **Attachment A**.

Following an internal meeting on September 6, 2000, the Division concluded we were unable to respond to the agenda discussion questions as posed by BioPartners in the meeting package. The meeting package did not clearly delineate whether the path BioPartners would seek for their 505(b)(2) application would be an AB rating or a non-AB rating. Thus, the Division proposed an alternate agenda for the meeting in which the Division would present the requirements, as best as could be delineated, by each discipline for each scenario. Then, any remaining questions would be addressed. The Division noted that the non-AB rating is the route with which we are most familiar. The AB rating route requirements for complex proteins remain under development, and any sponsor should exercise caution in attempting to follow this course. The Agency is developing a Guidance document on this topic. A date for publishing the draft Guidance for comment is not known.

The slides used by the Division to outline the requirements are appended as **Attachment B**. Additional significant comments are noted below and reference these slides.

Slide A (Filing Options)

Should BioPartners initially choose to submit an application under the non-AB rating route, and then, at a later point in time, choose to obtain an AB rating, this could be accomplished by submitting the necessary additional information (e.g., the results of a rigorous comparative PK/PD study).

Slide B (Chemistry)

All notations of "reference drug" listed for the comparator under "With AB Rating" refer to the US approved reference listed drug. (On the other hand, "Reference standard" refers to the WHO standard with regard to the requirements for a non-AB rating.) All release specifications must be comparable to the US approved comparator. The Division emphasized that in order to obtain an AB rating via the 505(b)(2) approach, comparisons must be made with a US approved reference product. We do not have any information on non-US products.

The use of Humatrope from French or German sources as the reference listed drug is problematic. The Agency has no way of knowing whether these products are equivalent to Humatrope from US sources.

A categorical exclusion for the environmental assessment requirement should be submitted.

Slide 3 (Biopharm)

The sponsor needs to demonstrate that the new product is as bioavailable as the approved reference product for either the rigorous comparative PK/PD study required for an AB rating submission or the comparative bioavailability study required for a non-AB rating. However, the non-AB rating comparative bioavailability study is less rigorous than the bioequivalence study required for an AB rating. (This is due to reliance on FDA findings of safety and efficacy for the reference approved drug.) For the non-AB rating PK study, 24 patients would be sufficient.

The Division indicated that although a one-week duration study may be sufficient for the AB rating PD trial, the Draft Guidance may recommend a two-week duration study.

Slides 5, ..., 8 (Clinical/Statistical, Children)

The following comments pertain only to the clinical studies required for the non-AB rating submission route:

1. The sample size required would depend upon the margin set for non-inferiority in an active controlled trial.
2. Naïve patients would be preferred (patients previously treated with rhGH would demonstrate greater variability in response).
3. The only indications granted would be those for which the sponsor demonstrated non-inferiority compared with the approved reference drug.
4. If the sponsor chooses to compare their product with historical data (rather than with an active control group), the historical information must be data specifically generated using the approved drug being referenced in the 505(b)(2) application. Moreover, the historical data selected should be derived from carefully selected, demographically well-matched children treated with the approved rhGH product for 12 months. The Freedom of Information Office can provide data summaries for approved products; published literature may be utilized, as well.
5. Although six-month data may be submitted at the time of filing, the Division will need 12-month data for approval.
6. BioPartners plans to develop a normogram to calculate HV SDS as well as height SDS for children in Moscow.

7. The Division reminded BioPartners that after achieving a non-AB rating, a sponsor may not state that their product is equivalent to the referenced drug; however, the labeling may state that their product is "not different" than an active control if this is adequately demonstrated in a well controlled trial.

The following comments pertain to the AB rating submission route:

1. If the sponsor demonstrates AB equivalence, the indications granted would likely be that of the reference product, excepting any applicable orphan designated indications.
2. With regard to the immunogenicity studies required to attain an AB rating, 50 patients followed for 6 months would be acceptable. However, the Division cautioned the sponsor that the antigenicity data for their product must be directly compared to the antigenicity of the reference drug in an actively controlled study (rather than a comparison with historical data).

Inclusion of published clinical studies in the submission is permissible under either the AB or non-AB route.

Slides 9, ..., 12 (Clinical/Statistical, Adults)

Note the primary endpoints are different for adults (e.g., measures of body composition). Otherwise, the comments made above regarding studies in children are applicable to studies in GHD adults.

Slide 13 (Regulatory)

BioPartners inquired about the requirement for all submissions to be electronic by 2001. C. King will confirm whether or not such a requirement has been issued.

Append: The PDUFA mandate is for FDA to be able to accept electronic submissions by FY 2002 (not 2001). We have been able to receive the NDA in electronic format since 1999. We are currently working on the capability to receive electronic IND submissions. Providing the NDA in electronic format is voluntary on the part of industry, although we do encourage it. Our guidance should be followed if a sponsor does elect to submit electronically.

Although FDA minutes are the official documentation of the meeting, we note that Sponsor minutes have not been provided at this time; therefore, no discrepancies are noted.

Prepared by: /Crystal King/ 10/24/00, Regulatory Project Manager
Crystal King, P.D., M.G.A. date

Concurrence: [signature] for RP 10/29/00, Meeting Facilitator
Robert Perlstein, M.D. date

Concurrences:	John Jenkins, M.D., Office Director	10.11.00
	David Orloff, M.D., Division Director	10.11.00
	Saul Malozowski, M.D., Ph.D., Medical Team Leader	ncr
	Stephen Moore, Ph.D., Chemistry Team Leader	10.11.00
	Janice Brown, Ph.D., Chemistry Reviewer	ncr
	Jeri El-Hage, Ph.D., Pharmacology Supervisor	ncr
	Dave Hertig, M.S., Pharmacology Reviewer	10.12.00
	Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader	10.18.00
	Jim Wei, M.D., Ph.D., Biopharmaceutics Reviewer	ncr
	Joy Mele, M.S., Biometrics Reviewer	10.10.00

Attachments:

A. Background package submitted 7/29/00
B. DMEDP presentation slides for 9/27/00

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cc: Division Subject File
HFD-510: C.King/D.Orloff/S.Malozowski/R.Perlstein/S.Moore/J.Brown/
J.El-Hage/D.Hertig/H.Ahn/J.Wei/J.Mele
HFD-102: J.Jenkins

Meeting Minutes

Drug Name:	Eutropin (somatropin [rDNA origin] for injection
Meeting Date:	Thursday, November 5, 1998
Time:	8:30 am
Location:	Parklawn Conference Room "M"
Indication:	Growth Hormone Deficiency
Sponsor:	LG Chemical and Merck KGaA
Type of Meeting:	Pre-NDA
Meeting Facilitator:	Sol Sobel, M.D.
Sponsor Participant Lead:	Bruce Bernard , Ph.D.
Regulatory Project Manager:	Crystal King, P.D., M.G.A.
FDA Participants:	Sol Sobel, M.D., Division Director
	Gloria Troendle, M.D., Deputy Director
	Saul Malozowski, M.D., Medical Team Leader (Acting)
	Stephen Moore, Ph.D., Chemistry Team Leader
	William Berlin, Ph.D., Chemistry Reviewer
	Duu-Gong Wu, Ph.D., Chemistry Team Leader
	Ronald Steigerwalt, Ph.D., Pharmacology Team Leader
	Dave Hertig, Pharmacology Reviewer
	Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
	Robert Shore, Pharm.D., Biopharmaceutics Reviewer
	Yuan Yuan Chiu, Ph.D., Deputy Director, Office of New Drug Chemistry, HFD-800
	Rita Hassall, Special Assistant to the Director, Office of Generic Drugs, HFD-600
Sponsor Participants:	Bruce Bernard, Ph.D., President, SRA International
	Dr. Thomas Hintze, Senior Manager, Merck BioPharmaceuticals, Merck KGaA
	Praveen Tyle, Ph.D., Scientific Advisor, Merck KGaA
	Ji-Yong Song, Ph.D., Director Biotech Research Institute, LG Chemical Ltd.
	Young-Phil Lee, Ph.D., Senior Research Scientist, Biotech Rosearch Institute, LG Chemical Ltd.

Meeting Objective:

Discussion on the submission of an ANDA vs. an NDA ; discussion on various submission issues.

Background:

Eutropin is a human growth hormone produced and marketed by LG Chemical, Seoul, Korea since 1993. It is synthesized by a specific strain of *Saccharomyces cerevisiae* and is a highly purified preparation. The partnership of LG Chemical and Merck KGaA in Germany seeks to market Eutropin in the U.S. through an - ANDA application.

Agenda Item 1: Does FDA agree that an ANDA submission is the appropriate regulatory approach?

Agreements: Due to the difficulty of establishing pharmacological equivalence with the innovator product, we recommend submitting a 505(b)(2) application. Alternatively, if the sponsor has the appropriate data, a 505(b)(1) could be submitted.

The NDA route allows us to address immunogenicity concerns for your product and for excipients, etc., accompanying the product. Immunogenicity studies cannot be done under a 505 (j) application.

Standards for substitutability are very high: chemical characterization and immunogenicity (non-concurrent). For immunogenicity, the Agency would need to see data for approximately 50 patients for three months. Antibody data would probably be sufficient. Comparative PK/PD data will also be needed.

The sponsor asked if the Lilly European product may be used for the comparitor study. FDA responded that if the sponsor can demonstrate that the European and United States Lilly products are identical, i.e., manufactured at the same site using the same process and release by the same Q.C. testing methods and acceptance criteria, that the European product may be used. This applies only if Humatrope is chosen as the reference drug.

Action Items: None.

***Note: Questions were presented by the sponsor in the context of an ANDA submission. It was decided by the Division and by the Office of Generic Drugs that an ANDA was not appropriate. The answers have been formatted as pertaining to a 505(b) application.*

Agenda Item 2: If an ANDA is the appropriate method for regulatory approval, can Nutropin be employed as the reference drug?

Agreements: Nutropin may be used as the reference drug for chemical and clinical comparisons.

Action Items: None.

Agenda Item 3: Based on the information provided in the background document, does FDA agree that there are no physical, chemical or biological differences between Eutropin and Nutropin which would preclude approval of an ANDA?

Agreements: An exhaustive pre-review of the data for the physico-chemical and biological comparison in the background package has not been performed; however, the following comments are offered: The comparison presented in the background package appears to be quite acceptable. Additionally, we would request 2-D NMR (NOSEY) or X-Ray structure comparison, rat bone growth assay, and protein content. This would be a one-time study, done on your product vs. the reference drug.

Action Items: None.

Agenda Item 4: Can Humatrope be used in the Bioavailability/Bioequilvalence clinical study due to the unavailability of sufficient quantities of Nutropin?

Agreements: No, pharmaceutical equivalence claims may only be made to the reference drug that you have chosen, Nutropin. Since the Office of Clinical Pharmacology and Biopharmaceutics usually assesses pharmaceutical equivalence on single-dose PK data, the protocol submitted will need revisions.

Action Items: For these pharmaceutical equivalence criteria, C_{max} as well as AUC should be investigated. Twelve subjects, which the sponsor proposed, may not have enough power to meet pharmaceutical equivalence criteria. The sponsor will conduct a power analysis and will submit a protocol.

Agenda Item 5: Will the results of this clinical study be acceptable to FDA if it is performed under GCP regulations and not performed under an IND?

Agreements: We can accept well performed studies not performed under an IND.

Action Items: None.

Agenda Item 6: Can we claim a categorical exemption from the Environmental Requirements?

Agreements: Yes; you will need to prepare and submit a request for a waiver of the requirement to prepare an EA (see 21 CFR 25.15, 25.30, and 25.31).

Action Items: None.

Agenda Item 7a: Does FDA agree with proposed ANDA table of contents?

Agreements: The proposed format appears acceptable. See also the guidance, "Chemistry, Manufacturing, and Controls Information for a Therapeutic

recombinant DNA-derived Product or a Monoclonal Antibody Product for in vivo Use," dated August, 1996 (CBER website).

Action Items: None.

b(4)

Agenda Item 7b: Does FDA agree that a ——— DMF can be submitted in support of the ANDA for information related to the synthesis and manufacture of the active drug substance?

Agreements: Yes.

Action Items: None.

Agenda Item 7c: Does FDA agree that ——— DMFs can be submitted in support of the ANDA for the drug substance and drug product manufacturing facilities? b(4)

Agreements: There is no ——— DMF requirement. The format for providing facility information is described in the Format Guidance (see 7a). Also, facility information for ——— is provided in the microbiology section for sterile-filling validation and is submitted in accordance with the Guidance in #7(a). See also ' ——— b(4)

Action Items: None.

Agenda Item 8: What specific CMC information is necessary to include in the ANDA for the diluent for drug product (i.e., manufacturing method, testing, stability data, compatibility with drug product, etc.)?

Agreements: The complete CMC information is needed, analogous to that required for the drug. The diluent should be validated according to the USP preservatives-efficacy for long-term storage. This test should also be performed for storage of the reconstituted drug. Further, a test and specification limit for m-Cresol needs to be included for release and stability.

Action Items: None.

Agenda Item 9a: Are the proposed stability programs for drug product and drug substance acceptable? (See also pages 5-8 of Attachment B.)

Agreements: The protocols appear to be acceptable. However, rat weight gain assay should be performed at infrequent intervals. We prefer measurements on the product at t_0, a middle timepoint during dossier review, and $t_{endpoint}$

Action Items: None.

Agenda Item 9b: Is it acceptable to provide 6 months stability data for drug product in the original ANDA and to update the ANDA during the review b(4

process with 12 months stability data to support the proposed expiration date of [redacted] b(4)

Agreements: Yes. However, explanation should be provided why the data are not available. Also, available Korean data may be submitted to support extended shelf life.

Action Items: None.

Agenda Item 10: Is it acceptable to submit executed batch records for one batch of final drug product, and the full unexecuted production record for drug product to fulfill requirements for batch documentation in the ANDA?

Agreements: Yes.

Action Items: None.

Agenda Item 11: Is it acceptable to limit the use of the rat weight gain assay to release of drug product and to implement the use of an alternative assay such as a radioreceptor or immunofunctional assay for bulk release and stability testing of bulk and final product and to include both methods for the proposed uses in the ANDA?

Agreements: Bioassay must be performed for drug product release. The proposed stability protocol provided in the package is quite acceptable; however, it should include bioassay at infrequent time points. Note that a cell-based assay is presented in the current proposed monograph for Somatropin in Pharmacopeal Forum.

Action Items: None.

Agenda Item 12a: Is it acceptable to implement a [redacted] change for the [redacted] for purification of bulk product from what was submitted in the background information by performing validation of the new process, and manufacture and stability testing of [redacted] drug substance and final product lots? b(4)

Agreements: Yes, provided the change is properly validated (i.e., impurity removal, etc.).

Action Items: None.

Agenda Item 12b: Is it acceptable to show equivalency of the [redacted] drug substance lots manufactured by the new process by testing according to release tests and specifications provided in table 3.4.1 in the background document, and comparing the results with drug substance manufactured according to the old process? b(4)

Agreements: This change will most likely affect purity. Therefore, validation of the ability of the new process to produce material of equivalent purity is most important. It may be necessary to include tests beyond those used for release testing to demonstrate equivalent removal of impurities, both process and product related.

Action Items: None.

Agenda Item 13: Do the process validation programs for fermentation, recovery, and purification processes fulfill FDA requirements?

Agreements: An exhaustive pre-review of the process and in-process controls in the background package has not been performed. However, the following comments are offered: It is necessary to validate these items; however, each process is unique and no standardized set of requirements exists. The proposed validations appear acceptable; still, it is not possible to determine their completeness in the absence of the entire package.

Action Items: None.

Prepared by: _____ 12-2-98 Regulatory Project Manager
Crystal King, P.D., M.G.A. date

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