CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-905

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

LG Life Sciences

LG Life Sciences, Ltd.

Patent Certification

Per 21 CFR 314.50 (h) (ii) No relevant patents, in the opinion and to the best knowledge of LG Life Sciences, Ltd., there are no patents that claim the drug on which investigations were conducted that are relied upon in this new drug application for Valtropin®, or that claim a use of such drug.

Date: Nov. 11, 2005

Youn Sung Choo, PhD
Vice-President, Product Development
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Appears This Way
On Original

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-905

NAME OF APPLICANT / NDA HOLDER
LG Life Sciences, Ltd.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Valtropin®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Somatropin (rDNA Origin)	5 mg (15 IU)

DOSAGE FORM
Subcutaneous Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	Feb, 24, 2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Youn Sung Choo, Ph.D. Vice-President, Product Development, LG Life Sciences, LTD.	
Address LG Life Sciences 20, Yoido-dong Youngdungpo-gu	City/State Seoul, Korea
ZIP Code 150-721	Telephone Number 822-3773-7803
FAX Number *(if available)*	E-Mail Address *(if available)*

PSC Media Arts (301) 443-1090 EF

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Steven Jensen for	Feb. 28, 2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official [US Agent]
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Alberto Grignolo, Ph.D. Corporate VP/ General Manager, PAREXEL Drug Development Consulting	
Address PAREXEL International 200 West Street	City/State Waltham, MA
ZIP Code 02451	Telephone Number 781-487-9900
FAX Number *(if available)* 781-487-0525	E-Mail Address *(if available)*

EXCLUSIVITY SUMMARY

NDA # 21-905 SUPPL # HFD # 510

Trade Name Valtropin

Generic Name somatropin [rDNA origin] for Injection

Applicant Name L.G. Life Sciences

Approval Date, If Known 4/19/07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-148 Norditropin

NDA# 21-413 Omnitrop

NDA# 20-656 Nutropin

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

BP-EU-003 BP-EU-002 TS-KOR-06102005
HGCL-001 BP-EU-001

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 62,376	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 62,376	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Jena Weber
Title: Project Manager
Date: 5/4/07

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
5/4/2007 08:12:34 AM

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PEDIATRIC PAGE

NDA 21-905 Supplement Type: NA Supplement Number: NA

Stamp Date: December 1, 2005 Action Date: October 1, 2006

Division of Metabolism & Endocrinology Products (DMEP)

Trade and generic names/dosage form: Valtropin (somatropin [rDNA origin] for Injection) 5 mg

Applicant: L.G. Life Sciences, Ltd. Therapeutic Class: 5

Indication previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 3

Indication #1: [redacted] b(4)

Indication #2: [redacted]

Indication #3: [redacted]

Is there a full waiver for this indication (check one)?

☒ Yes: Please proceed to Section A.

Please check all that apply: ___Partial Waiver ____Deferred __X__Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☒ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ▒ **Adult studies ready for approval – see indication #3**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments: Indications #1 and 2 are specified for use in the pediatric population.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Jena Weber, RHPM

{See appended electronic signature page}

Regulatory Project Manager

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

/s/

Robert Perlstein
2/16/2007 10:06:38 AM

LG Life Sciences

LG Life Sciences, Ltd.

Debarment Certification

LG Life Sciences, Ltd. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this new drug application for Valtropin®.

Date: Nov. 11, 2005

Youn Sung Choo, PhD
Vice-President, Product Development
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E-mail: yschoo@lgls.co.kr

Counter-signature

Date: Nov. 30, 2005

Alberto Grignolo, PhD
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Telephone: 781-487-9900

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Youn Sung Choo, PhD	Vice-President, Product Development
FIRM / ORGANIZATION: LG Life Sciences, Ltd	
SIGNATURE: YSC	DATE: Nov. 11, 2005

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts Branch (301) 443-1090 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

TO BE COMPLETED BY APPLICANT

The following information concerning P. Saenger (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study BP-EU-003 "Phase III study to compare efficacy and safety of a 12M treatment with two somatropins in GHD children" (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

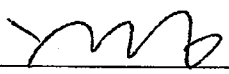
☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Youn Sung Choo, PhD	Vice-President, Product Development
FIRM / ORGANIZATION: LG Life Sciences, Ltd.	
SIGNATURE: 	DATE: Nov. 11, 2005

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

PSC Media Arts (301) 443-1090 EF

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

NAME	TITILE
Alberto Grignolo, Ph.D.	Corporate VP/ General Manager
FIRM/ORGANIZATION PAREXEL Drug Development Consulting	
SIGNATURE For Alberto Grignolo, Ph.D.	DATE Feb. 22, 2006

Appears This Way
On Original

FORM FDA 3454 – Additional Signature

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

✓ Privacy (b6)

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-905	Efficacy Supplement Type	Supplement Number	
Drug: Valtropin (somatropin [rDNA origin] for Injection)		Applicant: L.G. Life Sciences	
RPM: Jena Weber		DMEP	Phone: 301-796-1306

Application Type: (✓) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug referred to in 505(b)(2) application (NDA #(s), Drug name:

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	5
• Other (e.g., orphan, OTC)	N/A
User Fee Goal Dates	**October 1, 2006**
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(✓) Paid UF ID number: PD3006315
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No

• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	NN
• OC clearance for approval	NN
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(✓) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) (✓) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(✓) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	NO
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	✓

AP 4/19/07 ltr 4/18/06

General Information	
Actions	
• Proposed action	( ) AP ( ) TA (✓) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS: 9/8/06; 4/7/06 DDMAC: NR DSRCS: NN
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	✓
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NN
• Documentation of discussions and/or agreements relating to post-marketing commitments	NN
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	09/27/00
• Pre-NDA meeting (indicate date)	11/05/98 and 12/01/04
• Pre-Approval Safety Conference (indicate date; approvals only)	NN
• Other	08/06/03 (CMC)
❖ Advisory Committee Meeting	
• Date of Meeting	NN
• 48-hour alert	NN
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NN

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	~~9/x/06~~ 4/9/07
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NN
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MOR
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NN
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	~~10/xx/6~~ 2/16/07
❖ Demographic Worksheet *(NME approvals only)*	NN
❖ Statistical review(s) *(indicate date for each review)*	9/12/06
❖ Biopharmaceutical review(s) *(indicate date for each review)*	9/1/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NN
• Bioequivalence studies	NN
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	6/27/06 & 4/10/06
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	4/10/06
• Review & FONSI *(indicate date of review)*	NN
• Review & Environmental Impact Statement *(indicate date of each review)*	4/10/06
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	9/14/06 & 5/19/06
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable (✓) Withhold recommendation
❖ Methods validation	(✓) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/18/06
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NN
❖ CAC/ECAC report	NN

Division of Metabolism and Endocrinology Products

PROJECT MANAGER LABELING REVIEW

NDA Number: 21-905

Product: Valtropin (somatropin [rDNA origin] for Injection)

Sponsor: L.G. Life Sciences

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

Approval Date: April 19, 2007

Material Reviewed:

PI submitted December 20, 2006;
Carton, container and syringe (diluent) labels submitted on February 16, 2007.

Background and Summary Description: This new drug application provides for the use of Valtropin (somatropin [rDNA origin] 5 mg for injection, USP),

b(4)

Review:

Carton and Container Labels:

AP labeling for carton, container, and diluent syringe. No specific identifier noted or date of issue. Revisions made as per recommendations from DMETS.

Package Insert:
AP labeling submitted (SPL and final draft). No identifier noted or date of issue specified.

Conclusion: All labeling is acceptable. Issue AP letter request FPL in SPL.

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/s/

Jena Weber
5/11/2007 09:50:31 AM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-905

Parexel International Corporation
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, USP).

We also refer to your communication dated October 26, 2006, that was in response to our Discipline Review letter to you dated September 12, 2006, and to our approvable letter dated November 8, 2006.

In the review of the labels and labeling, The Division of Medication Errors and Technical Support (DMETS) has attempted to focus on safety issues relating to possible medication errors. Although you have accepted most of DMETS' recommendations, we note you did not agree with the remaining DMETS comments and enclosed their rationale. DMETS acknowledges your comments; however, we continue to stress the importance of the comments listed in the previous review. We note that these revisions are requested as a result of postmarketing surveillance of cases that have resulted in confusion with similarly labeled and packaged drug products. Therefore, we have repeated the following comments and request that you implement these revisions prior to approval. Please address these in writing to your NDA file.

A. General Comments

1. DMETS continues to recommend that the proprietary name not be presented in all capital letters. Research has demonstrated that words appearing in all capital letters are difficult to read and may increase the potential for confusion.

2. DMETS acknowledges and accepts your attempt to minimize the inadvertent administration of the diluent with the addition of the statement 'For Reconstitution Only'. However, DMETS continues to recommend the proposed diluent be packaged in a vial instead of a prefilled syringe. Post-marketing reporting for a similarly packaged diluent has shown errors with inadvertent injection of the diluent only even when clearly labeled as such.

B. Container Label and Carton Labeling
DMETS continues to recommend that the total drug content designation be revised to read "5 mg per vial" or "5 mg/vial." This further clarifies the total drug content per vial and minimizes confusion with the "per millimeter" statement.

C. Container Label (Diluent)
DMETS continues to recommend that you add a "per syringe" statement to help alleviate confusion with reconstitution. In some cases, diluents contain more than the amount needed for reconstitution. Including the statement "1.5 mL per syringe" or "1.5 mL syringe" ensures that patients and healthcare practitioners are aware of the actual volume contained in the syringe. If a fill line is present and marked 1.5 mL, this statement is not needed.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and 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/

Theresa Kehoe
12/26/2006 10:21:08 AM
Theresa Kehoe for Mary Parks

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

December 20, 2006

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

Re: **NDA 21-905; Amendment 13**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Response to FDA Request (facsimile dated November 13, 2006)**

Dear Dr. Parks,

On behalf of LG Life Sciences, Ltd. (LG), PAREXEL International (PAREXEL), acting as the US agent, is hereby submitting a response to the FDA Request (facsimile dated November 13, 2006) for New Drug Application (NDA) 21-905 for Valtropin®. The NDA was submitted to the Division on December 1, 2005 and filed under section 505 (b) of the Act on February 13, 2006.

Valtropin® is indicated for the treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone, as treatment of growth failure associated with Turner syndrome in patients who have open epiphyses, and as replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the criteria for childhood or adult onset etiology.

In addition to the Approvable Letter which was received from the Division on November 15, 2006, PAREXEL also received the FDA Request containing two required CMC related labeling changes. LG accepts these changes and submits the revised labeling which is also included in this submission as both paper copies (attached) and electronic files. Please note that requirement #2 from the FDA Request identifies the change from the word ——— to "diluent" for page 22, and it was actually on Page 23. For consistency, we have also implemented the same change on page 1, second paragraph: "After reconstitution with 1.5 mL <u>diluent</u> ——— the solution contains 3.33 mg/mL of somatropin." b(4)

Amendment 13 is being submitted on one CD (approximately 1 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: bruce.babbitt@parexel.com

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

PAREXEL International (US Agent)
Hoss Dowlat
Alberto Grignolo

MEMORANDUM	Division of Medication Errors and Technical Support (DMETS) Office of Surveillance and Epidemiology WO22, Mail Stop 4447 Center for Drug Evaluation and Research

TO: Mary Parks M.D.
Director, Division of Metabolism and Endocrinology Products (HFD-510)

FROM: Tselaine Jones Smith, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support,
Office of Surveillance and Epidemiology
White Oak Bldg. 22, Mail Stop 4447

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

DATE: November 20, 2006

SUBJECT: **DMETS LABELING REVIEW**
Drug: Valtropin
(Somatropin (rDNA origin) for Injection, USP)
5 mg
Sponsor: LG Life Sciences, Ltd.
NDA#: 21-905

OSE PROJECT #: 2006-775

This review was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510) for a review of the Sponsor's response to the Discipline Review letter (dated September 12, 2006), which contains revised labels and labeling, regarding Valtropin (Somatropin (rDNA origin) for Injection, USP). These changes are in response to DMETS' recommendations outlined in OSE Review number 2006-37.

Although most of DMETS' recommendations were accepted by the sponsor, we note that the sponsor did not agree with the remaining DMETS comments and enclosed their rationale. DMETS acknowledges the sponsor's comments; however, we continue to stress the importance of the comments listed in the previous review. We note that these revisions are requested as a result of postmarketing surveillance of cases that have resulted in confusion with similarly labeled and packaged drug products. Therefore, we have repeated the following comments and request that the sponsor implement these revisions prior to approval.

A. General Comments

1. DMETS continues to recommend that the proprietary name not be presented in all capital letters. Research has demonstrated that words appearing in all capital letters are difficult to read and may increase the potential for confusion.

2. DMETS acknowledges and accepts the sponsor's attempt to minimize the inadvertent administration of the diluent with the addition of the statement 'For Reconstitution Only'. However, DMETS continues to recommend the proposed diluent be packaged in a vial instead of a prefilled syringe. Post-marketing reporting for a similarly packaged diluent has shown errors with inadvertent injection of the diluent only even when clearly labeled as such.

B. Container Label and Carton Labeling (Valtropin)

DMETS continues to recommend that the total drug content designation be revised to read "5 mg per vial" or "5 mg/vial". This further clarifies the total drug content per vial and minimizes confusion with the "per millimeter" statement.

C. Container Label (Diluent)

DMETS continues to recommend that the sponsor add a "per syringe" statement to help alleviate confusion with reconstitution. In some cases, diluents contain more than the amount needed for reconstitution. Including the statement "1.5 mL per syringe" or "1.5 mL syringe" ensures that patients and healthcare practitioners are aware of the actual volume contained in the syringe. If a fill line is present and marked 1.5 mL, this statement is not needed.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

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/s/

Tselaine Jones-Smith
11/27/2006 03:59:52 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/27/2006 04:01:46 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/30/2006 08:45:09 AM
DRUG SAFETY OFFICE REVIEWER

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

November 20, 2006

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

Re: **NDA 21-905; General Correspondence 12**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Response to Approvable Letter (dated November 8, 2006)**

Dear Dr. Parks,

On behalf of LG Life Sciences, Ltd. (LG), PAREXEL International (PAREXEL), acting as the US agent, is hereby submitting a response to the Approvable Letter (dated November 8, 2006) for New Drug Application (NDA) 21-905 for Valtropin®. The NDA was submitted to the Division on December 1, 2005 and filed under section 505 (b) of the Act on February 13, 2006.

Valtropin® is indicated for the treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone, as treatment of growth failure associated with Turner syndrome in patients who have open epiphyses, and as replacement of endogenous growth hormone in adults with growth hormone deficiency b(4)

LG and PAREXEL wish to thank the Division for its diligence in reviewing the Valtropin® NDA, as well as for providing LG the opportunity to file several amendments to the NDA and engage the Division in scientific discussions, leading to an Approvable Letter, which PAREXEL received from the Division by US Postal Services on November 15, 2006.

In response to the Approvable Letter, LG intends to pursue an approval by FDA for NDA 21-905 through resolving the deficiency described (in the Approvable Letter) by obtaining an acceptable establishment evaluation. As instructed by Jena Weber during a telecon with Raymond Lamy, Sr. Consultant of PAREXEL International, on November

16, 2006, LG will continue to work directly with the FDA's Office of Compliance to resolve all PAI issues as expeditiously as possible.

Additionally, LG has received a facsimile from the Division dated November 13, 2006, containing two required CMC related labelling changes. LG accepts these changes and intends to submit a separate NDA Amendment with a revised final package insert and SPL reflecting these changes.

General Correspondence 12 is being submitted on one CD (approximately 308 KB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: 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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11/13/06

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: November 13, 2006

To: Bruce Babbitt, Ph.D. Consultant	**From:** Jena Weber Project Manager
Company: Parexel	Division of Metabolism and Endocrinology Products
Phone number: 781-434-4057	**Fax number:** 301-796-9712
Fax number: 978-848-2221	**Phone number:** 301-796-1306

Subject: Reference NDA 21-905, and revised labeling for Valtropin submitted on October 26, 2006.

Total no. of pages including cover: 2

After review of this revised labeling with the medical officer, the following CMC related labeling changes are required:

1. At the top of page 22 of the proposed package insert (tab 3), remove the following statement, [redacted]
2. At the bottom of page 22 of the proposed package insert (tab 3), change the word [redacted] to "diluent".

b(4)

Document to be mailed: ☐ YES ☑ NO

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/s/

Jena Weber
11/13/2006 08:16:06 AM
CSO

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

REQUEST FOR CONSULTATION

TO *(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: Response to DR letter (DMETS) dated 9/12/06	DATE OF DOCUMENT
11/03/06		21-905		10/26/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Valtropin (somatropin rDNA origin) for Injection	S	Growth Hormone	12/04/06

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)*: **LBL**

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 LG Life Science's response to our Discipline Review letter to them dated 9/12/06 (DMETS comments & recommendations).
PDUFA DATE: 10/1/06 – overdue, pending satisfactory 483.
Package Insert, Container, Vial – available via EDR dated 10/26/06.

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

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
11/3/2006 02:10:08 PM

Weber, Jena M

From: EDRAdmin@cder.fda.gov
Sent: Monday, October 30, 2006 3:51 PM
To: Weber, Jena M; Galliers, Enid M; Guilderson, Mary L; Johnson, Kati; Mauer, Ramou*; Prather, Mia; Tagoe, Ivan*; Thomas, Elmer *
Cc: Talastas, Hercules*; Emmons, Prentiss*; Langhnoja, Urvi *; Tokoli, Thomas*; CDER-EDRADMIN
Subject: EDR - NDA021905 from LG LIFE drug name VALTROPIN (SOMATROPIN)

Hi !

The EDR has received an Electronic Document on CD-ROM for division HFD-510:

NDA# N21905
Incoming Document Type: N
Incoming Document Type Sequence Number: 000
Supplement Modification Type: BL
Letter Date: 10/26/2006

It has sections 1, 2.
The network path location is: \\CDSESUB1\N21905\N_000\2006-10-26
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any questions concerning this electronic submission to:

EDRAdmin@cder.fda.gov

Thanks,
? Staff

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On Original

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

October 26, 2006

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

Re: **NDA 21-905; Amendment 11**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Response to Discipline Review Letter (dated September 12th, 2006)**

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. The NDA was filed under section 505 (b) of the Act on February 13, 2006.

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

This amendment contains LG's formal responses to the comments/requests for container (Valtropin 5mg and Diluent for Valtropin), carton, and insert labeling revisions contained in the Discipline Review Letter, dated September 12, 2006.

In addition to the above-mentioned comments/requests, the insert labeling also contains revisions based on recent communications between PAREXEL and Jena Weber or Dr. Perlstein, culminating on September 27, 2006. The sample revised labeling is also included in this submission as both paper copies (attached) and electronic files.

Amendment 11 is being submitted on one CD (approximately 1.32 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: bruce.babbitt@parexel.com

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

PAREXEL International (US Agent)
Hoss Dowlat
Alberto Grignolo

Weber, Jena M

From: Hill, John
Sent: Wednesday, September 27, 2006 1:43 PM
To: Fraser, Blair; Weber, Jena M
Subject: FW: NDA 21905

Attachments: ——.pdf b(4)

Howdy all:

I just received the following e-mail concerning the facilities inspections in support of Valtropin, NDA 21-905.

Just keeping you informed.

John C. Hill, Ph.D., CDR. USPHS
Chemist
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment, CDER, FDA
10903 New Hampshire AVE.
Bldg. 21, RM. 2545
Silver Spring. MD 20993-0002
(301) 796-1679

From: Adams, Shawnte L
Sent: Wednesday, September 27, 2006 11:18 AM
To: Hill, John
Subject: NDA 21905

Follow up to our telephone call, I wanted to let you know that the ——— inspection resulted in a Withhold recommendation from the inspection team. The investigator have recommended a Warning Letter be issued. OC has entered our Withhold recommendation for this facility. I am attaching the 483 for your information as well so you can see the issues from the inspection. b(4)

—— pdf (309 KB) b(4)

Thank you,

Shawnte L. Adams
Program Analyst
Division of Manufacturing and Product Quality
Foreign Inspection Team, HFD 325
301-827-9051 (Office)
301-827-2063 (Fax)

Thermolyne 65' is Unknown?

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER US Food And Drug Administration, CDER Division of Manufacturing & Product Quality Foreign Inspection Team, Rm 272 (HFD-322) 7520 Standish Place, Rockville, MD 20855 USA
TO: NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	PERIOD OF INSPECTION / C.F. NUMBER FEI: b(4)
TITLE OF INDIVIDUAL MANAGING DIRECTOR	TYPE ESTABLISHMENT INSPECTED
FIRM NAME	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME
STREET ADDRESS	STREET ADDRESS OF PREMISES INSPECTED SAME
CITY AND STATE (Zip Code)	CITY AND STATE (Zip Code) SAME

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED

This document list observations made by the FDA representatives during the inspection of your facility. They are inspectional observations, and do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation or have implemented or plan to implement corrective action in response to an observation you may discuss the objection or action with the FDA representative during the inspection or submit this information to FDA at the address above. If you have any questions please contact FDA at the phone number and address above.

1. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include a validation of the terminal sterilization process of ——— Specifically,

   a. The terminal sterilization cycle process used to ——— Valtropin, a lyophilized drug product has not been validated to demonstrate the efficacy of the sterilization cycle. The following batches of 2.25 ml syringes filled with 1.5 ml of the diluent (with ———) listed in the NDA-21-905: 080303, 100303, 120303, 130903 & 141004 consisted of different ——— of diluent ——— without any information to justify the placement of only ——— In addition, there is no information to demonstrate that these two locations represent the ——— b(4)

   b. The heating and cooling parameters, and over pressure parameters to be achieved have not been established as part of the sterilization operational parameters. Although they are recorded as part of the sterilization process, neither have established as predetermined specifications to be monitored and maintained as part of the operational parameters.

   c. No heat distribution study was conducted in the ——— used to ——— listed under NDA-21-905 for Valtropin (somatropin). No study has been conducted with the ——— to evaluate numerous locations throughout this ——— unit to determine the uniformity of the heat generated. b(4)

   d. No ——— studies has been conducted in the ——— for the established ——— of 2.25 ml syringes used for the Valtropin diluent. Although a ——— study was conducted for 100 ml bottles, no evaluation or study regarding the size of the container, the viscosity of the product, the size of the ——— and scientific justification of the selected parameter was available. There is no information or study establishing the correlation of the results of this ——— study conducted and the placement of the ——— in the ——— b(4)

   e. The ——— has not been established.

   f. No biological indicators were placed during the ——— runs performed for diluent batches listed under NDA 21-905 and ——— No ———

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Carmelo Rosa Susan T. Hadman	EMPLOYEE(S) NAME AND TITLE (Print or Type) Carmelo Rosa, Investigator Susan T. Hadman, Microbiologist	DATE ISSUED ——— b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER US Food And Drug Administration, CDER Division of Manufacturing & Product Quality Foreign Inspection Team, Rm 272 (HFD-322) 7520 Standish Place, Rockville, MD 20855 USA
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO	PERIOD OF INSPECTION / C.F. NUMBER FEI:
TITLE OF INDIVIDUAL MANAGING DIRECTOR	TYPE ESTABLISHMENT INSPECTED
FIRM NAME	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME
STREET ADDRESS	STREET ADDRESS OF PREMISES INSPECTED SAME
CITY AND STATE (Zip Code)	CITY AND STATE (Zip Code) SAME

g. No performance qualification with product was conducted to either

h. The coldest spot of the used to sterilize the batches of the NDA 21-905 has not been determined.

i. A different for your of up to study in conduced with diluent lot 160706 (SAP No. 0607270004) for which and temperature sensors were placed in different locations throughout the cycle was conducted. However, the scientific rational for the placement of these and temperature sensors is unknown. No correlation between the findings of the study (or mapping study) conducted for the sterilization in where were used, nor the study conducted with diluent lot 160706 (identified as a validation lot) has been conducted. Furthermore, the firm has not conducted a validation of the sterilization process for the diluent sterilized in this to demonstrate reproducibility of the sterilization cycle and that adequate lethality to the locations have been achieved.

2. Failure to monitor for non-viable particles during the filling of the diluent lots # : 080303, 100303, 120303, 130903 & 141004, with the

3. Failure to conduct a bioburden study to determined the bioburden of the diluent prior to sterilization and therefore be able to identify the presence of any gram negative microorganisms that may generate endotoxins that may be resistant to the sterilization process. Although the solution was through two prior to being terminally sterilized, the bioburden of the solution prior to is also unknown.

4. N studies were conducted for the currently used to sterilize the equipment, hoses, instruments, and utensils that are routinely used during the manufacturing of the diluent for Valtropin.

5. Your written procedure No. P-AW-026 related to the 100 Percent Visual Inspection is inadequate in that it fails to specify or require that the defects detected during the examination be classified by the type of defects found to assure proper follow up, determination of trends or investigation (if necessary) be conducted regarding the cause or origin of the defect found. Furthermore, according to your management your 100 percent visual inspection of the filled syringes required that the material be classified as "bad or good". However, there is no information regarding the quality of the defect (broken glass, turbidity, particles in the solution, etc...) that may be indicative a process defect.

6. The current Manufacturing Process described in your Master Batch Record P-HAL-219 is different to the manufacturing instructions described in the batch records completed for the NDA batches of the diluent lots m For example, the NDA manufacturing process for the diluent required that the solution be filtered through with the option of holding the product up to prior to being sterilized. The current Manufacturing Master Record for the

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Carmelo Rosa Susan T. Hadman	Carmelo Rosa, Investigator Susan T. Hadman, Microbiologist	

b(4)
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER US Food And Drug Administration, CDER Division of Manufacturing & Product Quality Foreign Inspection Team, Rm 272 (HFD-322) 7520 Standish Place, Rockville, MD 20855 USA
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TITLE OF INDIVIDUAL MANAGING DIRECTOR	TYPE ESTABLISHMENT INSPECTED
NAME OF FIRM	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME
STREET ADDRESS	STREET ADDRESS OF PREMISES INSPECTED SAME
CITY AND STATE (Zip Code)	CITY AND STATE (Zip Code) SAME

Commercial lots to be produced requires that the solution be prepared and filtered through , hold for a maximum , then through a and terminally sterilized.

b(4)

7. Neither the batch records related to the diluent for Valtropin NDA-21-905, nor the current production batch record includes time limits for the completion of each step related to the production of the sterile diluent.

8. The batch production and control records for the diluent used for Valtropin NDA 21-905 are incomplete. Specifically, the batch production records lacks a description of the assembling procedure of the installed during production. The records also lack a verification of each significant step by a second person. The batch records also require to purge with or at least once the is added, and to mix while purging with No maximum time of either operations are established in the batch record.

9. Your firm fails to have the appropriate written procedures and controls designed to assure that the drug products have the drug quality and purity it purports to possess. Specifically,

   a. NDA 21-905 for Valtropin indicates that the holding time of the diluent solution after being times is optional and should not exceed Our review found that lots were hold from min to up to hours/min.

   b. The microbiological impact that these holding times may have on the product have not been determined by study to justify a time of the intermediate solution (neither between nor after) have been conducted (NDA 21-905 also indicates that it will optional to hold the diluent at or up to after being sterilized).

   c. Although the NDA 21-905 indicates that the holding time at should not exceed at the NDA batch records allowed for a holding time

   d. Failure to have data to support the holding times established for the different lots of diluent for Valporin listed in your NDA 21.

10. Discrepancies in the production and control records are not investigated as required. Specifically, no investigation related to the discrepancy in the times (e.g. exceeding the limit in the NDA and/or the limit included in the batch production records). For example, diluent lots 120303 and 130903, were hold for 25.58 hrs/min & 25.50 hr./min. and no investigation was conducted.

11. The blue print diagram for the process is inadequate in that the locations of the different operational valves of one of the two holding tanks currently in use do not correlated to the actual positions and identification of the valves observed in the tank.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Carmelo Rosa Susan T. Hadman	Carmelo Rosa, Investigator Susan T. Hadman, Microbiologist	

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b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER US Food And Drug Administration, CDER Division of Manufacturing & Product Quality Foreign Inspection Team, Rm 272 (HFD-322) 7520 Standish Place, Rockville, MD 20855 USA
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FIRM NAME	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME
STREET ADDRESS CITY AND STATE	STREET ADDRESS OF PREMISES INSPECTED SAME CITY AND STATE (Zip Code) SAME

12. Your procedures for the receipt and handling of in-coming drug components are not written in sufficient detail to assure they are properly handled, identified and stored during testing and released by your quality unit. Specifically, you incoming material are received by your materials department, and there is no specific procedure to notify your quality unit that they are ready for sample. Your drug products and materials are not stored under a quarantined area until they have been tested, examined, as appropriate and released. The product is received by your material department but it is not until the moment that your QC representative sees the material in an opened or unrestricted area in the warehouse that he/she becomes aware that the material is ready to be sample.

13. Rejected components and/or drug products are not identified under a quarantine system to prevent their used in manufacturing or processing operations for which they are unsuitable. On [redacted], during a visit to your storage area/warehouse, we observed that rejected materials are stored in the same areas in which approved material are maintained. No identification regarding the status of such material is placed.

Laboratory/Microbiology Controls

14. The pH test conducted on the diluent solution batches listed under NDA 21-905 (Valtropin-Somatropin), as part of the Bacterial Endotoxin test was taken incorrectly. According to the firm's SOP, a portion of the sample diluted with [redacted] Buffer must fall within the pH range of [redacted]. This [redacted]ge is not in alignment with the manufacturer's requirement of a pH range of sample plus [redacted] mixture to b[redacted]. Moreover, the firm is not only allowing a potential pH of 6.0, which is below the manufacturer's specification, to be acceptable, but also is not performing the test as required to perform the pH to be valid. According to the USP, the pH of sample plus [redacted] mixture must fall within the pH range specified by th[redacted] manufacturer. b(4)

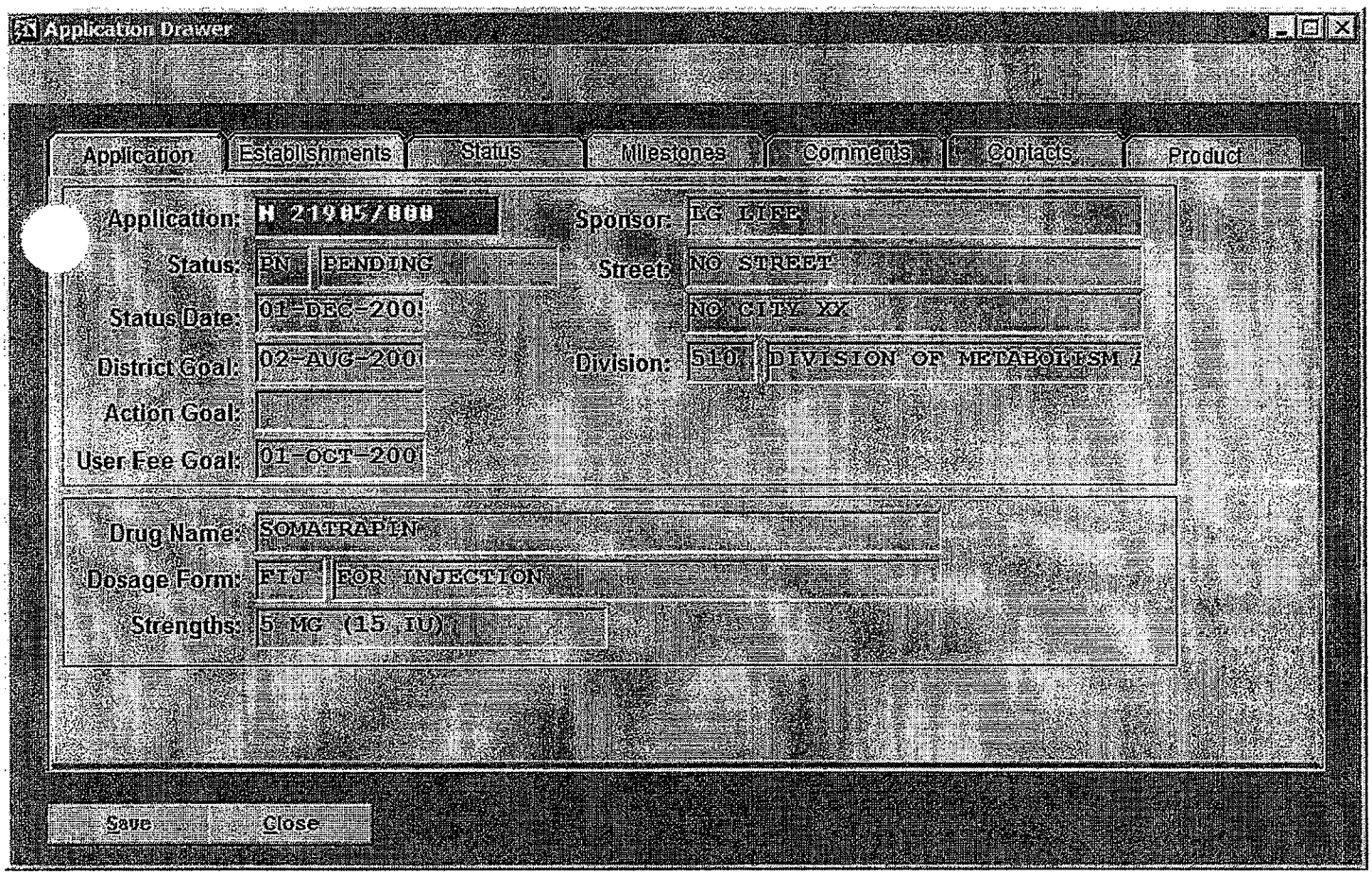
15. Laboratory records do not include the quantity of the sample received for testing, the date the sample was taken and the date the sample was received for testing. Specifically, the *Logbuch Wasserlabor Probeneingang* (Logbook) records data pertaining to testing of samples such as description of samples received and results of the tests. However, data pertaining to sampling including the date, time and the sampler's name are lacking.

16. Laboratory records in the Water laboratory do not include a statement of each method used in the testing of water. Specifically, the *Logbuch Wasserlabor Probeneingang* records results but lacks a statement of the method of each test performed.

17. Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards. Specifically, in the Microbiology laboratory, test records of Endotoxin testing lack data such as the pH meter and the heating block used in the test.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Susan T. Hadman	EMPLOYEE(S) NAME AND TITLE (Print or Type) Carmelo Rosu, Investigator Susan T. Hadman, Microbiologist	DATE ISSUED

b(4)



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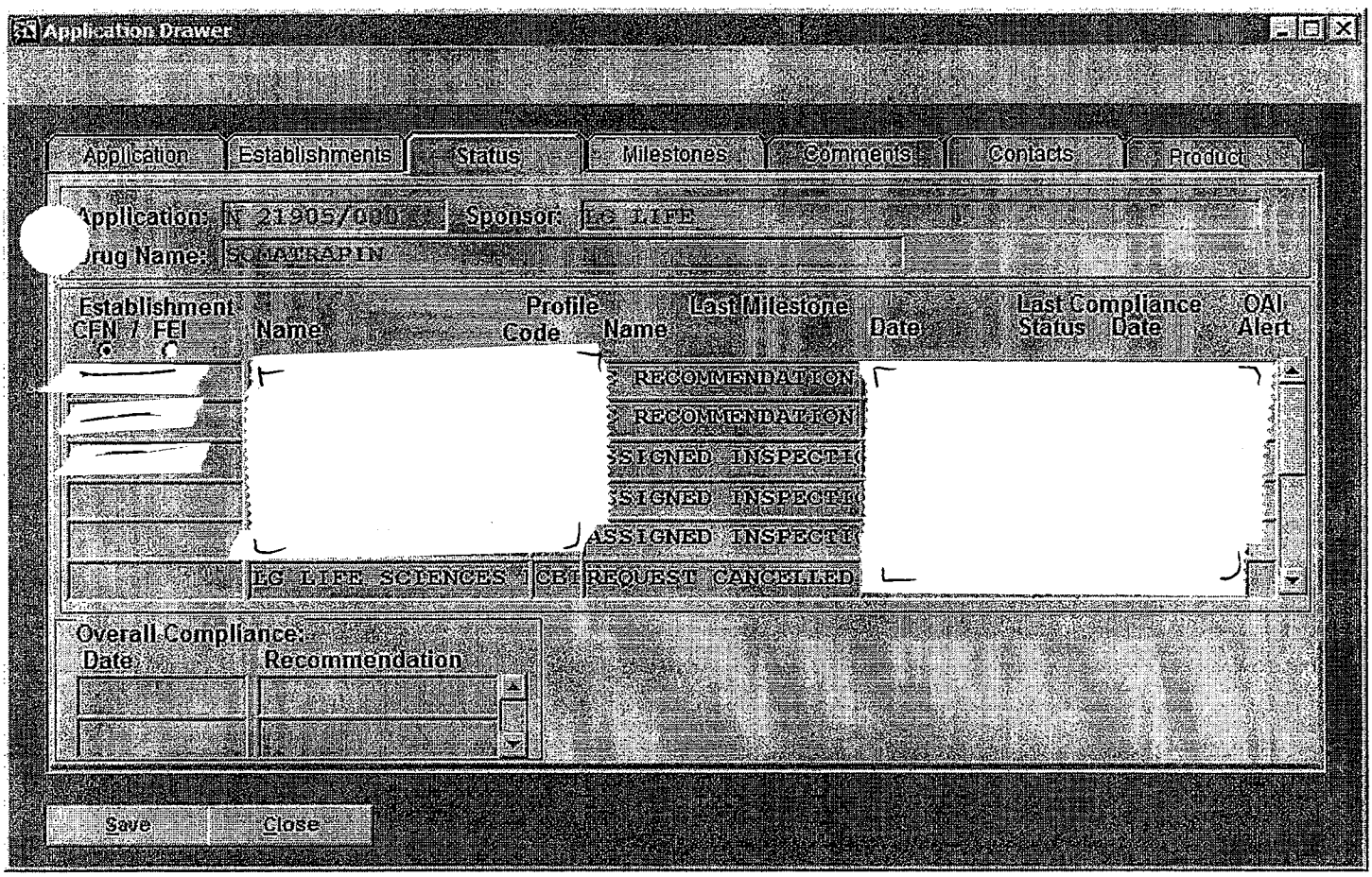

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PAREXEL International
200 West Street
Waltham, Massachusetts, 02451-1163
Tel: 781-487-9900; Fax: 781-487-0525
www.parexel.com

September 21, 2006

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

Re: **NDA 21-905; Amendment 10**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Responses to Information Request (dated June 1st, 27th and August 7th, 2006)**

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)

On June 1, 2006, June 27, 2006, and August 7, 2006, PAREXEL received requests from the Division to provide additional information to assist FDA's ongoing review of the clinical information of the Valtropin NDA.

Based upon prior discussions with Jena Weber (Project Manager), Cynthia Liu (Statistical Reviewer), and Robert Perlstein (Medical Reviewer), it was agreed that LG would first reply to all requests for additional clinical information via e-mail in order to expedite the NDA 21-905 review process, and thereafter, formally submit all responses to the Valtropin NDA as a single amendment.

Amendment 10 is being submitted on one CD (approximately 6.17 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: bruce.babbitt@parexel.com

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

PAREXEL International (US Agent)
Hoss Dowlat
Alberto Grignolo

Weber, Jena M

From: Weber, Jena M
Sent: Tuesday, September 19, 2006 6:56 AM
To: Vij, Kanika
Subject: Valtropin consult sent 12/23/05

Importance: High

The UFGD for NDA 21-905 (Valtropin) is **10/1/06.** Please let me know ASAP if DDMAC has any comments to be conveyed to the firm.

thanks,
Jena

Project Manager
Division of Metabolism & Endocrinology Products
New e-mail address: Jena.Weber@fda.hhs.gov

P.01

TRANSACTION REPORT

NOV-13-2006 MON 09:05 AM

DATE START	RECEIVER	TX TIME	PAGES	TYPE	NOTE	M#	DP
NOV-13 09:04 AM	919788482221	40″	2	SEND	OK	472	

TOTAL : 40S PAGES: 2

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: November 13, 2006

To: Bruce Babbitt, Ph.D. Consultant	**From:** Jena Weber Project Manager
Company: Parexel	Division of Metabolism and Endocrinology Products
Phone number: 781-434-4057	**Fax number:** 301-796-9712
Fax number: 978-848-2221	**Phone number:** 301-796-1306

Subject: Reference NDA 21-905, and revised labeling for Valtropin submitted on October 26, 2006.

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On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-905

DISCIPLINE REVIEW LETTER

9/12/06

Parexel International Corporation
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, USP).

We also refer to your communication dated August 11, 2006, that was in response to our Discipline Review letter to you dated June 20, 2006.

In the review of the labels and labeling, The Division of Medication Errors and Technical Support (DMETS) has attempted to focus on safety issues relating to possible medication errors. The following additional recommendations are offered in order to minimize confusion and error. Please address these in writing to your NDA file.

A. General Comments

1. Consider revising the all capitalization presentation of the proprietary name as it distracts from the remainder of the label.

2. DMETS continues to recommend the proposed diluent be packaged in a vial instead of a prefilled syringe. Post-marketing reporting for a similarly packaged diluent has shown errors with inadvertent injection of the diluent only.

B. Container Label (Valtropin)

1. In reference to the total drug content designation, add "per vial" of "/vial" following the "mg" amount to help alleviate confusion with the per milliliter statement. For example, "5 mg per vial" or "5 mg/vial."

2. Revise the '[redacted] statement to include the drug concentration per milliliter (3.33 mg/mL) following reconstitution. For example [redacted] This information is necessary to inform practitioners of the resultant drug concentration, which will minimize potential dosing confusion.

b(4)

3. The route of administration should be relocated to appear immediately after the presentation of strength as it currently gets lost in the text.

C. Container Label (Diluent)
1. Relocate and increase the prominence of "0.3% Metacresol in Water for Injection" to appear prior to the word "Diluent." This is the name of the product contained in the pre-filled syringe and thus, should have the most prominence on the label.

2. It is unclear from the information provided if the syringe has a fill line that is marked with 1.5 mL. If the syringe does not contain this information, add a "per syringe" statement to help alleviate confusion with reconstitution. For example, "1.5 mL per syringe" or "1.5 mL syringe." If the fill line is present and marked 1.5 mL, this statement is not needed.

3. To the "Single Use Syringe" statement, add "Discard after Use for Reconstitution" to avoid re-use of the syringe.

D. Carton Labeling
In reference to the total drug content designation, add "per vial" following the "mg" amount to help alleviate confusion with the milliliter content. For example, "5 mg per vial" or "5 mg/vial."

E. Insert Labeling
DOSAGE AND ADMINISTRATION
DOSAGE section, **Adult Patients** subsection:

b(4)

ADMINISTRATION

a. In the third sentence, add "or water for injection." Thus, the sentence will read '

b(4)

b. After the DO NOT SHAKE statement, add what occurs if the product is shaken and what is the resultant outcome. For example, if shaken the product may (foam, develop particulates, etc) and if this happens, the product should be (discarded, etc).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and 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/

Mary Parks
9/12/2006 04:31:12 PM

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MEMORANDUM	Division of Medication Errors and Technical Support (DMETS) Office of Surveillance and Epidemiology WO22, Mail Stop 4447 Center for Drug Evaluation and Research

TO: Mary Parks, MD
Division of Metabolism and Endocrinology Products (HFD-510)

THROUGH: Alina Mahmud, R.Ph., MS, Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Kimberly Pedersen, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

DATE: August 30, 2006

SUBJECT: **DMETS LABELING REVIEW**
Drug: Valtropin
(Somatropin (rDNA origin) for Injection, USP)
5 mg
Sponsor: LG Life Sciences, Ltd.
NDA#: 21-905

OSE PROJECT #: 2006-37

This consult was written in response to an August 18, 2006 request from the Division of Metabolism and Endocrinology Products (HFD-510) for a review of the revised labels and labeling for Valtropin. DMETS previously reviewed the name, labels, and labeling in January 2006 (OSE# 05-0273). At that time, DMETS did not recommend the use of the proposed proprietary name of Valtropin due to the potential for confusion with Nutropin and atropine. In this review, DMETS communicated multiple suggestions for revisions to the labels and labeling to help minimize potential confusion and error.

The sponsor has revised the labels and labeling and submitted these changes for review and comment. We note the majority of DMETS' recommendations were accepted by the sponsor. However, we have the following additional recommendations in order to minimize confusion and error.

A. General Comments

1. Consider revising the all capitalization presentation of the proprietary name as it distracts from the remainder of the label.

2. DMETS continues to recommend the proposed diluent be packaged in a vial instead of a prefilled syringe. Post-marketing reporting for a similarly packaged diluent has shown errors with inadvertent injection of the diluent only.

B. Container Label (Valtropin)

1. In reference to the total drug content designation, add "per vial" of "/vial" following the "mg" amount to help alleviate confusion with the per milliliter statement. For example, "5 mg per vial" or "5 mg/vial."

2. Revise the "Once reconstituted..." statement to include the drug concentration per milliliter (3.33 mg/mL) following reconstitution. For example, "Once reconstituted with 1.5 mL of diluent, the resultant solution contains 3.33 mg/mL." This information is necessary to inform practitioners of the resultant drug concentration, which will minimize potential dosing confusion.

3. The route of administration should be relocated to appear immediately after the presentation of strength as it currently gets lost in the text.

C. Container Label (Diluent)

1. Relocate and increase the prominence of "0.3% Metacresol in Water for Injection" to appear prior to the word "Diluent." This is the name of the product contained in the pre-filled syringe and thus, should have the most prominence on the label.

2. It is unclear from the information provided if the syringe has a fill line that is marked with 1.5 mL. If the syringe does not contain this information, add a "per syringe" statement to help alleviate confusion with reconstitution. For example, "1.5 mL per syringe" or "1.5 mL syringe." If the fill line is present and marked 1.5 mL, this statement is not needed.

3. To the "Single Use Syringe" statement, add "Discard after Use for Reconstitution" to avoid re-use of the syringe.

D. Carton Labeling

In reference to the total drug content designation, add "per vial" following the "mg" amount to help alleviate confusion with the milliliter content. For example, "5 mg per vial" or "5 mg/vial."

E. Insert Labeling

1. Dosage

As the recommended starting dose for adult patients with growth hormone deficiency is 0.33 mg/day and the reconstituted concentration is 3.33 mg/mL, DMETS is concerned that the similarity in numbers may result in inadvertent overdose. To avoid potential confusion, add the milliliter (0.1 mL) content for 0.33 mg adjacent to this dose in the "Dosage" section of the labeling.

2. Administration

a. In the third sentence, add "or water for injection." Thus, the sentence will read "[redacted]" b(4)

b. After the DO NOT SHAKE statement, add what occurs if the product is shaken and what is the resultant outcome. For example, if shaken the product may (foam, develop particulates, etc) and if this happens, the product should be (discarded, etc).

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

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

/s/

Kimberly Culley-Pedersen
9/8/2006 11:09:57 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/8/2006 11:25:57 AM
DRUG SAFETY OFFICE REVIEWER

Weber, Jena M

From: Lamy, Ray [Ray.Lamy@parexel.com]

Sent: Thursday, August 31, 2006 11:42 PM

To: Weber, Jena M

Subject: Valtropin NDA 21-905 - Amendment 9

Attachments: Valtropin NDA 21905 - Amendment 9 - Cover Letter - 30Aug2006 - Final.pdf; Valtropin NDA 21905 - Amendment 9 - Form FDA 356h.pdf; Valtropin NDA 21905 - Amendment 9 - Responses_FINAL_060830.pdf; Valtropin NDA 21905 - Amendment 9 - Appendix_A_CH mediaSOP.pdf

Hello Jena,

Thank you for your reply voice-mail and your kind words. Also, thank you for allowing us to send Amendment 9 to you now as PDF files (to facilitate completion of the CMC review before the PAIs), and as an official electronic submission to the NDA next week.

Attached are the files that will be used to create the electronic submission (only the cover letter will change slightly when the size of the electronic submission is filled in on the second page). As described in the cover letter, this is the sponsor's response to the FDA Information Request, dated August 7, 2006, sent to Bruce Babbit via e-mail from Anastasia G. Lolas, Reviewer, New Drug Microbiology Staff on the same day.

<<Valtropin NDA 21905 - Amendment 9 - Cover Letter - 30Aug2006 - Final.pdf>> <<Valtropin NDA 21905 - Amendment 9 - Form FDA 356h.pdf>> <<Valtropin NDA 21905 - Amendment 9 - Responses_FINAL_060830.pdf>> <<Valtropin NDA 21905 - Amendment 9 - Appendix_A_CH mediaSOP.pdf>>

Please forward these documents to Anastasia G. Lolas and others, as appropriate.
Thank you and best regards,

Ray

Raymond C. Lamy, MS
Senior Consultant
Drug Development Consulting (DDC)
PAREXEL Consulting

Direct Dial/Voicemail (Arizona): 480.836.0374
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August 30, 2006

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

Re: **NDA 21-905; Amendment 9**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Responses to Information Request (dated August 7, 2006)**

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 [redacted] b(4)

PAREXEL received (via facsimile) FDA's Information Request, dated August 7, 2006, requesting additional information related to Chemistry, Manufacturing, and Controls section of the Valtropin® NDA. This NDA Amendment 9 contains LG's formal and complete responses to the Division's statements or requests for additional information related to the Valtropin® solvent or lyophilized powder. The responses are provided both as paper copy (following this cover letter) and electronically. Addenda or attachments to support the responses are included electronically only, (with electronic hyperlinks to the documents) as appropriate.

Amendment 9 is being submitted on one CD (approximately ## MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, and no viruses were detected.

Amendment 7 is being submitted on one CD (approximately 1.65 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: 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

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-905

Trade Name: Valtropin
Established Name: somatropin (rDNA origin) for Injection
Strengths: 5 mg

Applicant: LG Life Science
Agent for Applicant: Parexel (Bruce Babbitt)

Date of Application: 11/30/05
Date of Receipt: 12/1/05
Date clock started after UN: N/A
Date of Filing Meeting: 1/20/06
Filing Date: 1/30/06
Action Goal Date (optional): User Fee Goal Date: **10/1/06**

Indications requested: For the [redacted] b(4)

Type of Original NDA:	(b)(1) X	(b)(2) ☐
OR		
Type of Supplement:	(b)(1) ☐	(b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification:	S	P ☐
Resubmission after withdrawal?	No	Resubmission after refuse to file? No
Chemical Classification: (1,2,3 etc.)	5	
Other (orphan, OTC, etc.)	N/A	

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO X
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO X

- Does the submission contain an accurate comprehensive index? YES X NO ☐

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES X NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES X NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO X
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? YES, _____ Years NO X
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,*

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES X NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (copy of the CMC technical section)? Yes X NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES X NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 62,376

- End-of-Phase 2 Meeting: Date: 9/27/00 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meetings Dates: 11/5/98 and 12/1/04 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES X NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES X NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☐ NO X

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Yes X NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A X YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A X ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES X NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/20/06

BACKGROUND: For the [redacted] b(4)

Clinical data provided from 5 studies in support of these indications.

ATTENDEES: Karen Mahoney, Robert Perlstein, Todd Sahlroot, Cynthia Liu, Jeri El-Hage, John Hill, Su Tran, Hae-Young Ahn, Jim Wei.

ASSIGNED REVIEWERS (including those not present at filing meeting): Herman Rhee (PCL).

Discipline	**Reviewer**
Medical:	Perlstein
Secondary Medical:	Parks (Team Leader)
Statistical:	Sahlroot/Liu
Pharmacology:	El-Hage/HRhee
Statistical Pharmacology:	
Chemistry:	Hill/Tran
Environmental Assessment (if needed):	Hill/Tran
Biopharmaceutical:	Ahn/Wei
Microbiology, sterility:	Lolas/Hussong
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	Not requested
Regulatory Project Management:	Weber
Other Consults:	DDMAC/DMETS

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO X
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A FILE X REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS		FILE	X	REFUSE TO FILE	☐
• Biopharm. inspection needed?				YES ☐	NO X
PHARMACOLOGY	N/A ☐	FILE	X	REFUSE TO FILE	☐
• GLP inspection needed?				YES ☐	NO X
CHEMISTRY		FILE	X	REFUSE TO FILE	☐
• Establishment(s) ready for inspection?				YES X	NO ☐
• Microbiology				YES X	NO ☐

ELECTRONIC SUBMISSION:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

Convey document review issues/no filing issues to applicant by Day 74.

JMWeber
Regulatory Project Manager, HFD-510

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
8/17/2006 02:16:14 PM
CSO

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August 11, 2006

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

Re: **NDA 21-905; Amendment 8**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Response to Discipline Review Letter (dated June 20, 2006)**

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. The NDA was filed under section 505 (b) of the Act on February 13, 2006.

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

This amendment is a response to the Discipline Review Letter, dated June 20, 2006, regarding FDA use of the proprietary name "Valtropin" and comments/requests for container (Valtropin 5mg and Diluent for Valtropin), carton, and insert labeling revisions. The attached document lists LG's responses to each of the FDA's comments/requests (Discipline Review Letter, dated June 20, 2006). Sample revised labeling is also included in this submission as both paper copies (attached) and electronic files (PDF). Also, since the sponsor has been informed by Dr. Perlstein during a telecon on Monday, August 7, 2006 that further requests from FDA for labeling revisions can be expected, we propose to only submit revised SPL when the final labeling is agreed upon.

Amendment 8 is being submitted on one CD (approximately 808 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: 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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August 4, 2006

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

Re: **NDA 21-905; Amendment 7**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Supplement to the 4-Month Safety Update**

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. The NDA was filed under section 505 (b) of the Act on February 13, 2006.

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

At the end of April 2006, an SAE was discovered during an internal audit of Study HGCL001 (Korean Adult GHD Study). Further review of the documentation showed that this SAE was unrelated to the study drug, as the SAE occurred during the placebo phase of the study. Due to the timing of this finding it was not included in the 4-Month Safety Update, submitted as NDA Amendment 4, dated April 28, 2006.

Included in this submission is a (retrospectively) completed MedWatch Form FDA 3500 as well as LG's original internal SAE report. A total of 3 SAEs was previously reported in the NDA for this study, thus, this finding would increase the total number to 4 SAEs occurring during this study.

Amendment 7 is being submitted on one CD (approximately 1.65 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
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e-mail: bruce.babbitt@parexel.com

cc: **LG Life Sciences**
Youn Sung Choo
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PAREXEL International (US Agent)
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ORIGINAL

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July 18, 2006

CDER/CDR

JUL 19 2006

RECEIVED JUL 21 2006

ORIG AMENDMENT White Oak DR 1

N-000-BM

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

Re: **NDA 21-905; Amendment 6**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Responses to Discipline Review Letter (dated April 11, 2006)**

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 [redacted] b(4)

PAREXEL received (via facsimile) two separate Information Requests from the Division, dated May 18, 2006 and June 22, 2006, requesting additional information related to the Chemistry, Manufacturing, and Controls section of the Valtropin® NDA. This Amendment 6 contains LG's formal and complete responses to the Division's statements or requests for additional information related to the Valtropin® solvent or lyophilized powder. The responses are provided both as paper copy (following this cover letter) and electronically. Addenda or attachments to support the responses are included electronically only, (with electronic hyperlinks to the documents) as appropriate.

Amendment 6 is being submitted on one CD (approximately 10 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: 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

NDA 21-905

DISCIPLINE REVIEW LETTER

6/20/06

Parexel International Corporation
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).

The Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety (ODS) has completed their review of your tradename proposal. DMETS has stated their objection to the use of the proprietary name, "Valtropin." However, the Division of Metabolism and Endocrinology Products disagrees with their assessment and finds your tradename selection acceptable. This decision is considered tentative. The name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

In the review of the labels and labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error. Please address the following comments in writing to your NDA file.

1. **CONTAINER LABEL (Valtropin 5 mg)**

a. The proprietary and established names should be the most prominent information on the label. Please ensure that the information is prominent and legible. We recommend increasing the prominence of the proprietary and established names as they tend to blend in with the other information listed in black font on the vial label.

b. In order to provide clear and accurate information on the label, a space should be inserted between the "5" and "mg" following the proprietary name.

c. The statement "Once reconstituted with solvent . . ." should be more clearly worded to include the name of diluent and the amount needed for reconstitution (i.e., XX mL of XXX solvent).

d. It appears that the product is the subject of a USP monograph. Please ensure that the appropriate USP designation appears in the established name.

e. We recommend differentiating the route of administration "Subcutaneous use only" with a contrasting color, boxing, or some other means as it currently blends in with the other information listed in black font on the vial label.

f. If space permits, include a quantitative and qualitative list of inactive ingredients.

g. If space permits, we recommend the "Rx only" statement appear on the principal display panel.

h. The "LG Life Sciences" logo that appears in red distracts from the label and should be deleted. As currently presented, this logo is more prominent than the established name, storage, and reconstitution information.

2. **CONTAINER LABEL (Diluent for Valtropin)**

a. We note that you propose to label the diluent (solvent) with the proprietary name Valtropin and the established name (metacresol). Labeling the diluent as Valtropin is misleading as it implies that the Valtropin is already prepared and ready for use, and therefore, does not require reconstitution. As a result, we recommend clearly labeling the syringe of the diluent as follows and completely removing the name "Valtropin:"

Metacresol (0.3%w/v) in Water for Injection
Diluent Only

Additionally, the word "solvent" should be replaced with the above term.

b. The statement "Single use syringe" should appear on the principal display panel of the diluent.

c. See comments 1b, 1f, and 1h.

3. **CARTON LABELING**

a. See comments 1a, 1b, 1d, 1e, and 1h.

b. The statement "5 mg (approximately 15 IU)" should be deleted from the principal display panel as the total strength of the drug powder already appears in conjunction with the proprietary name. However, if the statement is kept on the labeling, the abbreviation "IU" should be written as International Unit to avoid confusion and error.

c. The principal display panel of the carton should be revised to include a statement such as "Each carton contains: 1 multiple dose vial containing somatropin . . .
1 pre-filled syringe containing 1.5 mL of Metacresol (0.3% w/v) in Water for Injection."

d. The instructions found on the carton labeling are not clear and could lead to confusion. Revise as follows: "Reconstitute each vial with 1.5 mL of the enclosed diluent of Metacresol (0.3% w/v) in Water for Injection. After reconstituting with 1.5 mL of Metacresol (0.3% w/v) in Water for Injection the solution contains 3.33 mg/mL of somatropin."

4. **INSERT LABELING**

a. See comment 2b.

b. Under **DOSAGE AND ADMINISTRATION** section:

This section of the labeling is not clear and could lead to confusion. Revise to include the drug preparation instructions, final concentration, and other information important to the proper dosing and administration of the drug product.

c. Under the section **STABILITY AND STORAGE, After Reconstitution With Water for Injection** subsection:

We note this product when reconstituted with metacresol (0.3% w/v) in Water for Injection is stable for 21 days. However, when reconstituted with Sterile Water for Injection without preservative, the product can only be used for one single dose and the remainder must be immediately discarded.

Therefore, metacresol (0.3% w/v) in Sterile Water for Injection is the optimal diluent and use of Sterile Water for Injection without preservative should be reserved only for patients who have an allergy or sensitivity to Metacresol or when the supplied diluent is unavailable.

DMETS recommends that this section note that Sterile Water for Injection without preservative should only be used in these scenarios. This will prevent practitioners and/or patients from using Sterile Water for Injection without preservative to reconstitute the drug and storing the bottle for 21 days.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and 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/

Mary Parks
6/20/2006 02:03:29 PM

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

May 26, 2006

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

Re: **NDA 21-905; Amendment 5**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Responses to Discipline Review Letter (dated April 11, 2006)**

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 [redacted] b(4)

PAREXEL received (via facsimile) FDA's Discipline Review Letter, dated April 11, 2006, listing deficiencies per FDA review of the Chemistry, Manufacturing, and Controls section of the Valtropin® NDA. In this NDA Amendment, LG is submitting responses to the deficiencies listed in the aforementioned Discipline Review Letter. The responses are provided both as paper copy (following this cover letter) and electronically. The format of the responses is as follows; the deficiency (request or statement) from the FDA's Discipline Review Letter is listed first, followed by a response. Appendices to support the responses are included electronically only, (with electronic hyperlinks to the documents) as appropriate.

Amendment 5 is being submitted on one CD (approximately 8.2 MB). The CD has been scanned using Symantec™ Antivirus, version 10.1.0.394, 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
e-mail: 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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May 26, 2006

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

Re: **NDA 21-905; Amendment 5**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – Responses to Discipline Review Letter (dated April 11, 2006)**

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)

PAREXEL received (via facsimile) FDA's Discipline Review Letter, dated April 11, 2006, listing deficiencies per FDA review of the Chemistry, Manufacturing, and Controls section of the Valtropin® NDA. In this NDA Amendment, LG is submitting responses to the deficiencies listed in the aforementioned Discipline Review Letter. The responses are provided both as paper copy (following this cover letter) and electronically. The format of the responses is as follows; the deficiency (request or statement) from the FDA's Discipline Review Letter is listed first, followed by a response. Appendices to support the responses are included electronically only, (with electronic hyperlinks to the documents) as appropriate.

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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)
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Tel: 781-434-4057
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cc: **LG Life Sciences**
Youn Sung Choo
Hyi-Jeong Ji

PAREXEL International (US Agent)
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April 28, 2006

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

Re: **NDA 21-905; Amendment 4**
Somatropin (rDNA origin) for Injection, Valtropin®

Subject: **Amendment to a Pending Application – 4-Month Safety Update and Additional Clinical Study Data**

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)

As I discussed directly with Dr. Perlstein on March 31, 2006, LG is submitting updated 4-month safety data for Valtropin derived from two completed Valtropin RO ("rollover") studies: BP-EU-002-RO (girls with Turner Syndrome) and BP-EU-003-RO (children with GHD). An additional 12 months of safety and efficacy data, derived from both studies, are provided in the Clinical Study Reports included in this NDA Amendment. Dr. Perlstein recommended that this information be submitted to the NDA on or about May 1, 2006, and Jena Weber, Project Manager, confirmed that the specified safety and efficacy information could be submitted per Dr. Perlstein's direction.

Following the specific recommendation of Dr. Perlstein, the 4-month safety data is presented as a modification of existing safety Tables for each indication provided in Module 2.7 of the original NDA submission, as follows:

CTD Module 2.7.4.A – Indication A (Tables 2.7.4-1, 2.7.4-2, etc.)
CTD Module 2.7.4.B – Indication B (Tables 2.7.4-1, etc.)

In addition, LG is submitting final clinical study reports (BP-EU-002-RO and BP-EU-003-RO) and amendments (BP-EU-003 Amendment 2; BP-EU-003-RO Amendment 1) as source documents for the updated 4-month safety data.

A more detailed description of the overall content of this submission follows this cover letter ("Overview").

Amendment 4 is being submitted on one DVD (approximately 733 MB). A separate instruction sheet (*revinstr.pdf*) is included (electronically only) on the DVD, 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 DVD has been scanned using Sophos Anti-Virus® Remote Update software, Version 1.1.2, 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
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e-mail: 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

NDA 21-905

DISCIPLINE REVIEW LETTER

4/4/06

Parexel International Corporation
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 February 6, 2006.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

For the Drug Substance

1. Please confirm that no lots of the drug substance labeled as "Eutropin™ Bulk" have been shipped to [redacted] for the manufacture of Valtropin™ drug product. b(4)

2. Submit a copy of the Valtropin™ Bulk shipping label.

3. Establish rejection criteria (alert and action limits) for all in-process controls, or provide justification as to why no action is required when a lot fails to meet a specific in-process control (IPC).

4. For lots UTP3030and UTP3041, explain why the failure to meet in-process control specifications did not lead to rejection of these lots.

5. We recommend that you consider developing a "use test" as part of the acceptance criteria for [redacted] material that would control for lot-to-lot functional variations in the bulk [redacted] b(4)

6. Describe the manufacture, characterization and specificity of the anti-hGH antibody reagent (3.2.S.3.1.3.3.1).

For the Drug Product

7. Indicate if the co-packaged diluent syringe is intended to be used for administration of the reconstituted drug product.

8. You should validate an appropriate alternate method for the evaluation of Valtropin™ drug product potency. This alternate assay will be acceptable for determining potency of the drug product, provided that potency testing (rat weight gain) is performed at release and expiry.

For the Recombinant Bacillus Aminopeptidase

9. Submit characterization data for the [redacted] used for the manufacture should be submitted. b(4)

10. Tabulate the scale and time(s) for each step in the recombinant manufacturing process.

11. Identify the steps in the manufacture and purification of as either open or closed processes.

12. Revise the specification for residual endotoxin in the recombinant [redacted] to that proposed for the Valtropin™ drug product. b(4)

13. Include a test for chemical identity in the specification.

14. Establish and submit a stability program including real-time stability data and an expiry period.

15. Please describe the manufacture, characterization and specificity of polyclonal antibody reagents raised against recombinant aminopeptidase (3.2.S.3.1.2.3.2).

General

16. Please identify each process step in the manufacture of Valtropin™ (drug substance and drug product), including all [redacted] steps, as either an [redacted] b(4)

17. Report Valtropin™ (drug substance and drug product) lot release data and stability data as actual values or observations and not as "pass" or "+".

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Supervisory Project Management Staff
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/

Kati Johnson
4/11/2006 09:18:23 AM

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