CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-426

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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
21,426

NAME OF APPLICANT / NDA HOLDER
Sandoz Inc.

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)
OMNITROPE™

ACTIVE INGREDIENT(S)	STRENGTH(S)
Somatropin (rhGH)	1.5 mg

DOSAGE FORM
lyophilized powder

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.

each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the ormation 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

PSC Media Arts (301) 443-1090 EF

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)

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

Drug Product (Composition/Formulation)

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
Beth Brannan	4/9/04

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 Beth Brannan, Director of Regulatory Affairs, Sandoz Inc.	
Address 2555 West Midway Boulevard	City/State Broomfield, Colorado
ZIP Code 80038	Telephone Number (303) 438-4237
FAX Number *(if available)* (303) 438-4600	E-Mail Address *(if available)* beth.brannan@gx.novartis.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

Department of Health and Human Services
Food and Drug Administration

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TRADE NAME (OR PROPOSED TRADE NAME)
OMNITROPE™

ACTIVE INGREDIENT(S)	STRENGTH(S)
Somatropin (rhGH)	5.8 mg

DOSAGE FORM
lyophilized powder

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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)*

s 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

PSC Media Arts (301) 443-1090 EF

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)

	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

Drug Product (Composition/Formulation)

	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	

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B Brannan	4/9/04

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☐ 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 Beth Brannan, Director of Regulatory Affiars, Sandoz Inc	
Address 2555 West Midway Boulevard	City/State Broomfield, Colorado
ZIP Code 80038	Telephone Number (303) 438-4237
FAX Number *(if available)* 303-438-4600	E-Mail Address *(if available)* beth.brannan@gx.novartis.com

PSC Media Arts (301) 443-1090 EF

EXCLUSIVITY SUMMARY

NDA # 21-426 SUPPL # HFD # 510

Trade Name Omnitrope

Generic Name somatropin (rDNA origin) for injection; 1.5 mg/vial, 5.8 mg/vial

Applicant Name Sandoz Inc.

Approval Date, If Known 5.30.06

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)(2)

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# 20-280 Genotropin

NDA# 19-640 Humatrope

NDA# 20-604 Serostim

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:

A clinical investigation was required to approve this 505b2 recombinant growth hormone product. A single clinical safety and efficacy study (with an immunogenicity [safety] extension) was conducted in pediatric patients of short stature with growth hormone deficiency; the applicant did not conduct any clinical study for the second approved indication, adult growth hormone deficiency. (CDER has not established a clear path for demonstrating bioequvialence between recombinant protein products.) A clinical study to assess immunogenicity (safety) of this drug product was necessary for approval.

(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:

EP2K-00-PhIIIAQ

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"):

EP2K-00PhIIIAQ

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 # 58,980	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	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: Enid Galliers
Title: CPMS, DMEP, ODE II, CDER
Date: 13-JUNE-2006

Name of Office/Division Director signing form: Robert J. Meyer, MD
Title: Director, ODE II. CDER

Appears This Way
On Original

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

/s/

Enid Galliers
6/13/2006 04:10:02 PM

Robert Meyer
6/13/2006 04:16:38 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

A/BLA # : 21-426 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 12/31/01 (RTF); 7/31/03 (RS) Action Date: _____

HFD-510 Trade and generic names/dosage form: Omnitrope (somatropin [rDNA origin] for injection)

Applicant: Sandoz Inc. Therapeutic Class:

Indication(s) previously approved:

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

Number of indications for this application(s): 2

Indication #1: Treat short stature in children with growth hormone deficiency.

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

- ☐ Yes: Please proceed to Section A.
- ☑ No: Please check all that apply: ✓ Partial Waiver ____ Deferred ✓ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

tion 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 ranges being partially waived:

Min____	kg____	mo.__0__	yr.__0__	Tanner Stage____
Max____	kg____	mo.____	yr.__2__	Tanner Stage____

AND

Min____	kg____	mo.____	yr.__14__	Tanner Stage____
Max____	kg____	mo.____	yr.__16__	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**
- ☐ **Formulation needed**
- ☑ **Other: Children younger than 3 yr are usually not diagnosed, and adolescents greater than 13 years are usually not treated because there is very little benefit in terms of height increase after this age.**

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**_____

Reason(s) for deferral:

- ☐ **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.** 3 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 13 **Tanner Stage**_____

Comments:

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:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-426**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Adult growth hormone deificiency

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

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____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:**_____

tudies 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**
☐ **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_____

Reason(s) for deferral:

- ☐ **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:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-426**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Enid Galliers
5/30/2006 11:22:39 AM

BIOCHEMIE

Biochemie U.S., Inc.
101 Morgan Lane, 2nd floor
Plainsboro, NJ 08536

Tel 609 750 4700
Fax 609 750 4798

Dec 27, 2001

Debarment Certification

Pursuant to Section 306(k) of the Generic Drug Enforcement Act of 1992, Biochemie U.S., Inc, hereby certifies that, Biochemie U.S., Inc. and Biochemie GmbH, 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.

Biochemie U.S., Inc. further certifies that neither it nor any affiliated person responsible for the development or submission of this application has been subject to a conviction described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.

Very truly yours,

Jeremiah J. McIntyre
General Counsel
Biochemie U.S., Inc.

Section 01 / 00175

MEMORANDUM OF MEETING MINUTES

MEETING DATE: 3 MAY 2006

TIME: 9:15 AM – 9:35 AM

LOCATION: TELEPHONE

APPLICATION: NDA 21-426

DRUG NAME: Omnitrope (somatropin [rDA origin]) for Injection

TYPE OF MEETING: Other

MEETING CHAIR: Dr. Robert Meyer

MEETING RECORDER: Enid Galliers

FDA ATTENDEES:

Name of FDA Attendee	Title	FDA Organization
Robert J. Meyer, MD	Director	ODE II, CDER
Mary Parks, MD	Acting Director, Div. of Metabolism & Endocrinology Products (DMEP),	ODE II, CDER
Dragos Roman, MD	Medical Officer	DMEP
Enid Galliers	Chief, Project Management Staff	DMEP

EXTERNAL CONSTITUENT ATTENDEES:

External Participant	Title	Sponsor/Firm Name
Ingrid Schwarzenberger	Head, Biopharm Regulatory Affairs	Sandoz GmbH
Alexander Berghout	Head, Clinical Research	Sandoz GmbH
Beth Brannan	Director, Regulatory Affairs	Sandoz Inc. (U.S.)

BACKGROUND:
In an **April 21**, 2006, telephone meeting between Dr. Andreas Rummelt, CEO, Sandoz GmbH, and Dr. Steven Galson, Director, Center for Drug Evaluation and Research, FDA, with additional FDA and Sandoz participants, Sandoz GmbH agreed to provide to FDA a list of safety studies for Omnitrope so the Agency could specify which information should be included in a safety update to the NDA. On **April 27**, 2006, Sandoz faxed tables describing studies to the Agency. On Friday, **April 28**, 2006, FDA called Sandoz to arrange a teleconference for Monday, May 1, but learned that May Day was a holiday in Europe and two of the three required participants would not be available. It was agreed to discuss the information to be included in the safety update in a **May 3,** 2006, teleconference.

MEETING OBJECTIVES (5/3 Teleconference):

- To determine what safety data would be submitted to the Omnitrope NDA by Sandoz Inc. and the format of the submission.
- To provide Sandoz with a timeline for review of the safety information after FDA has received the complete safety update.

DISCUSSION POINTS:

- The Agency stated that it was interested in relevant immunogenicity data for the lyophilized formulation, such as the study submitted to the EU, Study EP2K-02-PhIII-Lyo, and Ms. Brannan replied that the 12-month report for that study was ready and would be submitted. She also said that it was likely the 24-month report would be ready and would be submitted. At FDA's query, Ms. Brannan estimated that the two reports would total approximately 170 pages. In discussing the format of the report, FDA requested that tables and a summary be submitted. Ms. Brannan said the information from the EU study would be submitted by May 5, 2006.
- FDA requested tabulations of immunogenicity data that included the number of subjects in the study and the number and percentage of patients who were antibody positive at each time point.
- FDA requested reports of serious adverse events (SAE's) from ongoing or recently completed trials, especially any looking like anaphylaxis or allergic reactions. Sandoz agreed to submit all such data in tabular format. FDA clarified its request by defining SAE's as any adverse event that required expedited reporting.
- Sandoz indicated that it would be difficult to obtain SAE data from an ongoing French study using [redacted], and FDA responded that it would not be necessary to include that information if it was particularly difficult to obtain – since the formulation was not fully relevant to the NDA.
- Sandoz indicated it would submit the tabulated serious safety report information by May 12, 2006, and FDA commented that it expected to have completed the clinical review and labeling discussions in two weeks, i.e. by May 26, 2006.
- Sandoz expressed its concern to not have these submissions coded as "amendments" and FDA replied that our system [i.e., DFS] requires having at least one submission coded as a "major amendment" in order to enter an action letter. FDA agreed to code submissions as "Correspondence" but would change one submission to a major amendment prior to taking an action, but that this would not trigger a review clock that would impact on the action timing.
- FDA thanked Sandoz for the April 27, 2006, table describing the safety data

DECISIONS (AGREEMENTS) REACHED:

1. Sandoz will submit to FDA the 12-month report (and any completed reports for longer extensions) for study EP2K-02-PhIII-Lyo by Friday, May 5, 2006.
2. Sandoz will submit to FDA the additional updated serious adverse event (SAEs) from completed and ongoing studies by Friday, May 12, 2006.
3. FDA estimates that it will have reviewed the safety information, completed labeling discussions, and be ready to take an action within two weeks of receiving the last part of the safety update; e.g., if everything were submitted by May 12th, the action would be by Friday, May 26, 2006.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION: None

ACTION ITEMS:

Sandoz will make the submissions by the dates specified.
FDA will review the data and continue labeling discussions concurrently.

Minutes Preparer: *{See attached electronic signature.}*
Enid Galliers, CPMS, DMEP, ODE II, CDER

Chair Concurrence: **/s/ 5.30.06**
Robert J. Meyer, M.D.
Director, Office of Drug Evaluation II, CDER

HANDOUTS (not attached):
Table 1 List of studies faxed by Sandoz U.S. to FDA on April 27, 2006.

POSTMEETING NOTE: Sandoz completed the report of SAEs on May 12 and delivered it Monday, **May 15**, 2006. Since the date two weeks following receipt of the last part of the pending safety update fell on May 29, a Federal holiday (Memorial Day), FDA mentioned to Sandoz Inc. (**May 16**, 2006, phone conversation between Enid Galliers and Beth Brannan) that the Agency expected to be ready for an action by the day after the holiday, **May 30**, 2006.)

MEETING MINUTES

Drafted by: E. Galliers/ 5.3.2006/
Revised by: R. Meyer/ 5.xx.06/
final: E.G./ 5.xx.06/

Appears This Way
On Original

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

/s/

Enid Galliers
5/30/2006 10:50:36 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-426 Supplement # N/A SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Omnitrope
Generic Name: somatropin [rDNA origin] for injection
Strengths: 1.5 mg/vial, 5.8 mg/vial

Applicant: Biochemie, U.S., Inc.
Agent: Sandoz, Inc., formerly Geneva Pharmaceuticals, Inc.

Date of Application: July 30, 2003 (RS)
Date of Receipt: July 31, 2003
Date clock started after UN: N/A
Date of Filing Meeting: Sept. 23, 2003
Filing Date: Sept. 29, 2003
Action Goal Date (optional): User Fee Goal Date: May 31, 2004
A major amendment received April 1, 2004, extended the goal date to August 31, 2004.
Indication(s) requested: Both indication for tentative approval because Paragraph III cert. of patent expiring on March 10, 2015.

(1) short stature in pediatric patients with growth hormone deficiency (GHD)
(2) adults with GHD of either childhood or adult onset

Type of Original NDA: (b)(1) _____ (b)(2) ____X____
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 ____X_____ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____X_____
Chemical Classification: (1,2,3 etc.) ____5_____
Other (orphan, OTC, etc.) _____

Form 3397 (User Fee Cover Sheet) submitted: **YES**

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

  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? **YES**
  The referenced listed drug, Genotropin, has orphan exclusivity for Indication #2, adult GHD, which expires on Oct. 31, 2004.

- 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

  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)? **NO**
  If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? **YES**

- Does the submission contain an accurate comprehensive index? **YES**

- Was form 356h included with an authorized signature? **YES**
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? **YES**

  If no, explain:

- If an electronic NDA, does it follow the Guidance? **YES**
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? **N/A**

- Is it an electronic CTD? **N/A**
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information submitted on form FDA 3542a? April 9, 2004 **YES**

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

- Correctly worded Debarment Certification included with authorized signature? **YES**
  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**
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES**
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. **YES**

- List referenced IND numbers: IND 58,980

- End-of-Phase 2 Meeting(s)? Date(s) _____ **NO**
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 11/30/1998; 5/14/2001
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? YES

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? **N/A**

- 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**

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES**
  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**

- If a parenteral product, consulted to Microbiology Team (HFD-805)? **YES**

ATTACHMENT

MEMO OF FILING MEETING

DATE: Sept. 23, 2003

BACKGROUND:

This is a resubmission of a 505(b)(2) application for recombinant growth hormone lyophilized powder in two strengths: 1.5 mg/vial, 5.8 mg/vial. The original submission also included an injectable solution, which is omitted from this resubmission. Also, the original submission had requested an immediately effective approval for the pediatric GHD indication and tentative approval for the adult GHD indication (orphan exclusivity expires Oct. 31, 2004), but the referenced listed product, Genotropin (NDA 20-280), has submitted another relevant patent subsequent the refusal to file action. Therefore, this applicant submitted a Paragraph III certification and requested tentative approval for both indications – delayed until March 10, 2015. The application contains a clinical study of the pediatric GHD indication, but relies on the Agency's finding of safety and effectiveness for Genotropin to support the adult GHD indication.

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	D. Roman
Secondary Medical:	D. Orloff
Statistical:	C. Liu
Pharmacology:	H. Rhee
Statistical Pharmacology:	N/A
Chemistry:	J. Brown
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	X. Wei
Microbiology, sterility:	D. Hussong → B. Riley
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	NN
Regulatory Project Management:	M. Johnson
Other Consults:	

Per reviewers, are all parts in English or English translation? **YES**
If no, explain:
CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: **NO**
- Advisory Committee Meeting needed? YES, date if known _____ **NO**
- 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 YES NO

MICROBIOLOGY (STERILITY) NA _____ FILE ___X___ REFUSE TO FILE _____

STATISTICS FILE ___X___ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE ___X___ REFUSE TO FILE _____
The firm has not provided dosage equivalence info for the 1.5 mg presentation, which can not be approved without it.

- Biopharm. inspection needed: YES **NO**

PHARMACOLOGY NA _____ FILE ___X___ REFUSE TO FILE _____

- GLP inspection needed: YES NO
  Not needed if there are no new excipients.

CHEMISTRY FILE ___X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? **YES** NO
- Microbiology **YES** NO

ELECTRONIC SUBMISSION:
Any comments: The statisticians requested a resubmission of an electronic table of contents (TOC) in the SAS folder in PDF format and requested clarification by the firm as to whether any interim analyses had been conducted. Reviewers requested correction of and verification that bookmarks and hyperlinks are working properly.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ 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.

_____ No filing issues have been identified.

___X____ Filing issues to be communicated by Day 74. List (optional):
Biopharm; statistics; electronic document

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Completed by Enid Galliers, CPMS, DMEDP for

Monika Johnson, Pharm.D. based on her notes and submissions made after Sept. 23, 2003.
Regulatory Project Manager, HFD-510

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? **YES**

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

   NDA 20-280 Genotropin (somatropin [rDNA origin] for injection) 1.5 mg, 5.8 mg

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? **YES**
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application is for a new manufacturer/applicant and requests some of the approved indications in the referenced drug.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). **NO**

CDER policy prevents acceptance of recombinant growth hormone products under 505(j).

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). **NO**

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise **NO**

made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9).

10. Are there certifications for each of the patents listed for the listed drug(s)? **YES**

Although the Orange Book lists five different patents and 14 products for Genotropin, Omnitrope only certifies against two of those patents, the two patents which claim the 1.5 mg and 5.8 mg lyophilized powder presentations. Consultation with E. Dickinson, FDA OCC, verified that the certifications of the two patents are complete and adequate.

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

__X__ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent # 5,633,352 March 10, 2015

__X_ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent # 4,968,299

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

YES

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

N/A

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND # _____ NO

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES

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

/s/

Enid Galliers
9/6/04 02:21:56 PM
CSO
Completed for Monika Johnson based on her notes and submissions made after the filing meeting.

8.31.04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-426

Biochemie U.S., Inc.
Sandoz Inc., Agent for Biochemie U.S., Inc.
Attention: Beth Brannon
Director, Regulatory Affairs
2555 Midway Boulevard
Broomfield, CO 80038

Dear Ms. Brannon:

Please refer to your new drug application (NDA) dated December 27, 2001, resubmitted July 30, 2003, received July 31, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Omnitrope (somatropin [rDNA origin] for injection), 1.5 mg and 5.8 mg.

We acknowledge receipt of your submissions dated January 23 and 25, February 1, 7, and 28, March 29, April 29, May 24(2), June 19, August 19, October 1 and 3, and November 1, 2002; August 8 and December 9(2) and 15, 2003; and January 15, March 31, April 1, 2, 9, and 27, July 6, 9, and 14, and August 18, 2004.

Your application proposes Omnitrope (somatropin [rDNA origin] for injection), 1.5 mg and 5.8 mg, for (1) long-term treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone and (2) long-term replacement in adults with growth hormone deficiency of either childhood or adult onset etiology.

We have completed our review of this application as submitted with draft labeling. However, we are unable at this time to reach a decision on the approvability of the application because of unresolved scientific and legal issues that relate to your NDA.

This application was submitted as a 505(b)(2) application that relies for approval in part on the agency's finding of safety and effectiveness for Genotropin, Pfizer's somatropin product approved in NDA 20-280. The active ingredient in the proposed Biochemie U.S., Inc. product and in the approved Pfizer product is recombinant human growth hormone (somatropin).

As you know, a number of parties have raised substantial legal and scientific challenges to the agency's ability to rely, even in part, on a prior finding of safety and effectiveness for one recombinant protein product in order to approve another such product. See April 14, 2004, Genentech Citizen Petition (Docket No. 2004P-0171); April 23, 2003, BIO Citizen Petition (Docket No. 2003P-0176); and May 13, 2004, Pfizer Citizen Petition (Docket No. 2004P-0231).

In addition, on August 16, 2004, FDA announced that it would be holding a public workshop on September 14 and 15, 2004, to discuss how a sponsor may demonstrate that its protein product is similar enough to a product that FDA has licensed under the Public Health Service Act or approved under the Federal Food, Drug, and Cosmetic Act that it may obtain licensure or approval without conducting certain studies that would otherwise be necessary. 69 Fed. Reg. 50386. The subjects expected to be addressed in that workshop and by comments submitted to a docket closing on November 12, 2004, include manufacturing, characterization, immunogenicity, preclinical and clinical studies, and efficacy surrogates. We also intend to co-sponsor a scientific workshop early in 2005 on these issues.

Because the Omnitrope application is a 505(b)(2) NDA for a recombinant protein product, our regulatory decision on the application will clearly involve legal and scientific issues within the scope of the issues raised in the pending citizen petitions and under consideration in the public process. Because of the nature and complexity of these issues, and the fact that resolution of the issues might affect the quantity and quality of data that might be required for approval of 505(b)(2) applications for human growth hormone, FDA is deferring a decision on whether the data submitted in NDA 21-426 are adequate to support a conclusion that Omnitrope is safe and effective for the proposed indications.

We note that because this application was submitted pursuant to section 505(b)(2), it contains patent certifications to the listed patents for Genotropin, the drug referenced in your NDA. Your certification under section 505(b)(2)(A)(iii) to U.S. Patent No. 5,633,352 indicates that you are not seeking approval of this application in any event until March 10, 2015, when the patent expires.

Although we cannot be certain when the Agency will be prepared to make a decision regarding the approvability of NDA 21-426, we will provide you with further updates on our plans for review of the application after we have completed review of the results of the scientific workshops we intend to hold on this issue as they apply to human growth hormone. If, during the course of the intervening consideration of the scientific and regulatory issues, the agency concludes that the Omnitrope application may be approved without submission of additional substantive data, we will notify you of this conclusion. At that time, we will advise you regarding any information needed to restart the review clock (e.g., safety update, revised labeling). We anticipate that any resubmission under these circumstances would be reviewed on a two-month clock (Class 1 resubmission). If the agency determines that additional substantive information and data may be necessary to support approval of this NDA, we will notify you as to what additional information and data should be submitted. Submissions of additional clinical data, new analyses, or other significant amounts of new information and data would likely be reviewed on a six-month clock (Class 2 resubmission). A final determination regarding the classification of the resubmission will be made by FDA on receipt of the resubmission, consistent with our existing procedures and standards under the Prescription Drug User Fee Act (PDUFA).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Enid Galliers, Chief, Project Management Staff, at 301.827.6429.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug 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/

David Orloff
8/31/04 02:18:24 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA: 21-426	Efficacy Supplement Type: N/A	Supplement Number: N/A	
Drug: Omnitrope (somatropin [rDNA origin] for Injection)		Applicant: Biochemie, U.S., Inc./ Agent = Sandoz	
RPM: Monika Johnson/ Enid Galliers		HFD-510	Phone: 301-827-9087/6429

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.** **(X)** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-280 Genotropin

❖ Application Classifications:	
• Review priority	(•) Standard ( ) Priority
• Chem class (NDAs only)	5
• Other (e.g., orphan, OTC)	NN
❖ User Fee Goal Dates	8/31/04
❖ 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# 4585, 4185
• 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	Comments received on 8/30/04
❖ 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.	(**Y**) 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).	**Patent # 5,633,352** **Expires March 10, 2015**
• [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) (**Y**) 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:	**Patent # 4,968,299**
(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).*	(**Y**) Yes ( ) No Notification received by Pfizer on 12/18/2003. Pfizer is the successor in interest to the applicant, Pharmacia & Upjohn, and to the patent holder, Kabi Vitrum AB.
(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 (**X**) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has	( ) Yes (**X**) No

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)?	( ) Yes (**X**) No
*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).* (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 (**X**) No
❖ Exclusivity (approvals only)	Not applicable
• 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.)	N/A
• 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.*	(**X**) Yes, Application # **NDA 20-280/S-008**; Orphan Exclusivity for adult GHD expires Oct. 31, 2004. ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	• •

❖ Actions	
• Proposed action	( )AP ( ) TA ( ) AE ( ) NA **(X)Deferral (tracked as NA)**
• Previous actions (specify type and date for each action taken)	RTF 3/1/02
• 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)	None
• Most recent applicant-proposed labeling	8/8/03
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS – 3/29/04 ODS, DSRCS 12/19/03 DDMAC – 2/10/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	None
• Applicant proposed	8//8/03
• 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)	N/A
• Pre-NDA meeting (indicate date)	5/14/01, 11/3/98
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	6/6/02 (RTF items), 12/12/02 (guidance)
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary/Administrative	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Division Director 8/31/04
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	8/30/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MOR for safety analysis
❖ 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)	NN
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	8/31/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	8/24/04, 9/24/03, 3/11/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NN
• Bioequivalence studies	NN
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	8/30/04(#1), 8/30/04 (#2)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	8/30/04
• Review & FONSI *(indicate date of review)*	NN
• Review & Environmental Impact Statement *(indicate date of each review)*	NN
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	8/2/04; 5/19/04
❖ Facilities inspection (provide EER report)	Date completed: 8/13/04 (•) 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)*	3/26/04, 8/8/03
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NN
❖ CAC/ECAC report	NN

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review (Amended 8/31/04)
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? **YES**

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): **Genotropin NDA 20-280**

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? **YES**
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

   YES NO

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

(b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This drug product claims to be a duplicate of the listed drug; however, because it is a recombinant protein CDER policy requires submission of a 505(b)(2) or 505(b)(1) application. The listed drug has five approved indications; this application requests two indications: long-term growth hormone replacement in pediatric patients with short stature and long-term growth hormone replacement in adults with growth hormone deficiency of either adult or childhood onset. The adult indication has orphan exclusivity until October 31, 2004. This NDA contains 1.5 mg and 5.8 mg lyophilized powder presentations. The listed drug has 14 products listed in the Orange Book.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). **Not eligible for approval under section 505(j).** **NO**

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). **NO**

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). **NO**

10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
There are certifications for the two patents which claim the two presentations submitted in this NDA. Consultation with OCC (E.Dickinson) confirmed that certification of the additional patents is not needed.

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
(Paragraph I certification)

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

__X__ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent # 5,633,352 March 10, 2015

__X__ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent # 4,968,299

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. **Notification was received on December 18, 2003.**

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): **Exclusivity was Not Requested**

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES

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/s/

Enid Galliers
8/31/04 07:07:55 PM
505(b)(2) NDA - Appendix B NDA Filing Rev. Form
is appended to the Action Package Checklist

5.20.04 T-con

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 24, 2004

TO: HFD-510, DMEDP

FROM: Monika Johnson, PharmD, Regulatory Project Manager

SUBJECT: **IR letter dated 5.20.04 with CMC comments and information requests**
NDA 21-426, Omnitrope (somatropin [rDNA origin] for injection)

Dr. Janice Brown, chemistry reviewer, requested a teleconference with Sandoz, Inc. US Agent for Biochemie, to discuss the IR letter dated 5.20.04.

The application PDUFA goal date had been extended from May 31, 2004 to August 31, 2004. The main purpose of the t-con was to acquire tentative timelines for receiving responses from Biochemie to issues raised in the IR letter.

Biochemie agreed to submit most of the items to the Agency on or before the end of June 2004. The remaining items, nos. 1, 6, 9, and 18 of the IR letter are to be submitted on or before July 12, 2004.

Dr. Brown requested that Biochemie work with her, prior to submission, on drug substance release, drug product release, and shelf-life specifications. This interaction ahead of time is an effort to assist and expedite the review of this material once it is officially submitted to the Agency.

6 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 7

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/s/

Monika Johnson
5/24/04 12:09:48 PM
CSO

5.17.04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426

Sandoz, Inc., US agent for Biochemie, US., Inc.
Attention: Beth Brannon
Director, Drug Regulatory Affairs
2555 W. Midway Blvd.
Broomfield, CO 80038

Dear Ms. Brannon:

Please refer to your July 30, 2003 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Omnitrope (somatropin rDNA for injection).

On April 1, 2004, we received your March 31, 2004, major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 31, 2004.

If you have any questions, call me at (301) 827-9087.

Sincerely,

{See appended electronic signature page}

Monika Johnson, Pharm.D.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Monika Johnson
5/17/04 03:18:23 PM

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

ATE RECEIVED:	**DESIRED COMPLETION DATE:** April 30, 2004	**ODS CONSULT #:** 03-0243
September 12, 2003	**PDUFA DATE:** May 31, 2004	

TO: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Monika Johnson, Pharm.D.
Project Manager
HFD-510

PRODUCT NAME:	**Manufacturer:**
Omnitrope™ [Somatropin (rDNA origin) for Injection] 1.5 mg and 5.8 mg **NDA:** 21-426	Biochemie

SAFETY EVALUATOR: Linda Y. Kim-Jung, R.Ph.

COMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name Omnitrope™.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Omnitrope™, acceptable from a promotional perspective.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 12, 2004

NDA#: 21-426

NAME OF DRUG: Omnitrope™
[Somatropin (rDNA origin) for Injection]
1.5 mg and 5.8 mg

NDA HOLDER: Biochemie

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proprietary name, Omnitrope™, regarding potential name confusion with other proprietary and established drug names.

PRODUCT INFORMATION

Omnitrope Lyophilized Powder is indicated for long term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone, long term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood or adult onset etiology. GHD should be confirmed by an appropriate growth hormone stimulation test, and other causes of short stature in pediatric patients should be excluded. The dosage of Omnitrope must be adjusted for the individual patient but generally, a dose of 0.16 to 0.24 mg/kg body weight per week is recommended. Daily administration by subcutaneous injection in the evening is recommended. Omnitrope may be given in the thigh, buttocks, or abdomen; the site of subcutaneous injections should be rotated daily to help prevent lipoatrophy. Omnitrope Lyphilized Powder is available in the following two packages: Omnitrope 1.5 mg lyophilized powder (without preservative), Concentration of 1.33 mg/mL (approximately 4 International Units/mL), Package of 1 glass vial of somatropin and 1 glass vial of diluent; and Omnitrope 5.8 mg lyophilized powder (with preservative), Concentration of 5 mg/mL (approximately 15 International Units/mL), Package of 8 glass vials of somatropin and 8 glass vials of diluent.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[4] The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Omnitrope. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not identify any proprietary names that were thought to have the potential for confusion with Omnitrope.

2. DDMAC finds the proprietary name, Omnitrope, acceptable from a promotional perspective.

---

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.

[3] The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/main/trademarks.htm

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

B. PHONETIC AND ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA identified Humatrope which was thought to have significant orthographic similarities to Omnitrope. The available dosage forms and usual dosage are listed in Table 1 (see below).

Table 1: Potential Sound-Alike/Look-Alike Names Identified by POCA

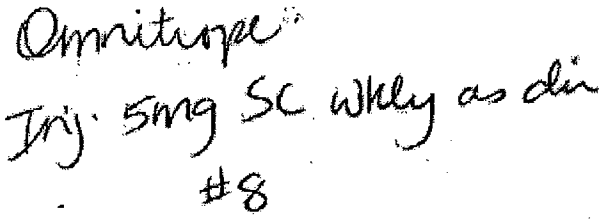
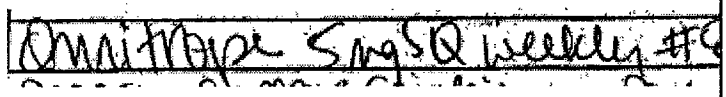
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Omnitrope	[Somatropin (rDNA) for Injection] Injection 1.5 mg and 5.8 mg	The dosage of Omnitrope must be adjusted for the individual patient but generally, a dose of 0.16 to 0.24 mg/kg body weight per week is recommended for pediatric GHD patients.	N/A
Humatrope	Somatropin	***Pediatric patients:*** The recommended weekly dosage is 0.18 mg/kg (0.54 International Units/kg) of body weight. The maximal replacement weekly dosage is 0.3 mg/kg (0.9 International Units/kg) of body weight. Divide into equal doses given either on 3 alternate days, 6 times a week, or daily. Administer by SC or IM injection. Individualize dosage and administration schedule. **Turner syndrome:** A weekly dosage of up to 0.375 mg/kg (1.125 International Units/kg) of body weight administered by SC injection is recommended. Divide into equal doses given either daily or on 3 alternate days. ***Adult patients:*** The recommended dosage at the start of therapy is 0.006 mg/kg/day (0.018 International Units/kg/day) given as a daily SC injection. The dose may be increased according to individual patient requirements to a maximum of 0.0125 mg/kg/day (0.0375 International Units/kg/day).	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Omnitrope with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Omnitrope (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX:  	Omnitrope Inject 5 mg SC weekly as directed. #8.
Inpatient RX:  	

2. Results:

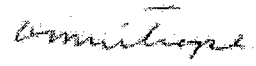
None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

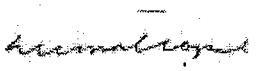
D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Omnitrope, the Expert Panel did not identify any names as having the potential to sound or look similar to Omnitrope. Nor were any additional names identified through independent review. However, a POCA search identified the name, Humatrope as having orthographic similarities to Omnitrope.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any existing approved drug products. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Omnitrope.

Omnitrope and Humatrope may look-alike when scripted. Humatrope (Somatropin) is indicated for the treatment of growth failure in children who have growth failure caused by an inadequate secretion of endogenous growth hormone (GH) and growth hormone deficiency (GHD) in adults and short stature associated with Turner syndrome. Both Omnitrope and Humatrope end with the letters, 'trope' which contributes to the look-alike similarity between the two names. In addition, the beginning portion of the name, 'Omni' and 'Huma' could potentially look-alike as well. If the 'O' in Omnitrope is not closed all the way, the letter 'O' can look like the small letter 'h'. Moreover, 'ni' in Omnitrope and 'ma' in Humatrope could also potentially look-alike. Although, the usual recommended dosages are different for the two drugs and each drug will have individualized dosing requirements, there is the potential for these two drugs to have overlapping dosage. The usual dosage for Omnitrope is 0.16 mg to 0.24 mg/kg body weight per week and the dosing for Humtrope ranges from 0.006 mg/kg to 0.375 mg/kg and thus, these two drugs may result in having an overlapping dosage, which may compound the confusion between the two drug names. Omnitrope and Humatrope contain the same active ingredient and have the same indication of use and thus the potential medical consequence of taking the wrong drug may not be too significant. Nevertheless, the orthographic similarities and the overlapping dosage increase the likelihood for potential confusion between the two drugs which may result in medication errors.

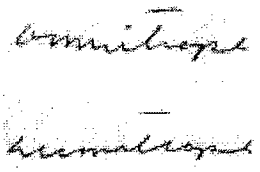




III. COMMENTS TO THE SPONSOR

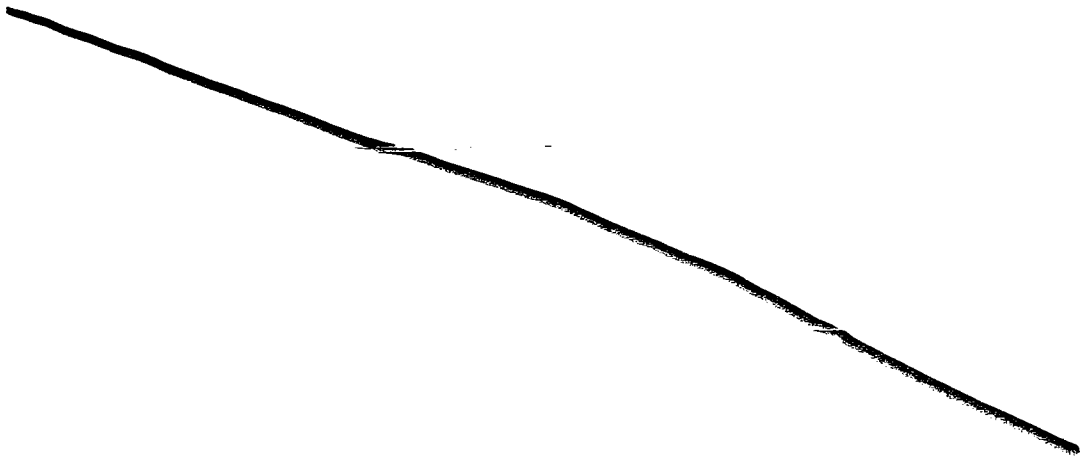
DMETS does not recommend the use of the proprietary name, Omitrope. In reviewing the proprietary name, Omnitrope, the primary concerns were related to look-alike confusion with Humatrope.

Omnitrope and Humatrope may look-alike when scripted. Humatrope (Somatropin) is indicated for the treatment of growth failure in children who have growth failure caused by an inadequate secretion of endogenous growth hormone (GH) and growth hormone deficiency (GHD) in adults and short stature associated with Turner syndrome. Both Omnitrope and Humatrope end with the letters, 'trope' which contributes to the look-alike similarity between the two names. In addition, the beginning portion of the name, 'Omni' and 'Huma' could potentially look-alike as well. If the 'O' in Omnitrope is not closed all the way, the letter 'O' can look like the small letter 'h'. Moreover, 'ni' in Omnitrope and 'ma' in Humatrope could also potentially look-alike. Although, the usual recommended dosages are different for the two drugs and each drug will have individualized dosing requirements, there is the potential for these two drugs to have overlapping dosage. The usual dosage for Omnitrope is 0.16 mg to 0.24 mg/kg body weight per week and the dosing for Humtrope ranges from 0.006 mg/kg to 0.375 mg/kg and thus, these two drugs may result in having overlapping dosage, which may compound the confusion between the two drug names. Omnitrope and Humatrope contain the same active ingredient and have the same indication of use and thus the potential medical consequence of taking the wrong drug may not be too significant. Nevertheless, the orthographic similarities and the overlapping dosage increase the likelihood for potential confusion between the two drugs which may result in medication errors.



In the review of the insert labeling of Omnitrope, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS



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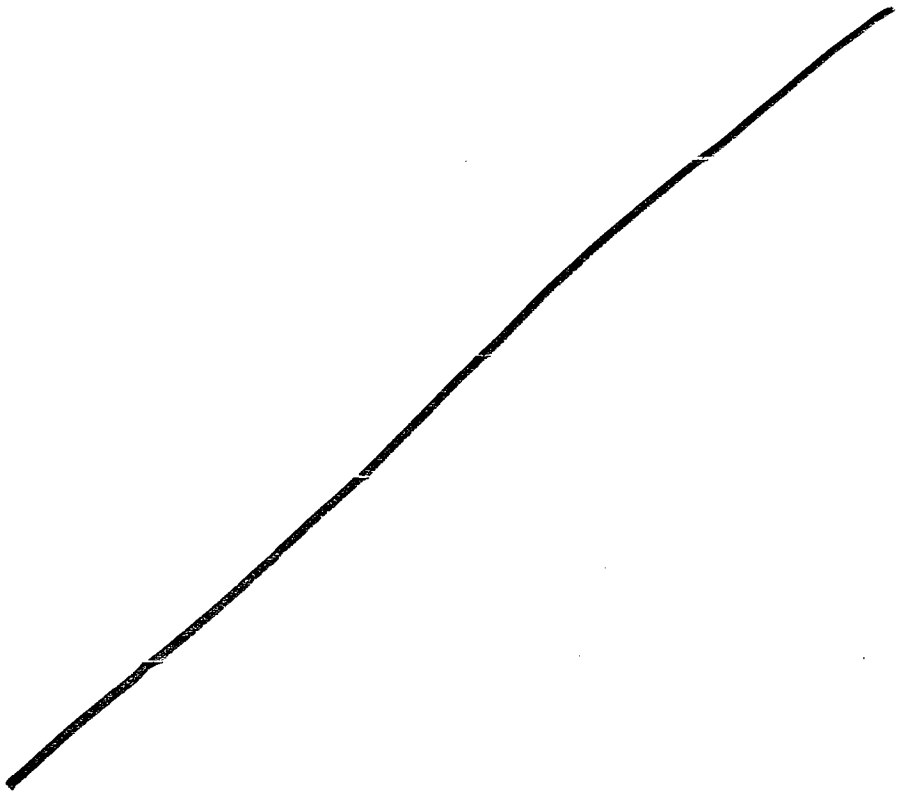

V. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name Omnitrope.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name, Omnitrope, acceptable from a promotional perspective.

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 Sammie Beam, project manager, at 301-827-3242.

Linda Y. Kim-Jung, R.Ph.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. Results of Prescription Analysis Studies.

Outpatient	Voice	Inpatient
	Omni	
Omintrope	Drops	Omitrope
Omintrope	Omnitrop	Omitrope
Omnitape	Omnitrop	Omitrope
Omnitrop	Omnitrop	Omitrope
Omnitrope	Omnitrope	Omitrope
Omnitrope	OmniTrope	Omnitrope
Omnitrope	Omnitrope	Omnitrope
Omnitrope	Omnitrope	Omnitrope
Omnitrope	Omnitrope	Omnitrope
Omnitrope	Omnitrope	Omnitrope
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Omnitrope	Omnitrope	Omnitrope
Omnitrope	Omnitrope	Omnitrope
Omnitrope	omnitrope	Omnitrope
Omnitrope,	Omnitrope	Omnitrope
Omnitrope,	Omnitrope	Omnitrope
	Omnitrope,	Omnitrope,
	Romnitrop	Omnitroupe
		Omritrope
		Onritrope
		Onritrope
		Qunitrope

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/s/

Linda Kim-Jung
3/25/04 04:19:45 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/25/04 04:45:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/26/04 08:27:37 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
3/29/04 07:51:05 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-426

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Please refer to your July 30, 2003, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Omnitrope (somatropin [rDNA origin] for injection) 1.5 mg and 5.8 mg.

We also refer to your submission dated August 8, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 30, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues, however, we have the following comments:

- You submitted a biowaiver request to claim that Omnitrope 1.5 mg is bioequivalent to Genotropin 1.5 mg. This biowaiver request may not be granted because there is no basis to judge the relative bioavailability of Omnitrope 1.5 mg. In order to market Omnitrope 1.5 mg formulation, a bioequivalence study should be performed.
- Please re-submit the table of contents (TOC) files under the SAS folder in PDF format.
- Please confirm if any interim analysis was done.
- Please ensure that the bookmarks and hypertext links are working properly.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Monika Johnson, Regulatory Project Manager, at (301) 827-9087.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation Research

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/s/

Enid Galliers
10/16/03 05:12:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426

Geneva Pharmaceuticals, Inc. US Agent for Biochemie
Attention: Beth Brannan
Director, Drug Regulatory Affairs
506 Carnegie Center Drive
Suite 400
Princeton, NJ 08540

Dear Ms. Brannan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our March 1, 2002, refusal to file letter for the following:

Name of Drug Product: Omnitrop (somatropin [rDNA origin] for injection)

Review Priority Classification: Standard

Date of Application: July 30, 2003

Date of Receipt: July 31, 2003

Our Reference Number: NDA 21-426

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 30, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 31, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-9087.

Sincerely,

{See appended electronic signature page}

Monika Johnson, PharmD
Regulatory Review Officer
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Monika Johnson
8/18/03 03:53:22 PM

JUL 3 0 2003

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS
Biochemie U.S., Inc.

506 Carnegie Center Drive
Suite 400
Princeton, NJ 08540

2. TELEPHONE NUMBER (*Include Area Code*)
(609) 627 8500

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21,426

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

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

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

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

21,426
(APPLICATION NO. CONTAINING THE DATA).

3. PRODUCT NAME.
OMNITROPE ™, Somatropin (rhGH) for injection

6. USER FEE I.D. NUMBER
4185

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

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

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

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

See Explanation in Cover letter

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (*See item 7, reverse side before checking box.*)

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

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

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

and

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

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Beth Brannan Director Regulatory Affairs Geneva Pharmaceuticals, Inc.	

FORM FDA 3397 (3/01) Created by: PSC Media Arts (301) 443-2454 EF

A user fee of USD 533,400 has been paid under our user fee ID no. 4185 to support the review of NDA 21,426.

Enclosed are a FDA form 3397 (user fee cover sheet) and a confirmation of the payment.

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS
Biochemie U.S., Inc.

506 Carnegie Center Drive
Suite 400
Princeton, NJ 08540

2. TELEPHONE NUMBER (*Include Area Code*)
(609) 627 8500

3. PRODUCT NAME.
OMNITROPE ™, Somatropin (rhGH) for injection

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21,426

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

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

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

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

21,426
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4585

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

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

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

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

See Explanation in Cover letter

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(*See item 7, reverse side before checking box.*)

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
☐ YES ☒ NO
(*See Item 8, reverse side if answered YES*)

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

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

and

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

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Beth Brannan /ZP	Beth Brannan Director Regulatory Affairs Geneva Pharmaceuticals, Inc.	7/28/03

FORM FDA 3397 (3/01) Created by: PSC Media Arts (301) 443-2454 EF

Jean Pederson
Associate

Geneva Pharmaceuticals, Inc.
Development
Drug Regulatory Affairs
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Tel +1 303 438 4242
Fax +1 303 438 4600
Internet: jean.pederson
@gx.novartis.com

Geneva
PHARMACEUTICALS

Fax

Attention: Monica Johnson
FDA

Fax no.: 301-443-9282
Number of pages: 2 including cover page

Date: 28 July 2003

Concerning: **User Fee Cover Sheet**

Dear Monica,

Last Thursday, 7/24/03, I sent you a copy of the User Fee Cover Sheet for the Omnitrope NDA. After talking with the Document Control Room, a new number was assigned. Therefore, I am sending you a copy of the revised User Fee Cover Sheet which reflects the correct user fee I.D.

If you have any questions or comments, please don't hesitate to contact me at (303) 438-4242.

Sincerely,

Jean Pederson

Jean Pederson, Senior Associate
Drug Regulatory Affairs

/jep

9.13 02

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426

Geneva Pharmaceuticals, Inc
US Agent for Biochemie US, Inc.
Attention: Beth Brannan
Director, Drug Regulatory Affairs
2555 W. Midway Blvd.
Broomfield, CO 80038

Dear Ms. Brannan:

We received your August 19, 2002 correspondence on August 21, 2002, requesting a meeting to discuss the necessary steps required for resubmitting Omnitrop, NDA 21-426, which was refused to file on March 1, 2002. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.

Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].

Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

You requested a type B meeting. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C. The meeting is scheduled for:

Date: November 4, 2002
Time: 10:30-11:30 am EST
Location: Parklawn Building Conference Room B
CDER participants:

David Orloff, MD	Division Director
Dragos Roman, MD	Medical Reviewer
Jon Sahlroot, PhD	Biometrics Team Leader

David Hoberman, PhD	Biometrics Reviewer
David Hussong, PhD	Microbiology Reviewer
Peter Cooney, PhD	Microbiology Team Leader
Stephen Moore, PhD	Chemistry Team Leader II
Janice Brown, MS	Chemistry Reviewer
Hae Young Ahn, PhD	Biopharmaceutics Team Leader
Xiaoxiong Wei, MD, PhD	Biopharmaceutics Reviewer
Duu Gong Wu, PhD	Deputy Director, Division of New Drug Chemistry
Enid Galliers	Chief, Project Management Staff
Monika Johnson, PharmD	Regulatory Project Manager

Provide the background information for this meeting at least one month prior to the meeting. If we do not receive it by October 4, 2002, we may need to reschedule the meeting.

If you have any questions, call me at 301-827-6370.

Sincerely,

{See appended electronic signature page}

Monika Johnson, PharmD
Regulatory Project Manager
Division of Metabolic and Endocrine Drug 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/

Monika Johnson
9/13/02 07:59:02 AM

Memorandum

Date: July 26, 2002

From: Dragos Roman M.D., Medical Officer, HFD-510

Through: David Orloff, M.D., Acting Team Leader and Division Director, HFD-510

Subject: Medical Officer's background material for the Refuse to File Review Committee Meeting scheduled for August 5, 2002.

To: File (NDA 21-426, Omnitrop)

Summary

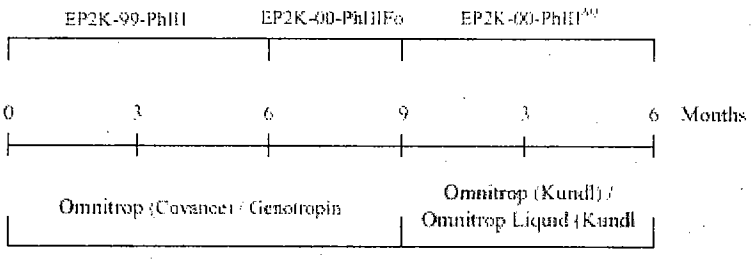
This review briefly summarizes the clinical issues raised at the Filing Meeting for NDA 21-426 (Omnitrop=recombinant human growth hormone). It includes a brief description of the Omnitrop clinical trials, an analysis of the immunogenicity data collected during these clinical trials, references to the draft "Guidance for Industry" for somatropin (growth hormone) drug products, and concludes with this reviewer's comments on whether the application is sufficient for filing.

I. Description of the clinical trials.

The applicant (Biochemie GmgH) submitted data derived from three clinical trials (EP2K-99-PhIII, EP2K-00-PhIIIFo and EP2K-00-PhIII^{AQ}). All trials were performed in growth hormone deficient children (89 patients enrolled). The first trial (EP2K-99-PhIII) was six month in duration and compared a lyophilized Omnitrop formulation against the previously approved growth hormone (GH) product Genotropin. The second trial (EP2K-00-PhIIIFo) was a three month continuation of the first trial. For practical purposes these two trials can be considered a single trial.

The third trial (EP2K-00-PhIII^{AQ}) was initiated in the 86 patients who completed the first two trials. Patients who previously received the lyophilized Omnitrop ("Covance" Omnitrop) treatment were switched to another, [redacted] lyophilized Omnitrop drug product ("Kundl" Omnitrop). Patients who previously received Genotropin were switched to a new Omnitrop drug formulation (liquid Omnitrop). Thus, the third clinical study is no longer a comparison of Omnitrop against the reference drug Genotropin, but a comparison between two different Omnitrop drug formulations. The design of the three studies is depicted in Figure 1, below.

Figure 1. Design of Phase III Omnitrop Clinical Studies



It should be re-iterated that two lyophilized Omnitrop drug products were used during the clinical trials. For the first two studies the lyophilized Omnitrop drug product was produced by Covance,USA, and for the third study it was produced in Kundl, Austria. This change appears to have been determined by the unfavorable immunogenic profile of the "Covance" lyophilized Omnitrop. The "Kundl" lyophilized Omnitrop (a to-be-marketed product) includes an [redacted] step that further reduces host cell protein content and makes the drug product potentially less immunogenic.

II. Anti-GH antibodies.

A significant difference in the number of patients who developed anti-GH antibodies was noted between the lyophilized Omnitrop and the Genotropin treated groups during the first two clinical trials (EP2K-99-PhIII and EP2K-00-PhIIIFo). The number and the proportion of patients who developed anti-GH antibodies are presented in Table 1. After nine months of treatment 57% of the patients receiving lyophilized Omnitrop developed anti-GH antibodies compared to only 2% in the Genotropin group.

Table 1: Anti-GH antibody - EP2K-99-PhIII and EP2K-00-PhIIIFo studies

	Anti- lyophilized Omnitrop antibodies	Anti-Genotropin antibodies
Month 0	0/44	0/45
Month 3	11/44 (26%)	0/44
Month 6	14/42 (33%)	0/44
Month 9	24/42 (57%)	1/44 (2%)

Table 2 summarizes the anti-GH antibody data from the third clinical trial, EP2K-00-PhIII^{AQ}. When patients exposed to the "Covance" lyophilized Omnitrop were switched to the [redacted] Kundl" lyophilized Omnitrop, the proportion of patients with anti-GH antibodies decreased from 57% to 36% over 6 months. When patients exposed to Genotropin were switched to liquid Omnitrop, the percentage of patients with anti-GH antibodies remained low (2% after six months of treatment).

Table 2: Anti-GH antibody -EP2K-00-PhIII^{AQ} study (Months 3 and 6)

	Anti- lyophilized Omnitrop antibodies	Anti-liquid Omnitrop antibodies
Month 0*	4/42 (57%)**	1/44 (2%)***
Month 3 (Month 12)	16/42 (38%)	0/44
Month 6 (Month 15)	15/42 (36%)	1/44 (2%)

*Month 0=Month 9 of the EP2K-99-PhIII and EP2K-00-PhIIIFo study.
**Anti-"Covance" lyophilized Omnitrop antibodies.
***Anti-Genotropin antibodies.

III. Immunogenicity Data Requirements defined in the Growth Hormone Draft Guidance for Industry.

This draft guidance document plans to provide recommendations to sponsors and applicants on the scientific and technical documentation to support a 505(b)(2) application. It delineates the requirements for two approval pathways for 505(b)(2) somatropin submissions as either a stand-alone product (without a claim of interchangeability), or an interchangeable product to a listed somatropin product (with pharmaceutical equivalence). For each pathway, the guidance document requires comparative human immunogenicity data with a listed GH drug product. Table 3 summarizes the overall requirements for each of the two approval pathways, including the human immunogenicity requirements.

Table 3: Filing Options for 505(b)(2) Submissions for Somatropin Drug Product

Documentation	**Without a claim of interchangeability**	**With a claim of interchangeability (demonstration of pharmaceutical equivalence)**
Chemistry Data	Comparative Analysis	Rigorous comparative analysis
Bioassay Data	One comparative assay	Two comparative assays
Pharm-Tox	May be waived[1]	May be waived[1]
PK/PD	Comparative PK/Bioavailability studies to a listed drug PD studies NOT required[2]	Rigorous comparative PK and PD studies to a listed drug.
Human Immunogenicity Data	Comparative data (comparison with historical control or an active control; this data can be obtained during clinical efficacy trial described)	Comparative data (comparison with historical control or an active control)
Efficacy Data from Clinical Trials	Efficacy data required[3] (immunogenicity data can be obtained simultaneously).	Efficacy data ***not*** required[4]

[1]Only if CMC data are acceptable.
[2]PD studies are not required because the biological response of GH product will be measures by the clinical endpoint (growth) through an efficacy trial.
[3]Clinical efficacy studies are required because the new growth hormone product has not been shown to be pharmaceutically equivalent to a listed drug.
[4]Clinical efficacy studies are ***not*** required because the new growth hormone product is required to be pharmaceutically equivalent to a listed drug through rigorous comparative studies listed in this table.

IV. Reviewer's Comments

The applicant has provided human immunogenicity data in the January 3, 2002 NDA submission. The data show an unfavorable profile for lyophilized Omnitrop when compared to the Reference Drug Genotropin in the first two clinical trials (studies EP2K-99-PhIII and EP2K-00-PhIIIFo). A favorable immunogenicity profile is noted in the third clinical trial (study EP2K-00-PhIII^{AQ}) for both the [redacted] lyophilized Omnitrop drug product and for the liquid Omnitrop drug product. Although study EP2K-00-PhIII^{AQ} does not include a direct comparison with Genotropin, it is this reviewer's opinion that this is a review issue and not a filing clinical issue. This opinion has been conveyed to the applicant in the minutes of the May 7, 2002 Guidance Meeting following the Refuse to File Letter which state:

"There is an unfavorable clinical immunogenicity profile for the lyophilized Omnitrop powder preparation when compared to the lyophilized Genotropin powder formulation during studies EPK-99-PhIII/EP2K-00PhIIIFo. The favorable immunogenicity profile observed with the two other Omnitrop peparations (i.e." [redacted] lyophilized Omnitrop and liquid Omnitrop) during the subsequent study EP2K-00-PhIIIAQ does not result from side by side comparisons with Genotropin. Although not a filing issue per se, this will be an important consideration in the application review."

Dragos Roman M.D.
Medical Officer, HFD-510

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/s/

Dragos Roman
7/26/02 04:20:03 PM
MEDICAL OFFICER

David Orloff
7/26/02 05:44:27 PM
MEDICAL OFFICER

6.7.02

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 7, 2002

TO: DMEDP, HFD-510

FROM: Monika Johnson, PharmD, HFD-510

SUBJECT: **May 24, 2002 meeting request**
NDA 21-426, Omnitrop (somatropin [rDNA origin] for injection)

Geneva Pharmaceuticals, US Agent for Biochemie, requested a meeting, May 24, 2002, to further discuss proposals for resubmission of the [redacted] Omnitrop 1.5 mg and 5.8 mg lyophilized powders.

This meeting will not be necessary because these issues are addressed in the June 6, 2002, meeting minutes which were a result of the May 7, 2002, meeting with the firm in response to a refuse to file letter issued by the Agency March 1, 2002.

INSTRUCTIONS FOR THE DIVISION DOCUMENT ROOM:

Please close out the May 24, 2002, meeting request.

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/s/

Monika Johnson
6/7/02 11:27:26 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426

June 6, 2002

Geneva Pharmaceuticals
US Agent for Biochemie US, Inc.
Attention: Beth Brannan
Director, Drug Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Please refer to the meeting between representatives of your firm and FDA on May 7, 2002. The purpose of the meeting was to discuss the items contained in the refuse to file letter issued on March 1, 2002.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Monika Johnson, Pharm.D., Regulatory Project Manager, at 301-827-6370.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Division Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
Meeting Minutes for May 7, 2002

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 7, 2002
TIME:	1:00 pm -2:00 pm
LOCATION:	Conference Room O
APPLICATION:	NDA 21-426 [redacted] Omnitrop (somatropin [rDNA origin] injection), 1.5 mg and 5.8 mg lyophilized powder
TYPE OF MEETING:	Guidance Meeting following Refuse to File Letter dated March 1, 2002
MEETING CHAIR:	Dr. Duu Gong Wu
MEETING RECORDER:	Monika Johnson, PharmD

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. Duu Gong Wu, PhD	Deputy Director	Division of New Drug Chemistry II (ONDCII)
2. Stephen Moore, PhD	Chemistry Team Leader	Division of New Drug Chemistry II
3. Janice Brown, MS	Chemistry Reviewer	Division of New Drug Chemistry II
4. Hae-Young Ahn, PhD	Biopharmaceutics Team Leader	Division of Biopharmaceutical Evaluation II Office of Clinical Pharmacology & Biopharmaceutics
5. Xiaoiong (Jim) Wei, PhD	Biopharmaceutics Reviewer	Division of Biopharmaceutical Evaluation II Office of Clinical Pharmacology & Biopharmaceutics
6. Kati Johnson	Chief, Project Management Staff	Division of Metabolic and Endocrine Drug Products HFD 510
7. Jon (Todd) Sahlroot, PhD	Biometric Team Leader	Division of Biometrics II HFD 715
8. Monika Johnson, PharmD	Regulatory Project Manager	Division of Metabolic and Endocrine Drug Products HFD 510
9. Enid Galliers	Chief, Project Management Staff	Division of Metabolic and Endocrine Drug Products HFD 510
10. David Hussong, PhD	Microbiologist	Office of Pharmaceutical Science HFD-805

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Dr. Friedrich Nachtmann	Research & Development Head Bioproducts	Biochemie GmbH
2. Dr. Jorg Windisch	Head Process Development Biopharmaceuticals	
3. Mag. Ingrid Schwarzenberger	Head Scientific Affairs	
[redacted]		
6 Ms. Beth Brannan	Director, Regulatory Affairs	Geneva Pharmaceuticals

BACKGROUND:

[redacted] Omnitrop (somatropin [rDNA origin] injection), 1.5 mg and 5.8 mg lyophilized powder submitted December 27, 2001, is the first somatropin 505(b)(2) application, for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. A series of pre-NDA meetings were held to discuss various submission types that may be appropriate for a recombinant human growth hormone; November 3, 1998 and March 14, 2000 respectively. The Agency issued a refuse to file (RTF) letter March 1, 2002, due to chemistry and clinical issues. Biochemie requested a meeting on March 29, 2002, and subsequently provided a background package for the meeting. The meeting was requested to discuss solutions to the issues raised in the RTF letter and to offer suggestions and provide guidance.

MEETING OBJECTIVES:

1. Agency assessment of firm's responses to issues listed in the RTF letter.

2. Advise 505(b)(2) recombinant growth hormone (rGH) development and subsequent resubmission based on draft 505(b)(2) guidance.

3. Discuss whether the current NDA or resubmission of an NDA with only the lyophilized powder 1.5 mg and 5.8 mg could be immediately pursued, as well as to clarify the immunogenicity data requirement.

4. [redacted]

DISCUSSION POINTS:

Although the refuse to file letter was comprehensive, the filing issues raised by the chemistry and clinical reviewers as well as the biopharmaceutical non-filing issues were the main focus of the meeting.

Due to the absence of the clinical reviewers, the clinical issue raised in the RTF letter will be addressed in the clinical section of these meeting minutes.

Following introductions, Biochemie presented responses/proposals to the issues in the RTF letter in overhead format.

Prior to the slide presentation, FDA informed Biochemie that the verbal guidance received today represents our current thinking and is not official final guidance, as the rGH 505(b)(2) guidance document is still in draft. Issues of 505(b)(2) recombinant growth hormone are currently under review by agency officials.

___1___ Page(s) Withheld

___✓___ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*___9___

AGENDA ITEM TWO:

CLINICAL

A. Your application does not contain information to establish comparable immunogenicity between lyophilized Omnitrop and the listed drug. Comparative immunogenicity data are required.

Firm's response: Comparative immunogenicity data between the lyophilized Omnitrop and reference listed drug (Genotropin) have been included in sections (d)(5)(vi) "Integrated Summary of Safety Information", item 5.6 section (d)(5)(viii) "Integrated Summary of Risks and Benefits" of the NDA submitted December 27, 2001.

FDA response: There is an unfavorable clinical immunogenicity profile for the lyophilized Omnitrop powder preparation when compared to the lyophilized Genotropin powder formulation during studies EPK-99-PhIII and EP2K-00-PhIIIFo. The favorable immunogenicity profile observed with the two other Omnitrop preparations (i.e., "further purified" lyophilized Omnitrop powder and Omnitrop liquid) during the subsequent study EP2K-00-PhIIIAQ does not result from side by side comparisons with Genotropin. Although not a filing issue per se, this will be an important consideration during the application review.

AGENDA ITEM THREE:

BIOPHARMACEUTICS

A. The application must contain data to establish comparability between the drug substance used in the clinical trials (made at Covance USA) and the to-be-marketed product (made at Kundl, Austria). There are no such data in the application.

Firm's response: Physiochemical comparisons of the drug substance for Covance and Kundl have been performed and are included in the NDA in section D1 (i) Drug substance, Appendix 3 Description & Characterization.
The comparability of the drug substance made at Covance and that made in Kundl was shown in the bioequivalence study EP2K-00-PHIAQ, performed at [redacted] (clinical volume 33, section 8, pages 18-23). The integrated study report is presented in clinical volume 29, section 06, pages 2106-3094.

The study established the bioequivalence between Omnitrop lyophilized powder made with Covance drug substance and the Omnitrop liquid made with Kundl drug substance.

FDA response: During the initial review of the application, the study report could not be located. However, based upon the above referenced information, we find the response provided acceptable.

B. You requested a biowaiver for Omnitrop for the 1.5 mg lyophilized powder. Because the composition of the formulation for Omnitrop 1.5 mg is not proportional to Omnitrop 5.8 mg lyophilized formulation, the biowaiver cannot be granted. A bioequivalence study should be conducted to establish dosage form equivalence.

Firm's response: We are surprised by the Agency's request for a bioequivalence study on the Omnitrop lyophilized powder 1.5 mg. In the pre-NDA meeting of November 30, 1998, FDA responded to the agenda item 3b (page 4 of the November 30, 1998 meeting minutes) as follows: "Since the 1.5 mg products (Genotropin) are compositionally and proportionally identical and the 1.5 and 5.8 mg Biochemie products will be manufactured with the same growth hormone substance, there is no need to perform a separate bioequivalence study with the 1.5 mg product.

FDA response: Based on the information presented at the November 30, 1998 meeting, that statement was true. However, the information submitted in the December 27, 2001, NDA is different, indicating that the sponsor has changed the formulation of Omnitrop 1.5 mg and therefore, the composition of the formulation for Omnitrop 1.5 mg is not proportional to Omnitrop 5.8 mg lyophilized formulation. Therefore, a biowaiver for Omnitrop powder 1.5 mg can not be granted.

C. New drug applications that claim interchangeability require rigorous comparative characterization of the drug product with the listed drug with respect to pharmacokinetics/pharmacodynamics (PK/PD) to establish pharmaceutical equivalence. Your application has not provided sufficient evidence to demonstrate pharmaceutical equivalence.
If you wish to achieve an AB rating, you need to prove comparability between the to-be-marketed Omnitrop and the listed drug with respect to PK/PD at the therapeutic dose administered over a one-week period to adults with growth hormone deficiency.

Firm's response: Biochemie would like to confirm that upon positive conclusion of a comparative PK/PD study between the to-be-marketed Omnitrop and the reference listed drug Genotropin at the therapeutic dose administered (adult dose = 0.006 mg/kg) over a one-week period to adult patients with growth hormone deficiency, Omnitrop would receive AB rating.

FDA response: The draft guidance reflects the Agency's current thinking. However, the guidance is still draft and not final. The draft guidance is subject to change. Therefore, an AB rating can not be promised at this time.

The firm is committed to working with the Agency to provide a complete, reviewable application, including a comprehensive table of contents.

DECISIONS (AGREEMENTS) REACHED:

NONE

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Biochemie will remit in writing proposals for resolving the issue of a suitable manufacturer for the cartridges that have specialized filing equipment.

HANDOUTS:

The firm distributed one handout. The information contained in that handout is the proposals included in these meeting minutes.

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/s/

David Orloff
6/6/02 07:14:28 PM

MEMORANDUM OF TELECON

DATE: February 11, 2002

APPLICATION NUMBER: NDA 21-426, [redacted] Omnitrop (somatropin [rDNA origin] for injection)(1.5 mg and 5.8 mg lyophilized powder).

BETWEEN:

Name: Beth Brannan, Director, Drug Regulatory Affairs
Phone: 303-438-4237
Representing: Geneva Pharmaceuticals, Inc. US agent for Biochemie US, Inc.

AND

Name: Monika Johnson, Regulatory Project Manager
Kati Johnson, Chief Regulatory Project Management
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: DEFICINECIES NOTED IN THE APPLICATION

BACKGROUND AND DISCUSSION

The application, the first 505(b)(2) application for recombinant human growth hormone (rHGH), was submitted December 27, 2001, and received December 31, 2001, for the proposed long-term treatment of growth hormone failure due to an inadequate secretion of endogenous growth hormone. Several conversations between Monika Johnson, FDA, and Beth Brannan had taken place, January 8, 19, and 24, 2002, in an effort to resolve issues regarding this application. After a more thorough review of the application, we needed further clarification from the sponsor regarding the following items:

- Environmental Assessment- Firm asked for a categorical exclusion [redacted] t but not for the lyophilized powders.
- Table of contents (TOC) does not clearly direct the reader to desired information. There was no TOC in each of the technical review sections.
- Raw data in paper form was not readily available.
- A complete list of studies and investigators for this application could not be located.
- Define which study or studies are pivotal for the stated indication (s).
- We brought to Ms. Brannan's attention that different sections of the application contained different manufacturing facilities and functions.

Monika Johnson, PharmD
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/

Monika Johnson
5/6/02 10:02:54 AM
CSO

NDA REGULATORY FILING REVIEW

NDA 21-426, [redacted] ,
Omnitrop (somatropin [rDNA origin] for injection), 1.5 mg and 5.8 mg lyophilized powder

Applicant: BIOCHEMIE US, INC
US AGENT : GENEVA PHARMACEUTICALS, INC

Date of Application: December 27, 2001
Date of Receipt: December 31, 2001
Date of Filing Meeting: February 14, 2002
Filing Date: March 1, 2002

Indication(s) requested:

(1) Long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.

(2) Other caused of short stature in pediatric patients should be excluded.

(3) Although not listed in either of the proposed package inserts, the firm is also seeking tentative approval for long-term replacement therapy in adults with growth hormone deficiency as demonstrated by an appropriate growth hormone stimulation test.

Type of Application: Full NDA ___XX___ Supplement _____
(b)(1) _____ (b)(2) ___XX__

Therapeutic Classifications: STANDARD
Resubmission after a withdrawal or refuse to file __NO_____
Chemical Classification: (1,2,3 etc.)___5___
Other (orphan, OTC, etc.)_____

User Fee Status: Paid ___XX_ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES___XX____
User Fee ID#_____4185_____
Clinical data? YES ___XX____ Referenced to _____
Date clock started after UN _____N/A_____

User Fee Goal date: _____October 31, 2002_____

Action Goal Date (optional) ___N/A_____

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES, Yes but not so accurate
- Form 356h included with authorized signature? YES

If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

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

- If electronic NDA, does it follow the Guidance? NO, parts of the submission could not be loaded in EDR

- Patent information included with authorized signature? YES

- Exclusivity requested? YES; If yes, _____years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Pediatric Rule appears to be addressed for all indications? YES

- Pediatric assessment of all ages? No
  Children ages 0-14 were studied, however the application supports a waiver for 0-2 years of age. No information about ages 15-16 could be located.
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? 0-2 years
  For what ages was a deferral requested? N/A

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? YES
If not, have the Document Room make the corrections.

List referenced IND numbers: 58,980

End-of-Phase 2 Meeting? Date_____ NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? YES November 30, 1998 and March 14, 2001

Project Management

Copy of the labeling (PI) sent to DDMAC? NO

Trade name and labeling (PI) sent to ODS? NO

Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? [redacted]
  not lyophilized powders

  If no, did sponsor submit a complete environmental assessment?
- EA consulted to Nancy Sager (HFD-357)? YES
- Establishment Evaluation Request (EER) package submitted? YES
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES

  Genotropin for Injection 1.5 mg, 5.8 mg and 13.8 mg

505(b)(2) **YES**

Describe the change from the listed drug(s) provided for in this (b)(2) application
Omnitrop for Injection –1.5 mg (1.33mg/ml with reconstitution)
--5.8 mg (5.0 mg/ml with reconstitution)

Name of listed drug(s) and NDA/ANDA #: NDA 20-280 Genotropin (somatropin [rDNA origin] for injection), approved for 1.5mg cartridge lyophilized powder.

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? No

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
Yes _____ No ___XXX_____
If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
Yes _____ No _XXX_____
If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

__X__ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? YES
- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity? YES
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? NO

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES _____ NO _____

ATTACHMENT

FILING MEETING MINUTES

DATE: Feb 14, 2002

BACKGROUND

[redacted]

Omnitrop (somatropin [rDNA origin] for injection 1.5 mg and 5.8 mg lyophilized powder products are the first somatropin 505(b)(2) application submitted December 27, 2001, and received December 31, 2001, for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. A series of pre-NDA meetings were held to discuss various submission types appropriate for recombinant human growth hormone; *November 30, 1998, March 14, 2000, respectively*. During this time, the Division was developing guidance regarding the 505b2 requirements for human growth hormone with justification for AB rating (pharmaceutical equivalence). We informed Biochemie that the division responses were based upon the prerequisites for a non-AB rating. FDA further informed Biochemie that we will review 505(b)(2) applications for recombinant human growth hormone (rHGH) for AB rating. However, the standards for establishing that a rHGH product should be AB rated have not yet been established.

ATTENDEES:

David Orloff, MD	Division Director (Acting Medical Team Leader)
Dragos Roman, MD	Medical Officer
Janice Brown, MS (via telephone)	Chemistry Reviewer
Stephen Moore, PhD	Chemistry Team Leader I
Xiaoxiong (Jim) Wei, PhD	Biopharmaceutics Reviewer
Hae Young Ahn, PhD	Biopharmaceutics Team Leader
Herman Rhee, PhD	Pharmacology/Toxicology Reviewer
Roy Blay	DSI
David Hoberman, PhD	Statistician Reviewer
Jon T. Sahlroot, PhD	Biometrics Team Reviewer
Enid Galliers	Chief Project Management

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Dragos Roman, MD
Secondary Medical:	

Statistical:	David Hoberman, PhD
Pharmacology:	Herman Rhee, PhD
Statistical Pharmacology:	
Chemist:	Janice Brown, MS
Environmental Assessment (if needed):	
Biopharmaceutical:	Xiaoxiong (Jim) Wei, PhD
Microbiology, sterility:	David Hussong, PhD
Microbiology, clinical (for antimicrobial products only):	
DSI:	Roy Blay
Project Manager:	Monika Johnson, PharmD
Other Consults:	Von Nakayama

Is the application affected by the application integrity policy (AIP) NO

Per reviewers, all parts in English, or English translation? YES

CLINICAL – File _____ Refuse to file _ XXX_____

- Clinical site inspection needed: YES_____ NO_____XXX___

MICROBIOLOGY CLINICAL – File_____ Refuse to file___XXX_____

STATISTICAL – File ____XXX_____ Refuse to file _____

BIOPHARMACEUTICS – File ____XXX_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO __XXX_____

PHARMACOLOGY – File ___XXX_____ Refuse to file _____

CHEMISTRY –

- Establishment ready for inspection? NO_XX____File_____ Refuse to file ___XXX_____

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____The application, on its face, does not appear well organized and indexed. The application appears to be unsuitable for filing.

__XXX_____ The application is unsuitable for filing. Explain why:

Chemistry, Manufacturing and Controls

- [redacted]

- Chemistry, manufacturing and control information, including stability data, for the products

[redacted] is not provided in this submission.

- The application does not contain reviewable data concerning sterility assurance; therefore, no meaningful review can be accomplished.

Clinical

- The application does not contain information to establish comparable immunogenicity between the lyophilized Omnitrop and the listed drug. Comparative antigenicity data are required.

Monika Johnson, PharmD
Project Manager, HFD-510

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426

Geneva Pharmaceuticals, Inc
US agent for Biochemie US, Inc.
Attention: Beth Brannan
Director, Drug Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [redacted] Omnitrop (somatropin [rDNA origin] for injection) (1.5 mg and 5.8 mg lyophilized powder).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Chemistry, Manufacturing, and Controls

1. All manufacturing facilities must be ready for a Good Manufacturing Practices (GMP) inspection. According to your January 23, 2002, submission, [redacted]

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 10

Administrative

11. The index of the paper version of the NDA should be revised; each technical section should contain a comprehensive index. The overall table of contents in volume one of the NDA should be a compilation of each of the technical review section indexes. We would be pleased to comment on revised drafts prior to resubmission of the application.

12. Parts of the electronic version of the NDA could not be loaded in the electronic document room. There appear to be faulty links, and the electronic NDA is not compliant with the FDA Guidance for Industry "Providing Regulatory Submissions in Electronic Format-- General Considerations."

    These problems were also identified:

    You submitted Items 1, 2, 3, 4, 5, 6, 8, and 10. Item 10 is marked as item 9 in the electronic submission Table of Contents (TOC). Item 11 CRT is marked as item 10 in the electronic submission TOC; however, actual CRT data are not submitted. Item 12 CRF is marked as item 11 in the electronic submission, but actual CRF data are not submitted. You submitted two CD_ROMs, each of which has a separate TOC containing links to the files or items available in only the same CD_ROM. From Item 3 "Summary," links to the appropriate file are not available.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Monika Johnson, Pharm.D., Regulatory Project Manager, at 301-827-6370.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug 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/

David Orloff
3/1/02 06:43:00 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-426

Geneva Pharmaceuticals, Inc.
U.S. Agent for Biochemie U.S., Inc.
Attention: Beth Brannan
Director, Regulatory Affairs
101 Morgan Lane, 2nd Floor
Plainsboro, NJ 08536

Dear Ms. Brannan:

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

Name of Drug Product:	Omnitrop (somatropin) Injection
Review Priority Classification:	Standard (S)
Date of Application:	December 27, 2001
Date of Receipt:	December 31, 2001
Our Reference Number:	NDA 21-426

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 1, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 31, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

This drug is granted a partial waiver of the pediatric study requirement for the treatment of neonates and infants up to the age of 2 years.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for full pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6370.

Sincerely,

{See appended electronic signature page}

Monika Johnson, Pharm.D.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug 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/

Monika Johnson
2/19/02 03:18:28 PM

3.1.02 RF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-426

Geneva Pharmaceuticals, Inc
US agent for Biochemie US, Inc.
Attention: Beth Brannan
Director, Drug Regulatory Affairs
2555 West Midway Boulevard
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [redacted] Omnitrop (somatropin [rDNA origin] for injection) (1.5 mg and 5.8 mg lyophilized powder).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Chemistry, Manufacturing, and Controls

1. All manufacturing facilities must be ready for a Good Manufacturing Practices (GMP) inspection. According to your January 23, 2002, submission, the Kustein (Austria) site, that will manufacture Omnitrop liquid 5.0 mg/1.5 ml and cartridge benzyl alcohol (for dilution of the 5.8 mg powder) is under construction and will not be ready to manufacture the proposed commercial product until the fall of 2003. This facility is therefore not ready for GMP inspection.
2. Chemistry, manufacturing and control information including stability data for the products manufactured at Kustein (Austria) is not provided.
3. [redacted]

Clinical

4. This application does not contain information to establish comparable immunogenicity between the lyophilized Omnitrop and the listed drug. Comparative antigenicity data are required.

Although the following items are NOT filing issues, we request that you address them in your resubmission to facilitate our review of your application.

Biopharmaceutics

5. The application must contain data to establish comparability between the drug substances used in the clinical trials (made at Covance USA) and the to-be-marketed product (made at Kundl, Austria). There are no such data in this application.

6. You requested a biowaiver for Omnitrop for the 1.5 mg lyophilized powder. Because the composition of the formulation for Omnitrop 1.5 mg is not proportional to Omnitrop 5.8 mg lyophilized formulation, the biowaiver will not be granted. A bioequivalence study should be conducted to establish dosage form equivalence.

7. New drug applications that claim interchangeability require a rigorous comparative characterization of the drug product with the listed drug with respect to pharmacokinetics/ pharmacodynamics (PK/PD) to establish pharmaceutical equivalence. Your application has not provided sufficient evidence to demonstrate pharmaceutical equivalence. If you wish to achieve an AB rating, you need to prove comparability between the to-be-marketed Omnitrop and the listed drug with respect to PK/PD at the therapeutic dose administered over a one week period to adult patients with growth hormone deficiency.

Chemistry, Manufacturing, and Controls

8. Please include the name(s), address(es), FDA registration number, and other pertinent organizational information for any portion of the manufacturing or testing operations for the drug substance or drug product. Please include a brief description of the operations performed, their responsibilities, and a description of how you will ensure that each party fulfills their responsibility. All facilities, including contract facilities and test laboratories, must be identified with full street addresses and CFNs listed. This information is missing from your application; e.g., the contract tester, [redacted]

9. [redacted] However, the product quality microbiology description section (in the CMC summary section 03/00114) states that marketed product will be produced by Biochemie Plant Schaftenau, Kùstein (Austria). Please verify the information regarding the functions of every site involved with manufacturing and testing the drug substance and drug products.

10. When preparing an Environmental Assessment, please (1) include all dosage forms or (2) remove reference to the final dosage forms and only include the drug substance.

Administrative

11. The index of the paper version of the NDA should be revised; each technical section should contain a comprehensive index. The overall table of contents in volume one of the NDA should be a compilation of each of the technical review section indexes. We would be pleased to comment on revised drafts prior to resubmission of the application.

12. Parts of the electronic version of the NDA could not be loaded in the electronic document room. There appear to be faulty links, and the electronic NDA is not compliant with the FDA Guidance for Industry "Providing Regulatory Submissions in Electronic Format--General Considerations."

    These problems were also identified:

    You submitted Items 1, 2, 3, 4, 5, 6, 8, and 10. Item 10 is marked as item 9 in the electronic submission Table of Contents (TOC). Item 11 CRT is marked as item 10 in the electronic submission TOC; however, actual CRT data are not submitted. Item 12 CRF is marked as item 11 in the electronic submission, but actual CRF data are not submitted. You submitted two CD_ROMs, each of which has a separate TOC containing links to the files or items available in only the same CD_ROM. From Item 3 "Summary," links to the appropriate file are not available.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Monika Johnson, Pharm.D., Regulatory Project Manager, at 301-827-6370.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug 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/

David Orloff
3/1/02 06:43:00 PM

45-Day Screening of New NDA

Division of Biometrics II/HFD-715

NDA Number:	21-426
Applicant:	Biochemie U.S., Inc.
Name of Drug:	Omnitrope™ Somatropin (rhGH) Lyophilized Powder
Strengths / Route:	1.5- and 5.8-mg / Subcutaneous (Injection)
Indication:	Long-term treatment/replacement therapy for growth hormone deficiency in children and adult (2 indications)
Number of Controlled Studies:	1 Phase III open, randomized, and active-controlled study in Europe
Volume Numbers in Statistical Section:	Electronic submission
Priority Classification:	Standard (10-month)
Date of Submission:	[redacted]
Date of 45-Day Meeting:	09/23/03
Date of Anticipated Review Completion:	To be discussed
Date of User Fee Goal:	05/30/04
Project Manager:	Monika Johnson, PharmD (HFD-510)
Medical Reviewer:	Dragos Roman, MD (HFD-510)
Statistical Reviewer:	Cynthia Liu, MA (HFD-715)

1. What is the difference between 7/30/03 and 8/8/03 submissions?
2. According to EDR administration, under "SAS" folder, the contents (TOC) is given in MS Excel file which is not copied to EDR because, to be archived, TOCs should be submitted in PDF format. The sponsor should re-submit the TOC file under SAS folder in PDF format.
3. Sample size was determined mainly based on HVSDS; however, there were 5 primary efficacy endpoints in the study. In addition, no multiplicity adjustment was made for those 5 primary efficacy endpoints.
4. The study was done for 0.03 mg, but the submission is for 1.5- and 5.8-mg.

File-ability Concerns (Checklist)

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	The bookmarks and hypertext links for the main body text of the reports were not done correctly or sufficiently.
Original protocols & subsequent amendments available in the NDA	Yes.
Designs utilized appropriate for the indications requested	Need to check with medical reviewer.
Endpoints and methods of analysis spelled out in the protocols and followed in the study report	Any changes in the planned analysis were stated in the statistical analysis plan (Appendix 16.1.9)
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	It is not clear.
Appropriate references included for novel statistical methodology (if present)	NA
Sufficient data listings and intermediate analysis tables to permit a statistical review	Looks O.K.
Electronic data from primary studies submitted	Yes, they are in EDR.
Intent-to-treat analyses performed	Yes.
Effects of dropouts on primary analyses investigated	Three out of 89 withdrew from the study before 6 months. They did not enter the follow-up study. Therefore, no imputation was done for missing data.
Safety and efficacy for gender, racial, and age subgroups investigated	Yes for gender, but no for race (100% Caucasian) and age (2-14 years old).