

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-538**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**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*

NDA NUMBER

21538

NAME OF APPLICANT / NDA HOLDER

CANGENE CORPORATION

*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)

Accretropin

ACTIVE INGREDIENT(S)

Recombinant Human Growth Hormone

STRENGTH(S)

5mg/mL

DOSAGE FORM

Sterile liquid for injection.

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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

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

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

**1. GENERAL**

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

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

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

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

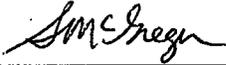
**6. Declaration Certification**

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

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

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

Date Signed



May 8, 2006

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

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
Stephen McGregor

Address  
Cangene Corporation  
3403 American Drive

City/State  
Mississauga ON

ZIP Code  
L4V 1T4

Telephone Number  
(905) 405-2905

FAX Number (if available)  
(905) 673-5123

E-Mail Address (if available)  
smcgregor@cangene.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.*

## EXCLUSIVITY SUMMARY

NDA # 21-538

SUPPL #

HFD # 510

Trade Name Accretropin injection

Generic Name somatropin [rDNA origin]

Applicant Name Cangene Corporation

Approval Date, If Known 1/23/08

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES

NO

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

505(b)(1)

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

YES

NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA# 19-640

Humatrope

NDA# 20-280

Genotropin

NDA# 21-148

Norditropin PLUS 6 others

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Study GA-005/5A-growth hormone deficiency indication  
Study GA-007/7A-Turner syndrome indication

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:



YES   
Explain:

! NO   
! Explain:  
Study conducted under a Canadian IND by  
Cangene

Investigation #2

!  
!

YES   
Explain:

! NO   
! Explain:  
Study conducted under a Canadian IND by  
Cangene

(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: Kati Johnson  
Title: Project Manager  
Date: 1/254/08

Name of Office/Division Director signing form: Mary Parks, MD  
Title: Division Director

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

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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.**  
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/s/

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Kati Johnson  
1/25/2008 07:27:20 AM  
signing for Mary Parks, MD

Revised

1/24/08

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-538 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 5/9/06 PDUFA Goal Date: 1/23/08

HFD 510 Trade and generic names/dosage form: Accretropin (somatropin [DNA origin]) Injection

Applicant: Cangene Corporation Therapeutic Class: growth hormone

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): \_\_\_\_\_

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 2

Indication #1: treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormong

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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: \_\_\_\_\_

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ 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.*

NDA ~~###-###~~  
Page 3

**This page was completed by:  
Kati Johnson**

*{See appended electronic signature page}*

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**Regulatory Project Manager**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH  
STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

**Attachment A**

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

**Indication #2: treatment of short stature associated with Turner syndrome in pediatric patients whose epiphyses are not closed.**

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

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: \_\_\_\_\_

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below)::

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below):

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

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 10/10/2006)

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this page is the manifestation of the electronic signature.**  
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/s/

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Kati Johnson  
1/24/2008 08:40:05 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-538

Chesapeake Biological Laboratories, Inc.  
US Agent for Cangene Corporation  
Attention: Minerva Devera  
Director of Quality Assurance and Regulatory Affairs  
Camden Industrial Park, 1111 S. Paca Street  
Baltimore, MD 21230-2591

Dear Ms. Minerva:

Please refer to your new drug application (NDA) Accretropin (somatropin [rDNA origin]) Injection.

By June 30, 2009, you must comply with the requirements on content and format of labeling for human prescription drug and biological products (21 CFR 201.56 and 201.57) for your application referenced above. These requirements, and the implementation plan for complying with the requirements, were published in the Federal Register in January 2006 (*Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 FR 3922, January 24, 2006). The implementation plan is as follows:

- For applications approved between June 30, 2005, and June 30, 2006, applicants must submit proposed labeling that complies with the new labeling regulations in a prior-approval supplement by June 30, 2009.
- For applications that were pending on June 30, 2006, and have since been approved with labeling in the old format, applicants must submit proposed labeling that complies with the new labeling regulations in a prior-approval supplement by June 30, 2009.
- For applications that were pending on June 30, 2006 and have not been approved, the labeling must comply with the new labeling requirements upon approval if the application is approved after June 30, 2009.

As stated above, please submit in a prior-approval supplement (PAS) updated labeling in the new format to your NDA 21-538 file.

Additional information about the labeling requirements can be found at <http://www.fda.gov/cder/regulatory/physLabel/default.htm>.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at 301-796-1234.

Sincerely,

*{See appended electronic signature page}*

Lina AlJuburi, Pharm.D., M.S.  
Chief, Project Management Staff  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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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.**  
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/s/

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Lina Aljuburi  
2/20/2009 03:41:41 PM

## REQUEST FOR CONSULTATION

TO (Division/Office):

**CDER OSE CONSULTS**

FROM: Kati Johnson, 301-796-1234

Division of Metabl & Endocrinology Products

DATE  
11/26/07

IND NO.

NDA NO.  
21-853

TYPE OF DOCUMENT  
no submission

DATE OF DOCUMENT  
N/A

NAME OF DRUG  
Accretropin (somatropin  
rDNA origin) Injection

PRIORITY CONSIDERATION  
high

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
1/14/08

NAME OF FIRM: Cangene

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                              |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                                     |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                                |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW   |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b> |
| <input type="checkbox"/> MEETING PLANNED BY            |  |   |

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- DISSOLUTION  
 BIOAVAILABILITY STUDIES  
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE  
 PROTOCOL-BIOPHARMACEUTICS  
 IN-VIVO WAIVER REQUEST

#### IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL  
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES  
 CASE REPORTS OF SPECIFIC REACTIONS (List below)  
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  
 SUMMARY OF ADVERSE EXPERIENCE  
 POISON RISK ANALYSIS

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The tradename, Accretropin, was found acceptable on 2/2/07 (OSE Review # 2006-820). The application is approvable pending resolution of some microbiology issues. The firm has responded to the AE letter and the goal date is 1/23/08. We are assuming that the response is adequate and that the application can be approved. This consult is to request final approval of the tradename prior to approval.

Thanks for your assistance.

**PDUFA DATE: 1/23/08**

**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA

HFD- /Division File

HFD- /RPM

HFD- /Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER  
K. Johnson 301-796-1234

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
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5/28/05

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/s/

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Kati Johnson  
11/26/2007 09:55:55 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-538

Chesapeake Biological Laboratories, Inc.  
US Agent for Cangene Corporation  
Attention: Minerva Devera  
Director, QA and Regulatory Affairs  
Camden Industrial Park  
1111 S. Paca Street  
Baltimore, MD 21230-2591

Dear Ms. Devera:

We acknowledge receipt on July 23, 2007 of your July 20, 2007 resubmission to your new drug application for Accretropin (somatropin [rDNA origin]) for injection.

We consider this a complete, class 2 response to our March 8, 2007 action letter. Therefore, the user fee goal date is December 23, 2007.

If you have any question, call me at 301-796-1234.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Kati Johnson

7/27/2007 05:45:55 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-538

Chesapeake Biological Laboratories, Inc.  
US Agent for Cangene Corporation  
Attention: Minerva Devera  
Director of Quality Assurance and Regulatory Affairs  
Camden Industrial Park  
1111 S. Paca Street  
Baltimore, MD 21230-2591

Dear Ms. Minerva:

Please refer to your May 10, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accretropin (somatropin [rDNA origin]) Injection, 5 mg/ml.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on July 9, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Microbiology

The following data and reports could not be found and will be required for review. It is recommended that they be submitted as an amendment to the application.

1)

b(4)

2)

3)

4)

b(4)

5)

6)

Administrative

1. Please provide a debarment certification signed by both the sponsor and the US agent.
2. Provide Volumes 32 through 46 for the statistical reviewer.

In addition, submit a risk management plan to ensure appropriate distribution, if approved.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

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

If you have any questions, call me at 301-796-1234.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Chief, Project Management Staff  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Kati Johnson  
7/12/2006 10:41:11 AM



NDA 21-538

**INFORMATION REQUEST LETTER**

Chesapeake Biological Laboratories, Ind.  
US Agent for Cangene Corporation  
Attention: Minerva Devera  
Director of Quality Assurance and Regulatory Affairs  
Camden Industrial Park, 1111 S. Paca Street  
Baltimore, MD 21230-2591

Dear Ms. Devera:

Please refer to your May 9, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accretropin (somatropin [rDNA origin]) Injection, 5 mg/ml.

We are reviewing the Statistical section of your submission and have the following comments and information requests for Studies GA-005/5A and GA-007/7A. We request a prompt written response in order to continue our evaluation of your NDA.

1. In both LOCEFF.XPt (local standard) and TANEFF.XPT (Tanner standard) data files, there are SGV\_XXX variables for the standard growth velocities. Please give an example to illustrate how they were derived. Also, please explain why the standard growth velocities for Month 6 (SGV\_W24) and Month 12 (SGV\_M12) are identical.
2. Submit a data set for the local GV standard.
3. Please advise where baseline and on-treatment SDS for growth velocity using local and Tanner standards can be found from the data sets submitted (the GVBASE.XPT only gives baseline growth velocity SDS using Tanner standard). If there are not submitted, please submit the electronic data sets.
4. Clarify whether LOCF (last-observation-carried-forward) was the method used in the analyses?

If you have any questions, call Kati Johnson, Chief, Project Manager, at (301) 796-1234.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, MD  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Mary Parks  
1/16/2007 07:37:26 PM



NDA 21-538

INFORMATION REQUEST LETTER

Chesapeake Biological Laboratories, Inc.  
US Agent for Cangene Corporation  
Attention: Minerva Devera  
Director of Quality Assurance and Regulatory Affairs  
Camden Industrial Park  
1111 S. Paca Street  
Baltimore, MD 21230-2591

Dear Ms. Devera:

Please refer to your May 9, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Accretropin (somatropin [rDNA origin]) Injection, 5 mg/ml.

We are reviewing the Clinical and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical

Please provide the following information or refer to where in the NDA such information can be located:

- 1) A list of individual baseline stimulated GH values and which stimulation test(s) has been used on each patient.
- 2) Descriptive statistics of baseline height velocity values (cm/year and SDS) for study GA-007/7A.
- 3) An analysis that compares height velocity (cm/yr and SDS) on treatment with baseline height velocity (cm/yr and SDS) for studies GA-005/5A and GA-007/7A.
- 4) Provide a figure that depicts individual responses on trial (e.g. a scatterplot) for height SDS and height velocity SDS for patients in studies GA-005/5A and GA-007/7A.
- 5) According to the table entitled "Listing of Growth Velocity at Baseline" in Appendix 16.2.4.6 (Listing of Baseline Growth Velocity) for study GA005/5A, several patients had baseline SDS for growth velocity above -1 SDS but are not listed as protocol violators (patient GD 101: 1.29; GD 103: 0.16; GD108:-0.59; GD113:-0.26; GD114:-0.65; GD207:0.27; GD211:-0.27; GD214:0.95). Explain if they were protocol violators and if so, provide an updated per protocol analysis for the primary efficacy endpoint.
- 6) According to the table entitled "Listing of Growth Velocity at Baseline" in Appendix 16.2.4.6 (Listing of Baseline Growth Velocity) for study GA007/7A, three patients had baseline SDS for growth velocity above -1 SDS but are not listed as protocol violators (patient GF507: -0.73; patient GF521: -0.80; patient GF527: 1.28). Explain if they were protocol violators and if so, provide an updated per protocol analysis for the primary efficacy endpoint.
- 7) According to the GA-005A study report Section 10.1 (Disposition of Patients) 6 subjects (subjects 102, 103, 109, 123, 124, and 204) were withdrawn at Month 30 because they reached puberty. However, information in the Clinical Summary Section 2.7.3.3.1.3 indicates that only 4 subjects have been withdrawn at Month 30 (subjects 102,109, 123, and 124.) Explain the following discrepancy and indicate the correct number of patients who withdrew at Month 30 in Study GA-005A.

- 8) Table 14-65 from the Study Report GA-005/GA-005A (“Vital sign results over time”) lists a minimal pulse measurement at Week 8 of “19.0”. Please confirm this value as a typographical error and provide the correct value.
- 9) Descriptive statistics for height velocity (cm/yr) in patients with anti-GH antibodies and in patients without anti-GH antibodies at Months 12, 24 and 36 in studies GA-005/5A and GA-007/7A.
- 10) An analysis of eosinophilia (descriptive statistics) in patients who had GH antibodies versus patients who did not develop anti-GH antibodies in studies GA-005/5A and GA-007/7A.
- 11) Explain how the Z-score for anti-E.coli antibodies was calculated (including what was the reference population that was used for calculating it) and why so many patients had antibodies at baseline (78.6%) in study GA-005/5A.
- 12) Throughout the submission you are referring to anti-Accretropin antibody “values” or “levels” in mg/mL and compare them to literature anti-hGH binding capacities expressed in mg/mL (e.g. Okada et al., Pirazzoli et al., and Lundin et al.). Please address this discrepancy and confirm that you are referring also to anti-hGH binding capacities.
- 13) The number (%) of patients who had anti-ECP antibodies at each timepoint in study GA-007/7A.
- 14) An analysis of bone age vs. chronological age in studies GA-005/5A and GA-007/7A (e.g. bone age/chronological age ratios, bone age advancement versus chronological age advancement, scatterplot of such values).
- 15) Submit a Safety Update as required under 314.50(d)(5)(6)(b).

#### Chemistry, Manufacturing and Controls

##### Drug substance:

1. Provide a copy of the Certificate of Analysis \_\_\_\_\_ used in the manufacture of the drug substance, \_\_\_\_\_
2. Provide an agreement to place one lot of Accretropin™ drug substance annually into the stability program. The results from the stability studies will be provided to the Agency in the annual reports.

b(4)

##### Drug product:

3. Include Particulate Matter testing (USP <788> *Particulate Matter in Injections*) in the proposed specifications for the drug product as per USP <1> *Injection*.
4. The proposed acceptance criterion \_\_\_\_\_ in the specifications for the drug product was miscalculated when changing from EU/mL to EU/mg.
5. Provide the revised specifications for the drug product (release and shelf life) in a tabulated format.
6. Reduce the acceptance criterion for Total Impurities \_\_\_\_\_ in the proposed stability specification for the drug product
7. Identify the clinical study in which the clinical batch 0440301 was used.
8. Provide an agreement to place one lot of Accretropin™ drug product annually into the stability program. The results from the stability studies will be provided to the Agency in the annual reports.
9. Provide an agreement to withdraw from the market any batches found to fall outside the approved specifications for the drug product.
10. The currently available stability data for your commercial formulation only include up to 9 months of data. The expiry of the commercial formulation will be determined accordingly unless updated stability data are provided.

NDA 21-538

Page 3

If you have any questions, call Kati Johnson, Project Manager, at (301) 796-1234.

Sincerely,

*{See appended electronic signature page}*

Mary Parks, MD  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Mary Parks  
1/10/2007 08:12:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Office/Division): CDER OSE CONSULTS (TRADENAME REVIEW)			FROM (Name, Office/Division, and Phone Number of Requestor): Kati Johnson, CPMS, Metabolic & Endocring Products	
DATE 11/14/06	IND NO.	NDA NO. 21-538	TYPE OF DOCUMENT N	DATE OF DOCUMENT 5/9/06
NAME OF DRUG Accretropin Injection, 5 mg/ml		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 2/15/07
NAME OF FIRM: Cangene Corporation				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT			
<b>II. BIOMETRICS</b>				
<input type="checkbox"/> PRIORITY P NDA REVIEW		<input type="checkbox"/> CHEMISTRY REVIEW		
<input type="checkbox"/> END-OF-PHASE 2 MEETING		<input type="checkbox"/> PHARMACOLOGY		
<input type="checkbox"/> CONTROLLED STUDIES		<input type="checkbox"/> BIOPHARMACEUTICS		
<input type="checkbox"/> PROTOCOL REVIEW		<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE		
<input type="checkbox"/> BIOAVAILABILTY STUDIES		<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS		
<input type="checkbox"/> PHASE 4 STUDIES		<input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY		
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES		<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE		
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)		<input type="checkbox"/> POISON RISK ANALYSIS		
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> NONCLINICAL		
COMMENTS / SPECIAL INSTRUCTIONS: Sponsor is requesting to use the tradename "Accretropin" for their growth hormone product. My apologies for the late consult, but firm told me when the NDA was submitted that they were not interested in this tradename, then apparently changed their mind. Goal date for the NDA=3/10/07 Medical Officer=Dragos Roman, 6-1285				
SIGNATURE OF REQUESTOR Kati Johnson, 6-1234		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

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Kati Johnson  
11/14/2006 12:48:27 PM

## DSI CONSULT: Request for Clinical Inspections

**Date:** 6/22/06

**To:** Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46  
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

**cc:** Joseph Salewski, , Acting Director, DSI, HFD-45  
Mary H. Parks, M.D., Acting Director,

**From:** Kati Johnson, Chief, Project Management Staff, HFD-510  
Division of Metabolic & Endocrine Staff

**Subject:** **Request for Clinical Site Inspections**  
NDA 21-538  
Cangene Corporation (Canada)  
Contact person=Minerva Devera (US Agent)  
410-843-5005 X 2147 (phone)  
410-843-4414 (Fax)  
Canadian Regulatory Affairs=Jonathan Kirkwood  
905-405-2914 (phone)  
905-673-5123 (Fax)  
Accretropin (somatropin {rDNA origin}) Injection

**Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

\*\*\*See note after chart

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Investigators= Prof. Tomasz Romer, Dr. Mieczyslaw Walczak  Site 100 Centrum Zdrowia Dziecka, Klinica Endocryholigii Aleja Dzieci Polskich 20 04-736 Warsaw, Poland	GA-005/5A	24 of the 44 total	Treatment of pediatric patients with growth failure due to growth hormone deficiency
Investigators= Prof. Tomasz Romer, Dr. Mieczyslaw Walczak  Instytut Pomnik, Centrum Zdrowia Dziecka Klinica Endokrynologii Aleja Dzieci Poklskich 20 04-736 Warsaw Poland	GA-007/7A	All 37 patients in the study	Treatment of short stature associated with Turner syndrome in pediatric patients whose epiphyses are not closed

**\*\*\*NOTE-WE WOULD LIKE TO BE CONTACTED BEFORE THE INSPECTOR GOES TO THE SITE SO THAT WE CAN PROVIDE A LIST OF ISSUES THAT WE WOULD LIKE THEM TO LOOK AT. DURING A FILING REVIEW OF THE APPLICATION, WE HAVE IDENTIFIED THE FOLLOWING ISSUES OF INTEREST, BUT WOULD APPRECIATE THE OPPORTUNITY TO EXPAND ON THIS AS OUR REVIEW PROGRESSES:**

- (1) the baseline height velocity data (did all patients have a pre-baseline measurement at 6 months or more before baseline?) and**
- (2) quality of height data collected on trial (were height measurements on trial collected in a standardized fashion?).**
- (3)It seems to medical officer that the vital signs data (e.g. blood pressure measurements) seem to have the same minimal values at**

**different visits (this may be a limitation of the instrument that measures the blood pressure or not).**

**Domestic Inspections:**

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify:)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: SPECIFY

**International Inspections:**

We have requested inspections because (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: SPECIFY

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) 2/1/07. We intend to issue an action letter on this application by (division action goal date) 3/09/07. The PDUFA due date for this application is 3/10/07.

Should you require any additional information, please contact Kati Johnson, 301-796-1234.

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/s/

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Mary Parks  
6/22/2006 06:33:13 AM

**REQUEST FOR CONSULTATION**

TO (Office/Division): **Office of Pharmaceutical Science-  
MICROBIOLOGY**

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of  
Metabolism & Endocrinology, DMEP**

DATE  
5/25/06

IND NO.

NDA NO.  
21-538

TYPE OF DOCUMENT  
original NDA

DATE OF DOCUMENT  
May 9, 2006

NAME OF DRUG  
**Accretropin (somatropin  
[rDNA origin] injection**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
1/31/07

NAME OF FIRM: **Cangene Corporation**

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input checked="" type="checkbox"/> PAPER NDA    | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

**II. BIOMETRICS**

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

**III. BIOPHARMACEUTICS**

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

**IV. DRUG SAFETY**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This NDA was submitted to market this growth hormone (GH) solution in 1 ml vials for the following indications:

- ~~txt~~ of peds patients with growth failure due to inadequate GH secretion **b(4)**
- txt of short stature associated with Turner syndrome

The chemist, Yvonne Yang, 301-796-1777 is requesting evaluation of the following:

- (1) Adequacy of the preservative excipients in the formulation and of the proposed container closure to assure sterility of the drug product throughout its proposed shelf life and usage.
- (2) Adequacy of the ~~process~~ process validation for the manufacture of Accretropin™, and
- (3) Adequacy of the Adventitious Agent Safety Evaluation

I am forwarding the 3 volumes submitted by the sponsor. The proposed labeling is included in volume 1 and is also available in the EDR (edr.cder.fda.gov).

The filing is scheduled for Wednesday, 6/21/06 at 1 pm in Room 3302 (may be moved to a larger room)

PLEASE LET ME KNOW WHO THE ASSIGNED REVIEWER IS.

Thanks for your assistance. Please call if you have any questions.

SIGNATURE OF REQUESTOR Kati Johnson, Chief, PM Staff, DMEP, 6-1234	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Kati Johnson

5/25/2006 06:25:10 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-538

**NDA ACKNOWLEDGMENT**

Chesapeake Biological Laboratories, Inc.  
US Agent for Cangene Corporation  
Attention: Minerva Devera  
Director of Quality Assurance and Regulatory Affairs  
Camden Industrial Park  
1111 S. Paca Street  
Baltimore, MD 21230-2591

Dear Ms. Devera:

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: Accretropin (somatropin [rDNA origin]) Injection, 5 mg/ml

Review Priority Classification: Standard

Date of Application: May 9, 2006

Date of Receipt: May 10, 2006

Our Reference Number: NDA 21-538

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 July 9, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 10, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

NDA 21-538

Page 2

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

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

If you have any questions, call me at (301) 796-1234.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
Chief, Project Management Staff  
Division of Metabolism & Endocrinology  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

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Kati Johnson  
5/18/2006 02:50:19 PM

7/23/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-538

Chesapeake Biological Labs, Inc.  
US Agent for Cangene Corporation  
Attention: Sam Mancuso  
111 South Paca Street  
Baltimore, MD 21230-2591

Dear Mr. Mancuso:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rhGH, \_\_\_\_\_ for injection.

b(4)

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2004. The purpose of the Pre-NDA meeting was to discuss the submission of a (b)(2) application.

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 me at (301) 827-9087.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: June 17, 2004 minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** June 17, 2004  
**TIME:** 3:30 pm-4:30 pm  
**LOCATION:** Parklawn Building, Conference Room C  
**APPLICATION:** 21-538, Cangene Corporation  
**DRUG NAME:** \_\_\_\_\_, Recombinant Human Growth Hormone  
**TYPE OF MEETING:** Pre-NDA  
**MEETING CHAIR:** David G. Orloff, MD  
**MEETING RECORDER:** Monika Johnson, PharmD

**b(4)**

**FDA ATTENDEES:** (Title and Office/Division)

Division of Metabolic and Endocrine Drug Products

David G. Orloff, MD/Director  
Dragos Roman, MD/Medical Reviewer  
Hae Young Ahn, PhD/Biopharmaceutics Team Leader  
Jim Wei, MD/PhD/Biopharmaceutics Reviewer  
Todd Sahlroot, PhD/Statistics Team Leader  
Cynthia Liu, PhD/Statistics Reviewer  
Monika Johnson, PharmD/Project Manager

Office on New Drug Chemistry

Eric Duffy, PhD/Director  
Blair Fraser/Deputy Director  
Stephen Moore, PhD/Chemistry Team Leader  
Janice Brown, MS/Chemistry Reviewer

Office of Drug Evaluation II

Robert J. Meyer, MD/Director

Office of Generic Drugs

Donald Hare

Office of Regulatory Affairs

Virginia Beakes

**EXTERNAL CONSTITUENT ATTENDEES:**

**b(4)**

Gregor Awang, Ph.D. - Associate Director, Research and Development

Wendy Johnson, Ph.D. - VP, Research and Development

Mark Langstaff, B.A., M.A. - Manager, Marketing and Business Development, Project Manager

Nora Matzner, M.V., D.M.V. - Regulatory Affairs Associate

Stephen McGregor, B.Sc. - Manager, Regulatory Affairs, Biotechnology

Susan Morency, B.Sc. - Regulatory Affairs Associate

Jodi Smith, Ph.D. - Clinical Research Scientist

Donald Stewart, Ph.D. - Director, Research

Andrew Storey, B.Sc. - VP, Quality, Clinical and Regulatory Affairs

Lindsey Wiebe, B.Comm (Honours) - Product Manager

Elizabeth Wishart, B.Sc., M.B.A. - Director, Regulatory Affairs

b(4)

**BACKGROUND:**

\_\_\_\_\_ is a rhGH produced by recombinant DNA technology in an *E.coli* expression system. The sponsor requested a pre-NDA meeting on March 29, 2004, to discuss the submission of a 505(b)(2) application. The reference listed drug is Humatrope, manufactured by Eli Lilly.

b(4)

**MEETING OBJECTIVES:**

- Review CMC for the drug substance and drug product.
- Review the comparability analysis \_\_\_\_\_ against the reference listed drug, Humatrope
- Review the pharmacokinetics equivalence data from the clinical study GA-002
- Review immunogenicity data obtained from safety/efficacy studies
- Review the proposed \_\_\_\_\_ labeling
- Clarification of current administrative requirements

b(4)

**DISCUSSION POINTS:**

Following introductions, Dr. Orloff had the following comments for the sponsor.

**We would like to remind you of the following:**

- 1) The Agency has not finalized an official position on follow-on biologics in general and on follow-on growth hormone (GH) in particular.
- 2) The Division does not have a final guidance for industry on how new GH drug products can be approved as 505(b)(2) applications (therefore, at this time the Division can only explore with sponsors this option without being able to give specific advice on 505(b)(2) GH applications).
- 3) Currently there are two Citizen Petitions pending that challenge the authority of the Agency to approve human GH under 505(b)(2); therefore proceeding alone on this pathway entails a certain legal risk.
- 4) The Division strongly encourages sponsors to consider applications under the 505(b)(1) pathway.

Cangene presented two slides as overview and proceeded into their proposed questions.

***I. Chemistry, Manufacturing and Controls***

A change in site of manufacture of the drug substance and modifications to the manufacturing strain and manufacturing process have been between the manufacture of the clinical batches and commercial batches. These changes and supporting comparability data is described in this pre-meeting package in Section 9.1.2 (p. 15-17), 9.1.3 (p. 17- 52) and 9.4 (p.79-111). Does the Division concur with our approach to establish the comparability of the product intended for commercial distribution?

**FDA comment:** In addition \_\_\_\_\_, the third genetic construct should be fully characterized according to the recommendations described in ICH Q5B and Q5D (cell line characterization, DNA sequence of the expression cassette for the end of production cells, etc).

**b(4)**

**Characterization tests for your product using the tests listed in table 9.4a is acceptable; however, we recommend amino acid sequence analysis of the recombinant hGH protein.**

**The structural and biological characterization studies may include an international reference standard or the USP somatotropin reference standard (when it becomes available), unless the analytical procedure is reference standard independent.**

2. Please comment on the adequacy of the proposed product characterization test and release specifications, especially with respect to the assays for residual DNA, E. coli protein and test for impurities (refer to 9.2, p 53-55 of the pre-meeting package).

**FDA comment:** Refer to our response in no. 1 regarding the product characterization tests.

**Drug Substance and Drug Product Specifications:**

- a. The specifications should distinguish between product related substances and product related impurities.
- b. Where there are a number of impurities identified in an assay; for example, \_\_\_\_\_ by RP-HPLC, a limit for single impurities should be included in the acceptance criteria.
- c. \_\_\_\_\_ should be reported as EU/mg somatotropin.
- d. Impurities should be qualified and the levels justified.

**b(4)**

e. the in-vitro biassay should be correlated with either the rat weight gain or rat tibia width assay.

3. A minor change in formulation of the drug product is being made between the lots used in the preclinical and clinical studies and commercial process lots. The concentration of the bacteriostatic agent (phenol) is \_\_\_\_\_ 0.34% \_\_\_\_\_, to ensure conformance with the current compendial testing for antimicrobial agents. We will perform full characterization release and stability testing on the commercial lots to support NDA approval. Does the Division have any comments regarding this change and our proposal for testing the commercial process lots to support NDA approval?

b(4)

**FDA comment: The effect of the change in the phenol concentration on the structure and biological activity should be investigated. Depending on the results of your analysis, you may need to perform an additional PD study.**

## II. Clinical

*The sponsor explained that they currently plan to pursue the 505(b)(1) pathway.*

*In response to the Division's questions, the sponsor provided the following clarifications concerning the \_\_\_\_\_ clinical program:*

- *The clinical program includes patients followed for periods of time longer than the 6 month interval for which data were presented in the in the meeting package (some patients were in the trial for up to 3 years)*
- *The highest percentage of patients who became anti-GH antibody positive on \_\_\_\_\_ treatment is approximately 40%.*
- *Most of the clinical trial protocol deviations and violations were relatively minor.*

b(4)

**FDA made the following comments that incorporate questions 1-3 of the sponsor:**

- **As GH registration trials for pediatric growth hormone deficiency (GHD) and Turner syndrome were at least one year in duration, the sponsor should present not only efficacy data at 6 months of \_\_\_\_\_ treatment but also at the end of one year of treatment.**
- **The efficacy data collected during the clinical trials (e.g. height velocity at 6-months and 12-months) should be compared to historical data from the published literature collected from patients with the same diagnosis, similar baseline characteristics, and treated with similar GH regimen for a comparale duration.**
- **The efficacy and safety data should be presented separately for the pediatric GHD and Turner syndrome indication.**
- **The current position of the Division is that animal toxicology data per se is not necessary for new growth hormone applications; there are, however, two exceptions for which toxicological characterization will be necessary: 1) novel impurities and 2) novel excipients.**
- **As all the immunogenicity data have been collected with the development \_\_\_\_\_ product, at the time of registration, 6 months of immunogenicity data with the to-be-marketed drug product will likely be required as a phase IV commitment.**

b(4)

b(4)

2. Does the Division have any comments regarding the approval on \_\_\_\_\_ with an intramuscular (IM) route of administration?

**FDA comments:** For the approval of an intramuscular (IM) administration a separate PK study will be required under a 505(b)(1) path (i.e., the subcutaneous data will not be extrapolated to the IM administration).

**Additional post meeting comments:**

The following additional recommendations were made relative to how the data should be presented in the — NDA;

b(4)

- Height, height velocity, and IGF-I information should be presented also as standard deviation scores
- An analysis of change in height velocity SDS on treatment relative to height velocity SDS at baseline should be included separately for GHD and Turner Syndrome patients.

**III. Administrative Matters**

1. Are there any particular format requirements for a CTD formatted NDA? Any sections of the application that should be provided electronically.

**FDA comment:** We appreciate getting most of the NDA submitted electronically, however, presenting the main sections of the submission in electronic format is strongly recommended (e.g. clinical summary, all labeling, Intergrated Summary of Efficacy and Safety, etc.) In addition, all questions regarding submissions in CTD format can be emailed to [esub@cder.fda.gov](mailto:esub@cder.fda.gov)

2. Does the Agency have any comments regarding user fees for 505(b)(2) applications?

**FDA comment:** If the application is considered a 505(b)(1) application, an application fee will be required. If clinical data (other than bioavailability or bioequivalence) with respect to safety or effectiveness is required for approval, then a full fee is required (for FY 2004, which ends September 30, 2004, the full application fee is \$573,500). If the application will be considered a 505(b)(2) application, then an application fee may apply. Please call Mike Jones, FDA user fee staff, at 301-594-2041 for more details.

**DECISIONS (AGREEMENTS) REACHED:**

The sponsor explained that they currently plan to pursue a 505(b)(1) drug development pathway.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

None

**ACTION ITEMS:**

None

Concur(s): June 18, 2004  
David G. Orloff, M.D.



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this page is the manifestation of the electronic signature.**  
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/s/

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Monika Johnson  
7/23/04 04:02:15 PM

4/9/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-538

Chesapeake Biological Laboratories, Inc.  
US Agent for Cangene Corporation  
Attention: Sam Mancuso  
111 South Paca Street  
Baltimore, MD 21230-2591

Dear Mr. Mancuso:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for — (recombinant human growth hormone).

b(4)

We also refer to your March 29, 2004, correspondence, received March 30, 2004, requesting a meeting to discuss the submission of a 505(b)(2) application.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: June 11, 2004  
Time: 12:30 p.m. – 1:30 p.m. EST  
Location: Parklawn Conference Room C, 3<sup>rd</sup> Floor, 5600 Fishers Lane, Rockville, MD, 20857

CDER participants (tentative): David Orloff, MD, Division Director  
Stephen Moore, PhD, Chemistry Team Leader  
Janice Brown, MS, Chemistry Reviewer  
Jeri ElHage, PhD, Pharmacology/Toxicology TL  
Hae Young Ahn, PhD, Biopharmaceutics TL  
Todd Sahlroot, PhD, Statistical Team Leader  
Robert Perlstein, MD, Medical Reviewer  
Dragos Roman, MD, Medical Reviewer  
Enid Galliers, Chief Project Management Staff  
Monika Johnson, PharmD, Project Manager  
Eric Duffy, PhD, Director DNDCII  
Justina Molzon, OIM  
Jim Wei, MD, PhD, Biopharmaceutics Reviewer  
Cynthia Liu, PhD, Statistics Reviewer  
Michael Jones, PharmD, User Fee Staff

NDA 21-538

Page 2

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are changes to the attendees that you provided, email that information to me at [johnsonm@cder.fda.gov](mailto:johnsonm@cder.fda.gov) so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Monika Johnson, (301-827-9087; or the division secretary, (301) 827-6430.

Provide the background information for this meeting (one copy to your NDA and 20 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the packages one month prior to the meeting, we may cancel or reschedule the meeting.

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

Sincerely,

*{See appended electronic signature page}*

Monika Johnson, PharmD  
Regulatory Project Manager  
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/

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Monika Johnson  
4/9/04 01:07:09 PM

## ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-538	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Accretropin Established Name: somatropin [rDNA origin] Dosage Form: injection		Applicant: Cangene Corporation
RPM: Kati Johnson		Division: DMEP      Phone # 301-796-1234
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed      <input type="checkbox"/> Corrected</p> <p>Date:</p>
❖ User Fee Goal Date		1/23/08
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input type="checkbox"/> None AE-3/8/07
❖ Advertising ( <i>approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed ( <i>indicate dates of reviews</i> )		<input type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed Requested in AE letter

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5  NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies  NDAs and NDA Supplements: <input type="checkbox"/> OTC drug  Other:  Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	X Included
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?             <ul style="list-style-type: none"> <li>• NDAs/BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i></li> <li>• NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> </ul> </li> </ul>	<p>X No      <input type="checkbox"/> Yes</p> <p><input type="checkbox"/> No      <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:</p> <p><input type="checkbox"/> No      <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:</p> <p><input type="checkbox"/> No      <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:</p> <p><input type="checkbox"/> No      <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:</p>
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>• 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.</li> <li>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<p>21 CFR 314.50(i)(1)(f)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii)    <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For <b>each paragraph IV</b> 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). (<i>If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews).</i>)</li> <li>• [505(b)(2) applications] For <b>each paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for <b>each</b> paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes      <input type="checkbox"/> No</p>

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).

- (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)?

Yes  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 section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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  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 section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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

<p>within the 45-day period).</p> <p><i>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 section below (Summary Reviews).</i></p> <p><i>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.</i></p>	
<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director) <i>(indicate date for each review)</i>	AE-3/8/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) <i>(indicate date)</i>	N/A
<b>Labeling</b>	
❖ Package Insert	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	X
❖ Patient Package Insert	N/A
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Medication Guide	N/A
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels)	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	X
❖ Labeling reviews and minutes of any labeling meetings <i>(indicate dates of reviews and meetings)</i>	<p>X DMETS 2/2/07, 1/8/08</p> <p><input type="checkbox"/> DSRCs</p> <p><input type="checkbox"/> DDMAC</p> <p><input type="checkbox"/> SEALD</p> <p><input type="checkbox"/> Other reviews</p> <p><input type="checkbox"/> Memos of Mtgs</p>

<b>Administrative Documents</b>	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	N/A
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	X Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>	N/A
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>Incoming submission documenting commitment</li> </ul>	X None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	X
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>EOP2 meeting (<i>indicate date</i>)</li> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	N/A <input type="checkbox"/> No mtg 6/17/04 X No mtg N/A
❖ Advisory Committee Meeting <ul style="list-style-type: none"> <li>Date of Meeting</li> <li>48-hour alert or minutes, if available</li> </ul>	X <input type="checkbox"/> No AC meeting
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	
<b>CMC/Product Quality Information</b>	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	6/12/06, 12/22/06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <li>X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> <li><input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> <li><input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	Page 95 of 12/22/06 review
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	1/2/08 <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 2/4/07 X Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul>	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	2/8/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	X None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	X No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	x None requested
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	2/21/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Page 18 of 2/21/07 review
❖ Clinical consult reviews from other review disciplines/divisions/Centers ( <i>indicate date of each review</i> )	X None
❖ Microbiology (efficacy) reviews(s) ( <i>indicate date of each review</i> )	X Not needed
❖ Safety Update review(s) ( <i>indicate location/date if incorporated into another review</i> )	Page 77 of 2/21/07 review
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date of each review</i> )	X Not needed
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
• Clinical Studies	1/24/07
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      3/7/07
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None      2/9/07

## Appendix A to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Kati Johnson  
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