# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER

## 21-256

# Administrative/Correspondence

1.4 Patent Information

In the opinion and to the best knowledge of ChiRhoClin, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Edward D. Purich, Ph.D.
Chief Executive Officer

## 13.0 PATENT INFORMATION ON ANY PATENTS WHICH CLAIMS THE DRUG (21 U.S.C. 355 (b) or (c))

There are no applicable patents on human secretin.

APPEARS THIS WAY
ON ORIGINAL

# PEDIATRIC PAGE

**NDA/BLA #:** NDA 21-256 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

**Stamp Date:** October 10, 2003 **Action Date:** April 10, 2004

**HFD-**180 **Trade and generic names/dosage form:** human synthetic secretin/lyophilized sterile powder

**Applicant:** ChiRhoClin, Inc. **Therapeutic Class:** 8013600

**Indication(s) previously approved:** N/A

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

**Number of indications for this application(s):** 3

**Indication #1:** Aid in the Diagnosis of Exocrine Pancreatic Dysfunction

**Indication #2:** Aid in the Diagnosis of Gastrinoma

**Indication #3:** Identification of the Ampulla of Vater During ERCP

**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 **(all 3 indications)**
☐ There are safety concerns
☐ Other:_____

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

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

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

**Reason(s) for partial waiver:**

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

☐ **Other:**_____

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

## Section C: Deferred Studies

**Age/weight range being deferred:**

| | | | | |
|---|---|---|---|---|
| **Min** ____ | **kg**____ | **mo.**____ | **yr.**____ | **Tanner Stage**____ |
| **Max**____ | **kg**____ | **mo.**____ | **yr.**____ | **Tanner Stage**____ |

**Reason(s) for deferral:**

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

**Other:**_____

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

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

## Section D: Completed Studies

**Age/weight range of completed studies:**

| | | | | |
|---|---|---|---|---|
| **Min** ____ | **kg**____ | **mo.**____ | **yr.**____ | **Tanner Stage**____ |
| **Max**____ | **kg**____ | **mo.**____ | **yr.**____ | **Tanner Stage**____ |

**Comments:**

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

**This page was completed by:**

*{See appended electronic signature page}*

**Gail Moreschi, M.D., M.P.H., F.A.C.P.**
**Medical Officer**

**cc: NDA 21-256**
**HFD-960/ Grace Carmouze**

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

(revised 12-22-03)

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/s/
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Gail Moreschi
4/7/04 09:14:08 AM

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: April 5, 2004**

| | |
|---|---|
| **To:** Edward D. Purich, Ph.D. | **From:** Ryan Barraco, B.A., B.S. |
| **Company:** ChiRhoClin, Inc. | Division of Division of Gastrointestinal & Coagulation Drug Products (DGCDP) |
| **Fax number:** 301-476-9529 | **Fax number:** 301-443-9285 |
| **Phone number:** 301-476-8388 | **Phone number:** 301-443-8017 |

**Subject:** NDA 21-256 – March 17, 2004 Micro Amendment

**Total no. of pages including cover:** 4

**Comments:**

Dear Dr. Purich,

I have attached the Microbiology Discipline Review Letter. Please respond to these deficiencies by tomorrow (April 6, 2004). Please submit a formal copy to the NDA, fax a copy to Dr. Stephen Langille (phone 301-827-7340, fax 301-827-3084), and also please fax a copy to me. If you have any questions, please call me at 301-443-8017. Thanks.

Ryan Barraco

**Document to be mailed:** ☒ **YES** ☐ **NO**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.**

4/5/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-256

**DISCIPLINE REVIEW LETTER**

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
Chief Executive Officer
4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129

Dear Dr. Purich:

Please refer to your June 14, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic human secretin for injection.

Please also refer to your October 10, 2003 resubmission, which constituted a complete response to our December 14, 2001 action letter.

We finally refer to your submission dated March 17, 2004, which included a response to our March 12, 2004 letter.

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

1. Please provide the following information regarding drug product validation:

   a.

   b.

2. Please provide the following information regarding validation:

   a.

   b.

c. —

d. The following information regarding stopper —

- The source of the —
-
- The — recovery and testing methods (including positive and negative controls)

3. Please provide the following information regarding the program:

a.
b.
c.

d.

e.

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

If you have any questions, call Ryan Barraco, Consumer Safety Officer, at (301) 443-8017.

Sincerely,

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
4/5/04 04:59:05 PM

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**

DATE: 4/5/04

TO: Julie Beitz, MD
Deputy Director
Office of Drug Evaluation III

FROM: Joyce A Korvick, MD, MPH
Deputy Director
Division of Gastrointestinal and Coagulation Drug Products

SUBJECT: **Division Director (Deputy) Review Summary**
**NDA 21-256**

APPLICANT: ChiRhoClin

SUBSTANCE: —— (synthetic human secretin) for Injection
(lyophilized sterile powder)
Chemical &Therapeutic Class: Type 1, GI Diagnostic
Review Cycle 2.
User Fee Goal Date: 4/10/04

## I. Background:

The subject of this application is the injectable synthetic human secretin (sHS) product manufactured by ChiRhoClin. Biologically derived porcine secretin (bPS), first marketed in the U.S. in 1981, has been utilized as an injectable agent to evaluate exocrine pancreatic function, as a diagnostic test for gastrinoma, and as an adjunct in obtaining desquamated pancreatic cells for cytopathologic examination. Ferring, the sole manufacturer in the US, ceased production of bPS in 1999. ChiRhoClin has an approved synthetic porcine secretin (sPS) product currently on the market.

ChiRhoClin is seeking approval of sHS for the following indications in the current application (all three have been designated as Orphan Drug Indications):

- diagnosis of pancreatic exocrine dysfunction (dose: 0.2µg/Kg $B_{wt}$);
- diagnosis of gastrinoma (dose: 0.4 µg/Kg $B_{wt}$);
- facilitation during ERCP in

## Orphan Drug Issues:

Although there is a two amino acid difference between the approved porcine product and the human secretin, this is not a substantial difference and there is no clinically significant difference in action between these two products. This degree of similarity

would block the approval of the human secretin according to the Orphan Drug Regulations, however ChiRhoClin is the manufacturer of both products. Therefore, a letter was sent from the Division of Orphan Drugs requesting that the company place in writing that it would waive the restrictions to marketing in the case of human secretin produced by ChiRhoClin(4/30/2002). The applicant responded writing on March 30, 2004 and was in agreement.

## II. Discipline review summary and commentary:

**A. OPDRA :** Review by the nomenclature committee did not recommended approval of the tradename — The division is in agreement with not approving this tradename.

The major issue with this tradename results from the potential confusion with Humulin both in look and sound. Both drugs are injectable. A mistake in calculation of a dose of human secretin with human insulin would potentially have serious health consequences. The maximum labeled dosing for human secretin is 0.4 mcg/kg. This would result in a 28 mcg dose being ordered for a 70 kg patient. Since human secretin is formulated to contain 0.2 mcg/0.1ml this would result in injectable volume of 14 ml. Humulin ordered as 14 units could be confused with a dose of human secretin 14 ml. Therefore, if there was confusion in the tradenames a patient might receive 14 units of insulin intravenously. In an extreme case, if one used 14 ml of Humulin R (500 units of insulin per 1 ml), this could have serious and life-threatening consequences. Therefore, the division recommends not accepting this tradename.

**B. Chemistry:** CMC reviewer recommends approval of this product pending resolution of Microbiology issues. All outstanding CMC issues have been resolved in this cycle, and cGMP inspection of facilities utilized to manufacture the drug substance and the drug product as well as used for analytical testing have been competed and are acceptable by the Office of Compliance. There are no Phase 4 commitments recommended by Chemistry.

The Microbiology Reviewer recommended approval status pending resolution of the following:

**LIST OF MICROBIOLOGY DEFICIENCIES ANDCOMMENTS**

1. Please provide the following information regarding drug product — validation:
   a. —
      at Bell-More laboratories.
   b. — for the drug product at Bell-More Laboratories. The values should not be greater than those used in the validation studies conducted at —
2. Please provide the following information regarding — validation:
   a. The —

b.

c. The following information regarding stopper

3. Please provide the following information regarding the environmental monitoring program:

a

b.

c.

d. The drug product

These microbiology issues were discussed with Chemistry and the Division was directed to request this information. The request was faxed April 4, 2004. The response is pending at the writing of this memo. It is the opinion of the Chemistry Team Leader that these issues may be easily resolved. In addition, this facility did pass inspection by compliance and this is an Orphan Drug Product, which would not be required to validate 3 additional lots. Due to the amount of drug sold, and the expiration dating additional lots would not be needed for several years. Resolution of these Microbiology concerns is pending.

C. **Pharmacology/Toxicology:** The biologic activity of sHS was found to be similar to that of the approved bPS in a cat model. Biologic activities of different sHS batches varied from —— when compared to either sPS or bPS. Synthetic human secretin showed no relevant toxicity up to 10 µg/kg/day in rats and up to 5µg/kg/day in dogs. The preclinical reviewer recommends that this NDA be approved on the first cycle. Labeling changes were recommended this cycle. The label appears vary similar to that of the approved porcine secretin product.

D. **Biopharmaceutics:** The application is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. This recommendation was based upon one sequential, uncontrolled, single dose study of the phamacokinetic profiles of 0.4 µg/kg sPS and sHS given one week apart in 12 normal subjects. After IV bolus administration, plasma concentration of synthetic human secretin rapidly declined to baseline secretin

levels within 60 to 90 minutes in most subjects. The mean AUC observed, which represented sampling to 120 min is nearly 79% of the estimated $AUC_{0-\infty}$. The alpha-half-life is 3.26 ± 0.28 minutes and the beta-half-life was calculated as 45 min. The clearance of synthetic human secretin is 580.9 ± 51.3 mL/minute and the volume of distribution is 2.7 liters. Labeling changes were recommended this cycle.

**E. Clinical: Efficacy /Safety:**

From a clinical point of view the medical reviewer, team leader and myself recommend approval of this product. See summary justification below.

The clinical development program for sHS, as described in the NDA, included clinical trials with small numbers of patients. The general assumptions were that this purified formulation of synthetic human secretin would be more specific, and similarly active to that of the biologically derived porcine secretin that has been on the market since 1981. In addition, if shown to have similar biological activity to the approved product, studies in the targeted population which demonstrated concordance between products would be adequate for the approval of sHS as a diagnostic product. The dose levels selected were based upon the equivalent biologic activity of bPS at the approved doses.

Literature evidences the use of secretin as a functional test in the diagnosis of chronic pancreatic insufficiency, and a provocative test for the diagnosis of gastrinoma. It describes values of serum gastrin for the diagnosis of gastrinoma (>110 pg/ml serum gastrin), and pancreatic secretion volume (< 80 mls per aliquot) and bicarbonate concentrations (< 80 mEq/L in each aliquot) for the diagnosis of pancreatic insufficiency.

**Statistical Review:**

Statistical review of the clinical trials, submitted for efficacy in the diagnosis of exocrine pancreatic dysfunction and gastrinoma, point out the wide variability of comparative values, the lack of statistical concordance, and the inability to specifically describe the sensitivity, specificity and negative predictive value of sHS due to the small sample size.

**Clinical Review:**

In contrast to the statistical review, the recommendation for approval by the clinical reviewers can be understood when one considers the limited number of available patients for study of these indications, and the previously described knowledge of the action of this specific amino acid molecule. The descriptive data are more informative in this case for the indications of pancreatic dysfunction and gastrinoma. Simply put, pharmacodynamic studies of gastrin levels (CRC99-10) and pancreatic secretion in normal subjects (CRC2000-1) reveal levels that are within the literature laboratory ranges described for normal patients. Comparatively, in the efficacy studies (CRC98-2, CRC99-9, CRC99-8), none of the patients with documented gastrinoma or pancreatic insufficiency had test results that would place them into a different diagnostic category. Given the limited use of this product in current clinical practice and the orphan nature of this drug, these data provide acceptable evidence for

the efficacy of this drug for a functional indication (see below). In addition, there exists a substantial level of previous knowledge and information regarding the interpretation of these test results. Therefore it becomes most important to demonstrate consistent biologic activity based upon GMP (Good Manufacturing Practice) which assures a pre-determined level of potency.

Both the statistic and medical reviewers recommend that the third indication, facilitation of during ERCP is approvable, pending additional clinical studies. The current study is inadequate (CRC98-4). However, if one further explores the reason that the study failed, on finds that it was due to the effect of sHS on pancreatic secretion. It was highly effective in increasing the pancreatic secretions so that the clinician performing the ERCP was unblinided to the study assignment. Thus, if the indication requested was to facilitate the identification of the ampula of Vater during ERCP no further studies would be necessary for this indication (see medication officer review addendum).

**F. Safety:**
Safety of this product has been described in a database that included 686 patients. No deaths resulted from these injections. For the diagnostic indications, adverse events were infrequent. It was the reviewer and team leader conclusion that this drug is safe to use for the diagnostic indications studied.

**G. Special Populations:**
the sample population was small and therefore no sub-analysis by age, race, or gender was meaningful.

**H. Pediatric Waiver Request:**
The applicant requested a waiver of pediatric study requirement due to the fact that the anticipated use in the pediatric population was extremely small and that this was an Orphan Drug and would be a hardship on the ChiRhoClin. The Division recommends granting a Pediatric Waiver to ChiRhoClin.

**Recommendations:**
At the time of writing this memo microbiology issues were pending. All other issues are resolved. The Division recommends that the NDA 21-256 be approved on this cycle if the Microbiology issues are resolved in an acceptable manner. At this time there are no Phase 4 commitments recommended by the Division.

The Division finds the following indications acceptable:
1. The stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction.
2. The stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangio-pancreatography (ERCP).
3. The stimulation of gastrin secretion to aid in the diagnosis of gastrinoma.

Clinical review regarding the indications requested by the applicant finds that the data submitted support a functional indication rather than a rigorously studied diagnostic test. The Division anticipates negotiating this wording tin labeling after the Chemistry issues are resolved. No further clinical efficacy studies will be necessary if the applicant agrees with the indications proposed by the Division.

Resolution of Microbiology concerns must be resolved before this drug is approved.

The labeling agreed upon during the March 31, 2004 Tele-conference is acceptable to the Division. This wording was sent to the sponsor on April 2, 2004.

Joyce A. Korvick, M.D., M.P.H.
Deputy Division Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
FDA.

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/s/
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Joyce Korvick
4/6/04 03:59:16 PM
MEDICAL OFFICER
division director summary

# mographic Worksheet

**Application Information** *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-256 Submission Type: N/A (pilot) Serial Number: N/A (pilot)

**Populations Included in Application** *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

| Category | | Number Exposed To Study Drug | | Number Exposed To Study Drug | | Number Exposed To Study Drug |
|---|---|---|---|---|---|---|
| Gender | Males | 206 | All Females | 377 | Females >50 | 157 |
| Age: | 0-≤1 Mo. | 0 | >1 Mo.- ≤2Year | 10 | >2-≤12 | 12 |
| | 12-16 | 2 | 17-64 | 465 | ≥65 | 90 |
| Race: | White | 535 | Black | 32 | Asian | 6 |
| | Other | 11 | | | | |

**Gender-Based Analyses** *(Please provide information for each category listed below.)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | | Was gender-based analysis included in labeling? | |
|---|---|---|---|---|---|---|
| | | | | | Yes | No |
| Efficacy | ☐ Yes | ☒ No | ☒ Inadequate #'s | ☐ Disease Absent | ☐ | ☒ |
| Safety | ☐ Yes | ☒ No | ☒ Inadequate #'s | ☐ Disease Absent | ☐ | ☒ |

Is a dosing modification based on gender recommended in the label? ☐ Yes ☐ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

**Age-Based Analyses** *(Please provide information for each category listed below)*

| egory | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | | Was age-based analysis included in labeling? | |
|---|---|---|---|---|---|---|
| | | | | | Yes | No |
| Efficacy | ☐ Yes | ☒ No | ☒ Inadequate #'s | ☐ Disease Absent | ☐ | ☒ |
| Safety | ☐ Yes | ☒ No | ☒ Inadequate #'s | ☐ Disease Absent | ☐ | ☒ |

Is a dosing modification based on age recommended in the label? ☐ Yes ☐ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

**Race-Based Analyses** *(Please provide information for each category listed below)*

| Category | Was Analysis Performed? | | If no is checked, indicate which applies or provide comment below | | Was race-based analysis included in labeling? | |
|---|---|---|---|---|---|---|
| | | | | | Yes | No |
| Efficacy | ☐ Yes | ☒ No | ☒ Inadequate #'s | ☐ Disease Absent | ☐ | ☒ |
| Safety | ☐ Yes | ☒ No | ☒ Inadequate #'s | ☐ Disease Absent | ☐ | ☒ |

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

1. SHS is an Orphan Drug
2. Efficacy studies were small (6 to 12 Patients)
3. SHS is identical to the Natural, Human Peptide, Secretin. It is the same in all races, age groups and both genders.
4. SHS is a single use diagnostic agent. The dose is similar to the normal, physiological secretion of secretin stimulated by meals.
5. Adverse Events were infrequent and often not drug related. There were only 29 patients who had and AE among the 584 studied.
6. Porcine Secretin has been FDA approved for these diagnostic uses for over 20 years.

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/s/
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Gail Moreschi
4/5/04 11:39:46 AM

| | |
|---|---|
| ❖ Exclusivity (approvals only) | |
| • Exclusivity summary | **(X)** |
| • Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!* | **(X) Yes, Application # 21-136**<br>( ) No |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | **(X) 7/24/01, 4/27/00 (RTF)** |
| **General Information** | |
| ❖ Actions | |
| • Proposed action | **(X)** AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | AE 12/14/01 |
| • Status of advertising (approvals only) | **(X)** Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | ( ) Yes **(X)** Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | **(X)** None<br>( ) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | **(X) 3/22/04** |
| • Most recent applicant-proposed labeling | **10/10/03** |
| • Original applicant-proposed labeling | **(X) 6/14/01** |
| • Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | **(X), DMETS 10/13/00, DDMAC 3/12/04, DMETS 3/30/04** |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | **(X)** |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | **N/A** |
| • Applicant proposed | **(X) 10/10/03** |
| • Reviews | **N/A** |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | **N/A** |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | **N/A** |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | **(X)** |
| ❖ Memoranda and Telecons | **(X)** |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | **N/A** |
| • Pre-NDA meeting (indicate date) | **N/A** |
| • Pre-Approval Safety Conference (indicate date; approvals only) | **N/A** |
| • Other | **N/A** |

| | |
|---|---|
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | **N/A** |
| • 48-hour alert | **N/A** |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | **N/A** |
| **Summary Application Review** | |
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | **(X) 4/7/04** |
| **Clinical Information** | |
| ❖ Clinical review(s) *(indicate date for each review)* | **(X) 11/28/01, 11/30/01, 12/12/01, 3/9/04** |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | **(X) 11/6/01, 3/12/04, 4/4/04** |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | **(X) see MO review dated 3/9/04** |
| ❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)* | **N/A** |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | **(X)** |
| ❖ Demographic Worksheet *(NME approvals only)* | **(X)** |
| ❖ Statistical review(s) *(indicate date for each review)* | **(X) 11/20/01, 11/26/01** |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | **(X) 5/25/00, 11/19/01, 3/5/04** |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | **N/A** |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | **N/A** |
| • Bioequivalence studies | **N/A** |
| **CMC Information** | |
| ❖ CMC review(s) *(indicate date for each review)* | **(X) 5/8/00, 7/26/01, 11/20/01, 12/12/01, 2/9/04, 2/12/04, 3/18/04** |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | **(X) see CMC review dated 3/18/04, p. 19** |
| • Review & FONSI *(indicate date of review)* | **N/A** |
| • Review & Environmental Impact Statement *(indicate date of each review)* | **N/A** |
| ❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | **(X) 11/6/01, 3/12/04, 4/2/04, 4/8/04** |
| ❖ Facilities inspection (provide EER report) | Date completed:<br>**(X) Acceptable, see CMC review dated 3/18/04, p. 19**<br>( ) Withhold recommendation |
| ❖ Methods validation | **(X) Completed, see CMC review dated 3/18/04**<br>( ) Requested<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | **(X) 11/8/01, 12/6/01, 1/19/04** |
| ❖ Nonclinical inspection review summary | **N/A** |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | **N/A** |
| ❖ CAC/ECAC report | **N/A** |

4/12/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-256

**DISCIPLINE REVIEW LETTER**

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
Chief Executive Officer
4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129

Dear Dr. Purich:

Please refer to your March 16, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic human secretin for injection.

We also refer to your resubmission dated October 10, 2003, which contained the response to our December 14, 2001 approvable letter.

We finally refer to your submission dated February 9, 2004, which included the proposed proprietary name, —— ™

Our review of the proposed proprietary name of your submission is complete, and we have found it unacceptable. The proposed proprietary name, —— was found to have look-alike and sound-alike similarities with Humulin and Humatin.

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

If you have any questions, call Ryan Barraco, Consumer Safety Officer, at (301) 443-8017.

Sincerely,

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/
---
Liang Zhou
4/2/04 01:30:05 PM

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: April 2, 2004**

| | |
|---|---|
| **To:** Dr. Edward D. Purich | **From:** Ryan Barraco |
| **Company:** ChiRhoClin, Inc. | Division of Gastrointestinal & Coagulation Drug Products |
| **Fax number:** (301) 476-9529 | **Fax number:** (301) 443-9285 |
| **Phone number:** (301) 476-8388 | **Phone number:** (301) 443-8017 |

**Subject:** Synthetic Human Secretin labeling comments

**Total no. of pages including cover:** 18

**Comments: Please find attached proposed revisions to your proposed labeling for Synthetic Human Secretin submitted on March 31, 2004, (received March 31, 2004). A listing of the proposed revisions is followed by a copy of the revised labeling which includes strikeouts for deletions and double underlines for additions. Please note: the template for the labeling is the label ChiRhoClinPI204.doc. This labeling contains the normal subjects in Figure 1 and Figure 2 and does not contain the Figure 1 entitled "Mean Human Secretin Plasma Concentration."**

**Document to be mailed:** ☐ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.

Attachment

Proposed revisions to NDA 21-256 package insert:

1. In the Heading for the package insert, replace the name [redacted] with the term "TRADENAME."

2. In the **DESCRIPTION** section, in the fourth paragraph that begins "[redacted] contains 16 mcg of purified . . ." replace the name "[redacted] with the term "TRADENAME."

3. In the **CLINICAL PHARMACOLOGY** section

   a. Made the subheading, Pharmacokinetics, bold.

   b. In the first paragraph, first sentence that begins, "The primary action of [redacted] . . ." replace the name "[redacted]" with the term "TRADENAME" so that the sentence reads "The primary action of [redacted] is to increase the volume and bicarbonate content of secreted pancreatic juices."

   c. In the first paragraph, second sentence that begins, "The standard unit . . ." replace the name "[redacted] with the term "TRADENAME" so that the sentence reads "The standard unit of activity used for [redacted] is the clinical unit as defined in the literature[1]."

   d. In the first paragraph, fourth sentence that begins, "sHS and sPS were found . . ." replace the term [redacted] with the term "similar" so that the sentence reads "sHS and sPS were found to have similar pharmacological activity in terms of stimulating the exocrine pancreas to secrete juice and bicarbonate."

4. **CLINICAL STUDIES (made the heading bold)** section

   a. In the heading that reads, "[redacted]" replace the phrase [redacted] with the phrase "Stimulation of pancreatic" so that the heading reads "Stimulation of pancreatic secretions, including bicarbonate to aid in the diagnosis of Exocrine Pancreas Dysfunction." Bold the words in this heading.

   b. In the first paragraph, first sentence that begins [redacted] administered intravenously . . ." replace the name [redacted] with the term "TRADENAME" so that the sentence reads "TRADENAME administered intravenously stimulates the exocrine pancreas to secrete pancreatic juice, which can assist in the diagnosis of exocrine pancreas dysfunction."

   c. Following Figure 1 and Figure 2 titled "Chronic Pancreatitis patients and Normal Volunteers" add the dosages studied in a legend or footnote.

d. Delete —

e. Delete the first sentence in the third paragraph that reads

f. In the fifth paragraph, first sentence that begins "A physician or institution . . ." replace the name — with the term "TRADENAME" so that the sentence reads "A physician or institution planning to perform secretin stimulation testing as an aid to the diagnosis of pancreatic disease should begin by assessing enough normal subjects (>5) to develop proficiency in proper techniques and to generate normal response ranges for the commonly assessed parameters for pancreatic exocrine response to TRADENAME."

g. In the sixth paragraph, first sentence that begins "In three crossover studies (CRC 98-1, CRC 98-2, and CRC 99-9) . . ." replace the name — with the term "TRADENAME" so that the sentence reads "In three crossover studies (CRC 98-1, CRC 98-2, and CRC 99-9) evaluating 21 different patients with a documented history of chronic pancreatitis, TRADENAME was compared to synthetic porcine secretin (sPS) and biologically derived secretin (bPS)."

h. Following the seventh paragraph that begins, "Pancreatic secretory response . . ." bold the subheading that reads "Stimulation of gastrin secretin to aid in the diagnosis of gastrinoma:"

i. In the eighth paragraph that begins — administered intravenously . . ." replace the name — with the term "TRADENAME" so that the sentence reads "TRADENAME administered intravenously stimulates gastrin release in patients with gastrinoma (Zollinger-Ellison Syndrome), whereas no or only small changes in serum gastrin concentrations occur in normal subjects and in patients with duodenal ulcer disease."

k. In the ninth paragraph, third sentence that begins, "Testing of — in 12 healthy . . ." replace the name — with the term "TRADENAME" so that the sentence reads "Testing of TRADENAME in 12 healthy volunteers demonstrated completely negative results for gastrinoma."

l. Following the ninth paragraph that begins, "In a three way crossover study . . ." bold the subheading that reads "Facilitation of identification of the ampulla of Vater and the accessory papilla during ERCP to assist in cannulation of the pancreatic ducts:" and add a space to separate the subheading from the following paragraph.

5. In the **INDICATIONS AND USAGE** section

   a. In the subheading that reads — is indicated for:" replace the term — with the term "TRADENAME" so that the sentence reads "TRADENAME is indicated for:"

   b. Added a space between (1) and (2).

   c. Changed type from italic to normal for (3).

6. In the **CONTRAINDICATIONS** section, in the first paragraph, first sentence that begins, "patients suffering from . . ." replace the term — with the term "TRADENAME" so that the sentence reads "Patients suffering from acute pancreatitis should not receive TRADENAME until the acute episode has subsided."

7. In the **WARNINGS** section, in the first paragraph, first sentence that begins, "Because of a potential allergic . . ." replace the term — " with the term "TRADENAME" so that the sentence reads "Because of a potential allergic reaction to TRADENAME, patients should receive an intravenous test dose of 0.2 mcg (0.1 mL)."

8. In the **PRECAUTIONS** section

   a. Made the subheadings bold

   b. Geriatric Use subsection, first paragraph, first sentence that begins, "Among the 533 patients . . ." replace the term ' — ' with the term "TRADENAME" so that the sentence reads "Among the 533 patients who have received TRADENAME in clinical trials 18% were 65 years of age or older and 6% were 75 years of age or older."

9. **ADVERSE REACTIONS** section

   a. In the first paragraph, third sentence that begins — revise the number — to read "1" so that the sentence reads "Table 1 details the type and number of patients with adverse events.

   b. In the **ADVERSE REACTIONS** section, revise the name of the table from — — to "TABLE 1 ADVERSE EVENTS WITH TRADENAME."

   c. In the second paragraph, first sentence that begins "Of the 584 patients . . ." replace the term — ' with the term "TRADENAME" so that the sentence reads "Of the 584 patients and healthy volunteers treated with TRADENAME, a total of 29 patients (5.0%) had at lease one adverse event."

10. In the **DOSAGE AND ADMINISTRATION** section, **Dosage** subsection, item number 1., the first sentence that begins —
revise the phrase — ' to read "STIMULATION OF" so that the item reads "1. STIMULATION OF PANCREATIC SECRETIONS INCLUDING BICARBONATE TO AID IN THE DIAGNOSIS OF EXOCRINE PANCREAS DYSFUNCTION: 02. mcg/kg body weight by intravenous injection over 1 minute."

11. **DOSAGE AND ADMINISTRATION** section, **Administration** subsection

a. In item number 1., the sub-subheading that begins —
— replace the phrase — with the phrase "STIMULATION OF" and replace the period at the end of the sentence with a colon so that the sub-subheading reads "STIMULATION OF PANCREATIC SECRETIONS, INCLUDING BICARBONATE TO AID IN THE DIAGNOSIS OF EXOCRINE PANCREAS DYSFUNCTION:" In addition, bold the sub-subheading and add a space to separate the subheading from the following sentence.

b. In item 1., in the second paragraph, third sentence that begins "A test dose of
— replace the term — with the term "TRADENAME" so that the sentence reads "A test dose of TRADENAME 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies."

c. In item 1., in the second paragraph, fourth sentence that begins "After one minute, if there are no untoward reactions. . ." replace the term — with the term "TRADENAME" and add the letter "c" after the letter "m" in the phrase "mg/kg" so that the sentence reads "After one minute, if there are no untoward reactions, TRADENAME at a dose of 0.2 mcg/kg of body weight is injected intravenously over 1 minute."

d. In item 2. replace the period at the end of the subheading with a colon so that the subheading reads "STIMULATION OF GASTRIN TO AID IN THE DIAGNOSIS OF GASTRINOMA:"

e. In item 2. in the second sentence that begins, "Prior to injection of — replace the term — with the term "TRADENAME" so that the sentence reads "Prior to injection of TRADENAME, two blood samples are drawn for determination of fasting serum gastrin levels (baseline values)."

f. In item 2. in the third sentence that begins, "Subsequently, a test dose . . ." replace the term — with the term "TRADENAME" so that the sentence reads "Subsequently, a test dose of TRADENAME 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies."

g. In item 2. the fourth sentence that begins "If no untoward reactions . . ." add the letter "c" between the letters "m" and "g" in the phrase "mg" and replace the term
— with the term "TRADENAME" so that the sentence reads

"TRADENAME at a dose of 0.4 mcg/kg of body weight is injected intravenously over 1 minute; post-injection blood samples are collected after 1, 2, 5, 10, and 30 minutes for determination of serum gastrin concentrations:"

h. In item 3. in the first paragraph, second sentence that begins "Administration of — may . . ." replace the term — with the term "TRADENAME" so that the sentence reads "Administration of TRADENAME may be given when difficulty is encountered by the endoscopist in identifying the ampulla of Vater for reasons including anatomic deformity secondary to prior surgery, radiation therapy, peptic ulcer disease, tumors, etc. or in identifying the accessory papilla in patients with pancreas divisum."

i. In item 3. in the first paragraph, second sentence that begins "A test dose of — 'replace the term — with the term "TRADENAME" so that the sentence reads "A test dose of TRADENAME 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies."

12. **HOW SUPPLIED** section

a. In the first paragraph, first sentence that begins, — is supplied as a . . . " replace the term — with the term "TRADENAME" so that the sentence reads "TRADENAME is supplied as a lyophilized sterile powder in vials containing 16 mcg."

b. In the **HOW SUPPLIED** section, in the sixth paragraph, that begins — — replace the term — ' with the term "TRADENAME" so that the sentence reads "TRADENAME is a registered trademark of ChiRhoClin, Inc."

APPEARS THIS WAY
ON ORIGINAL

11 pages redacted from this section of the approval package consisted of draft labeling

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

/s/

Ryan Barraco
4/2/04 01:51:03 PM
CSO

ORIGINAL
NEW CORRESP
NC

**_ChiRho_Clin, Inc.**
**4000 Blackburn Lane, Suite 270**
**Burtonsville, MD 20866-6129**
**(301) 476-8388**
**(301) 476-9529 FAX**

March 30, 2004

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
MAR 31 2004
FDA/CDER

**Re: NDA #21-136, 21-209, and 21-256**

Dear Dr. Justice:

ChiRhoClin is the holder of NDA #21-136 and NDA #21-209 for synthetic porcine secretin (sPS). This drug is designated as an Orphan Drug product and enjoys commercial exclusivity through 2009.

ChiRhoClin is also the holder of NDA #21-256 for synthetic human secretin (sHS), which is also designated as an Orphan Drug.

This letter serves as notification to FDA that ChiRhoClin gives its consent for FDA to approve NDA #21-256 for synthetic human secretin [redacted] for commercial distribution.

If you have any questions, please feel free to contact me.

Sincerely,

Edward D. Purich, Ph.D.
CEO and President

HumanNDA/2/RJ033004L2

3/30/04

**CONSULTATION RESPONSE**

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

| **DATE RECEIVED:** 02/17/04 | **DESIRED COMPLETION DATE:** 3/18/04 | **ODS CONSULT #:** 01-0183-2 |
|---|---|---|

**TO:** Robert Justice, M.D.
Director, Division of GastroIntestinal and Coagulation Drug Products
HFD-180

**THROUGH:** Ryan Barraco
Project Manager
HFD-180

| **PRODUCT NAME:** | **NDA SPONSOR:** |
|---|---|
| —<br>(Human Secretin for Injection)<br>16 mcg/vial<br><br>**NDA: 21-256** | ChiRhoClin, Inc. |

**SAFETY EVALUATOR:** Alina R. Mahmud, R.Ph.

**RECOMMENDATIONS:**

1. DMETS does not recommend the use of the proprietary name —
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review.
3. DDMAC finds the proprietary name acceptable from a promotional perspective.

/S/

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

/S/

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

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

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** March 24, 2004

**NDA #** 21-256

**NAME OF DRUG:** —
(Human Secretin for Injection) 16 mcg/vial

**NDA HOLDER:** ChiRhoClin, Inc.

## I. INTRODUCTION:

This consult was written in response to a request from the Division of GastroIntestinal and Coagulation Drug Products (HFD-180), to review the proprietary name — regarding potential name confusion with other proprietary and established drug names. Additionally, labels and labeling were submitted for review and comment.

This is the second proposed proprietary name for this application. The first proprietary name for this drug product, — (NDA 21-256), was reviewed on September 14, 2001. At that time, DMETS had no objections to the use of the name. However, on February 5, 2002, DMETS was asked to review the proprietary name Secreflo for a different application (NDA 21-136) by the same sponsor. Due to the similarities in name and product characteristics between Secreflo and —, DMETS recommended the approval of only one name. Consequently, the sponsor submitted the proprietary name — for NDA 21-256 while Secreflo was retained and approved for NDA 21-136.

PRODUCT INFORMATION

— contains synthetic human secretin, which is a gastrointestinal peptide hormone. The primary action of secretin is to increase the volume and bicarbonate content of secreted pancreatic juices. According to the package insert, synthetic human secretin (sHS) and synthetic porcine secretin (sPS) were found to have equivalent pharmacological activity in terms of stimulating the exocrine pancreas to secrete juice and bicarbonate. Synthetic human secretin is indicated for diagnosis of pancreatic exocrine and gastrinoma — and for the facilitation during endoscopic retrograde cholangiopancreatography (ERCP). The usual dose is 0.2 mcg/kg by intravenous injection over 1 minute for pancreatic function testing. For diagnosis of gastrinoma, the usual dose is 0.4 mcg/kg by intravenous injection over 1 minute. Synthetic human secretin is supplied as a lyophilized sterile powder in 10 mL vials containing 16 mcg of the unreconstituted product.

## II. RISK ASSESSMENT:

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

### A. EXPERT PANEL DISCUSSION

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

1. DDMAC found the name acceptable from a promotional perspective.

2. The Expert Panel identified four proprietary names as having the potential for confusion with — A fifth name, Augmentin, was identified in the Prescription Study Analysis conducted by DMETS. These products are listed in Table 1 (see below and page 4).

**Table 1. Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel**

| Product Name | Dosage form(s), Established name | Usual dose* | Other** |
|---|---|---|---|
| — | Human Secretin for Injection, 16 mcg/vial | Test dose: 0.2 mcg for potential allergic reaction<br>Pancreatic function testing: 0.2 mcg/kg by intravenous injection over 1 minute<br>Diagnosis of gastrinoma: 0.4 mcg/kg by intravenous injection over 1 minute | N/A |
| Arestin | Minocycline HCl Extended-Release Powder 1 mg | Administered to dental pocket by Dentist at 3-month intervals. | LA |

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

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

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

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

| | | | |
|---|---|---|---|
| Avastin | Bevacizumab Injectable<br>25 mg/mL in 4 mL and 16 mL single-use vials | 5 mg/kg given once every 14 days as a continuous IV infusion until disease progression. The initial dose should be delivered over 90 minutes as a continuous IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. | LA |
| Humatin | Paromomycin Sulfate Capsules 250 mg | *Intestinal amebiasis:*<br>Usual dose is 25 to 35 mg/kg/day, in 3 doses with meals for 5 to 10 days.<br>*Management of hepatic coma:*<br>Usual dose is 4 g/day in divided doses at regular intervals for 5 to 6 days | SA, LA |
| Humulin | Isophane Insulin<br>70/30, 50/50, L, N, R, U, R-500 | Individualized dosage based on patient's disease state. | LA/SA |
| Augmentin | Amoxicillin and Cluvulanate Potassium<br>*Tablets:* 250 mg/125 mg, 500 mg/125 mg, and 875 mg/125 mg<br>*Extended-Release Tablets:* 1 gram/62.5 mg<br>*Chewable Tablets:* 125 mg/31.25 mg, 200 mg/28.5 mg, 250 mg/62.5 mg, 400 mg/57 mg<br>*Oral Suspension (per 5 mL):* 125 mg/31.25 mg, 200 mg,/28.5 mg, 250 mg/62.5 mg, 400 mg/57 mg, 600 mg/42.9 mg | *Tablets:* 250 mg every 8 hours or 500 mg every 12 hours.<br>*Extended-Release Tablets:* 2 tablets every 12 hours.<br>*Chewable Tablets and Oral Suspension:* 125 mg to 250 mg every 8 hours or 200 mg to 400 mg every 12 hours.<br><br>*600 mg Oral Suspension:* 90 mg/kg/day given every 12 hours | LA |
| * Frequently used, not all-inclusive.<br>** L/A (look-alike), S/A (sound-alike) | | | |

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic database that is in the final stages of development for DMETS. The entered search term is converted into its phonemic representation before it runs though the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The results from the — queries did not indicate any additional product names that had strong phonetic or orthographic similarities.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of — with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for — (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were

recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

| HANDWRITTEN PRESCRIPTION | VERBAL PRESCRIPTION |
|---|---|
| Outpatient RX:<br>— 10 mcg IV over 1 minute x1 today | Give — 10 mcg IV over one minute for 1 dose today. |
| Inpatient RX:<br>— 10 mcg IV over 1 minute x1 today | |

3. Results

Two participants in the written in written outpatient prescription study commented that the name — looks similar to the currently marketed drug product Augmentin. Additionally, many respondents from the written outpatient study misinterpreted the letter The responses from the inpatient and verbal prescription studies were phonetic/mispelled interpretations of the proposed name — See Appendix A for a listing of all interpretations.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name — the primary concerns raised were related to potential confusion with the currently marketed products Arestin, Avastin, Humulin and Augmentin. Upon further review, the name Arestin was thought to have minimal potential for confusion with — due to differences in dosage form, route of administration, strength, dosing strength and the fact Arestin will be implanted by a trained healthcare professional. Additionally, the name Augmentin, which was identified in the prescription studies, was not further reviewed due to differences in dosage form, route of administration, strength, dose, dosing frequency and a lack of convincing look-alike potential.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that — can be confused with Avastin, Humulin and Augmentin. Although two participants in the written outpatient prescription study commented that — looks similar to Augmentin, DMETS acknowledges in the outpatient prescription study sample more closely resembles the letter (see prescription samples in section II.C). Therefore, many participants from the outpatient prescription study misinterpreted The majority of the interpretations from the verbal and inpatient studies were phonetic/mispelled variations of the proposed name —

1. Avastin has the potential to look similar to —. Avastin contains bevacizumab and is indicated for use in combination with intravenous 5-Fluorouracil-based chemotherapy as a treatment for patients with first-line, or previously untreated, metastatic cancer of the colon or rectum. Avastin was approved by the FDA in February 2004. . Additionally, Although both drug products are available in one strength, the strengths do not overlap numerically. Additionally, — is given intravenously as a one time dose of 0.2 to 0.4 mcg/kg over one minute whereas Avastin is given intravenously at a dose of 5 mg/kg once every 14 days over 90 minutes (initial dose) or 60 minutes (subsequent dose). Other differences between Avastin and — respectively, include storage conditions (refrigerated vs. kept in the freezer until ready for reconstitution), dosage form (solution vs. lyophyllized powder), and Avastin is approved for use in combination with 5-fluorouricil-based chemotherapy. Given these differences and a lack of convincing look-alike potential, confusion and error between Avastin and — should be minimal.

2. Humatin and — look and sound similar. Humatin contains paromomycin and is indicated for acute and chronic intestinal amebiasis and as adjunctive therapy in the management of hepatic coma. The drug products differ in dosage form (capsules vs. lyophylized powder), route of administration (oral vs. intravenous injection), dose, dosing frequency (divided doses given for 5 to 10 days vs. one time dose), and storage (room temperature vs. freezer). Although the likelihood for the administration of the wrong drug product is unlikely due to product differences, similarities in names may cause confusion and delays during the interpretation of a prescription for either — or Humatin. For example, a prescription for — misinterpreted for Humatin or vice versa will require the healthcare provider to clarify the prescription order. Clarification of the prescription order may cause delays and ultimately affect the patient's treatment. Additionally, healthcare practitioners and patients researching drug information for either of these products may confuse the names and ultimately retrieve incorrect information regarding their treatment. Therefore, despite the product differences, a strong orthographic and phonetic similarity may negatively impact the patient's treatment. DMETS believes that the potential for confusion between — and Humatin is likely.

Humatin —

3. Humulin and — were found to have look-alike and sound-alike similarities. Humulin contains isophane insulin and is indicated for use in the management of Type II diabetes.

Humulin and — also differ in storage (refrigerator vs. freezer), duration of use (chronic vs. one time dose), indication of use (diabetes vs. diagnostic), and preparation instructions (lyophylized powder reconstituted with Sodium Chloride vs. solution). — and Humulin share an overlapping route of administration (intravenous) and depending on the weight of the patient, numerically similar dosage strengths (i.e., 14 mcg for a 70 kg individual vs. 14 units). Although a modifier such as R, N, L, etc. will be written to clarify the formulation of Humulin, the modifier may be overlooked due to other similarities in name and dose. An inpatient order written for "Humulin R 14 Units, give at 1 pm" may be misinterpreted as " — 14 mcg, give at 1 pm." In this scenario, if the differentiating characteristics mentioned above are not included in the written order, the potential for confusion is possible. Additionally, if the prescription is written on an inpatient order, hanging letters from the line above may interfere with the prominence of the modifier "R" in Humulin thus increasing confusion between Humulin and — The inadvertent administration of Humulin instead of — may potentially cause life-threatening consequences depending on the formulation and dose given. The inadvertent administration of — instead of Humulin may further complicate the patient's hyperglycemic state and cause an allergic reaction. Despite many differences between the — and Humulin the potential for confusion exists due to proprietary name and dosage similarities.

Humulin R 14 Units i.m. — 14 mcg

## III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name — The primary concerns raised were related to potential for confusion with Humatin and Humulin.

a. Humatin and — look and sound similar. Humatin contains paromomycin and is indicated for acute and chronic intestinal amebiasis and as adjunctive therapy in the management of hepatic coma.

However,

Thus when scripted or pronounced the names are essentially indistinguishable. The drug products differ in dosage form (capsules vs. lyophylized powder), route of administration (oral vs. intravenous injection), dose, dosing frequency (divided doses given for 5 to 10 days vs. one time dose), and storage (room temperature vs. freezer). Although the likelihood for the administration of the wrong drug product is unlikely due to product differences, similarities in names may cause confusion and delays during the interpretation of a prescription for either — or Humatin. For example, a prescription for — misinterpreted for Humatin or vice versa will require the healthcare provider to clarify the prescription order. Clarification of the prescription order may cause delays and ultimately affect the patient's treatment. Additionally, healthcare practitioners and patients researching drug information for either of

these products may confuse the names and ultimately retrieve incorrect information regarding their treatment. Therefore, despite the product differences, a strong orthographic and phonetic similarity may negatively impact the patient's treatment. DMETS believes that the potential for confusion between — and Humatin is likely.

Humatin /

b. Humulin and — were found to have look-alike and sound-alike similarities. Humulin contains isophane insulin and is indicated for use in the management of Type II diabetes. The — in — Since Humulin is available in various formulations (R, N, L, 70/30, 50/50, U, and R-500) a prescription will have to indicate the appropriate modifier. Humulin and — also differ in storage (refrigerator vs. freezer), duration of use (chronic vs. one time dose), indication of use (diabetes vs. diagnostic), and preparation instructions (lyophylized powder reconstituted with Sodium Chloride vs. solution). — and Humulin share an overlapping route of administration (intravenous) and depending on the weight of the patient, numerically similar dosage strengths (i.e., 14 mcg for a 70 kg individual vs. 14 units). Although a modifier such as R, N, L, etc. will be written to clarify the formulation of Humulin, the modifier may be overlooked due to other similarities in name and dose. An inpatient order written for "Humulin R 14 Units, give at 1 pm" may be misinterpreted as — 14 mcg, give at 1 pm." In this scenario, if the differentiating characteristics mentioned above are not included in the written order, the potential for confusion is possible. Additionally, if the prescription is written on an inpatient order, hanging letters from the line above may interfere with the prominence of the modifier "R" in Humulin thus increasing confusion between Humulin and —. The inadvertent administration of Humulin instead of — may potentially cause life-threatening consequences depending on the formulation and dose given. The inadvertent administration of — instead of Humulin may further complicate the patient's hyperglycemic state and cause an allergic reaction. Despite many differences between the — and Humulin the potential for confusion exists due to proprietary name and dosage similarities.

Humulin R 14 units — 4 mcg

## IV. LABELING, PACKAGING AND SAFETY RELATED LABELING ISSUES

In the review of the draft container labels as well as carton and insert labeling of — DMETS has focussed on safety issues relating to possible medication errors, and has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

1. The sponsor's name is more prominent than the proprietary name. Please revise so that the proprietary name is the most prominent piece of information on the label.

2. Revise the statement "Reconstitute with 8 mL Sodium Chloride for Injection USP" to read "Reconstitute with 8 mL of Sodium Chloride Injection USP. —

3. Increase the prominence of the strength as it is not easily identifiable.

B. CARTON LABELING

1. See comments A1 and A3.

2.

## IV. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proposed proprietary name —

2. DMETS recommends the implementation of the label and labeling revisions as outlined in section III of this review.

3. DDMAC finds the proprietary name — acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

S

Alina R. Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

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

/s/
---
Alina Mahmud
3/30/04 09:28:48 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
3/30/04 10:57:26 AM
DRUG SAFETY OFFICE REVIEWER

Redacted 4

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ORIGINAL
NEW CORRES.

**ChiRhoClin, Inc.**
**4000 Blackburn Lane, Suite 270**
**Burtonsville, MD 20866-6129**
**(301) 476-8388**
**(301) 476-9529 FAX**

March 26, 2004

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
MAR 31 2004
FDR/CDER

**Re: Synthetic Human Secretin NDA #21-256**

Dear Dr. Justice:

Concerning NDA #21-256 for synthetic human secretin [redacted], ChiRhoClin requests a waiver of the requirement for pediatric studies. This request is based on the factors listed below:

1. Synthetic human secretin is designated by FDA as an Orphan Drug. Requiring clinical studies focused specifically on a pediatric population would constitute a hardship for ChiRhoClin.

2. Secretin is used very infrequently in the pediatric age group. It is a single use diagnostic agent for evaluation of exocrine pancreas function, diagnosis of gastrinoma and facilitation of [redacted] during ERCP. These medical conditions and procedures do not frequently involve pediatric patients.

3. ChiRhoClin has provided safety data in the NDA on 22 patients 10 years old or younger who had sHS during upper GI Endoscopy for assessment of exocrine pancreas function.

4. ChiRhoClin has provided safety data in the NDA on 155 pediatric patients with autism treated with sHS in 4 clinical studies.

5. There were no unusual types of adverse events or frequency of adverse events observed in the pediatric patients studies and reported in the NDA.

If you have any questions, please feel free to contact me.

Sincerely,

Edward D. Purich, Ph.D.
CEO and President

## 16.0 Debarment Certification (FD&C Act 306 (k)(1))

Debarment Certification

ChiRhoClin, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Edward D. Purich, Ph.D.
Chief Executive Officer

**There were no Federal Register Notices published on this drug product.**

RB 3/25/04

APPEARS THIS WAY
ON ORIGINAL

**No post-marketing commitments were requested in review cycle 2.**

RB 3/25/04

APPEARS THIS WAY
ON ORIGINAL

**An Advisory Committee Meeting was not requested during review cycle 2.**

RB 3/22/04

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

# FACSIMILE TRANSMITTAL SHEET

**DATE: March 22, 2004**

| | |
|---|---|
| **To:** Edward D. Purich, Ph.D. | **From:** Ryan Barraco, B.A., B.S. |
| **Company:** ChiRhoClin, Inc. | Division of Division of Gastrointestinal & Coagulation Drug Products (DGCDP) |
| **Fax number:** 301-476-9529 | **Fax number:** 301-827-1305 |
| **Phone number:** 301-476-8388 | **Phone number:** 301-443-8017 |

**Subject:** NDA 21-256 – Proposed revisions to the package insert

**Total no. of pages including cover:** 12

**Comments:**

Dear Dr. Purich,

I have attached the Divisions proposed revisions to the package insert for synthetic human secretin. After preliminary review of the revisions, please contact us to let us know of your intentions concerning this matter. We have set aside a meeting on March 25, 2004 from 1:00pm to 2:00pm to discuss these proposed revisions. Please let us know by March 24, 2004, if you plan to meet with the Division. If you have any other further questions, please call me at 301-443-8017. Thanks.

Ryan Barraco

**Document to be mailed:** ☐ **YES** ☒ **NO**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.**

11 pages redacted from this section of the approval package consisted of draft labeling

31 pages redacted from this section of the approval package consisted of draft labeling

**The sponsor was not on the AIP list during review cycle 2.**

RB 3/22/04

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: March 15, 2004**

| | |
|---|---|
| **To:** Edward D. Purich, Ph.D. | **From:** Ryan Barraco, B.A., B.S. |
| **Company:** ChiRhoClin, Inc. | Division of Division of Gastrointestinal & Coagulation Drug Products (DGCDP) |
| **Fax number:** 301-476-9529 | **Fax number:** 301-827-1305 |
| **Phone number:** 301-476-8388 | **Phone number:** 301-443-8017 |

**Subject:** NDA 21-256 – October 10, 2003 Resubmission

**Total no. of pages including cover:** 4

**Comments:**

Dear Dr. Purich,

I have attached the Microbiology Discipline Review Letter. After preliminary review of the deficiencies, please contact us to let us know of your intentions concerning this matter. If you have any other further questions, please call me at 301-443-8017. Thanks.

Ryan Barraco

**Document to be mailed:** ☒ **YES** ☐ **NO**

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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3/12/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-256

**DISCIPLINE REVIEW LETTER**

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
Chief Executive Officer
4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129

Dear Dr. Purich:

Please refer to your October 10, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for human synthetic secretin for injection.

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

1. Provide the following building and facility information:
   - Floor plans
   - Locations of equipment
   - Maps of air, personnel, component and product flow
   - Air pressure differentials

2. Provide the results of — validation studies.

3. Provide — validation data for stoppers, vials, manufacturing equipment and lyophilizers. Provide cycle parameters for validation and production cycles.

4. Provide the following information regarding
   - An explanation for the — units — (p.784)
   - The results of — testing (positive controls) for the — reported on p. 784
   - The inspection methodology for vials and — vials
   - A copy of validation protocol —

5. Provide the following information regarding —
   - Copies of SOPs —
   - Diagrams of the manufacturing facility and the locations monitored within the manufacturing area
   - The frequency of monitoring in each area of the manufacturing facility

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

If you have any questions, call Ryan Barraco, Consumer Safety Officer, at (301) 443-8017.

Sincerely,

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Liang Zhou
3/12/04 05:18:47 PM

**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Drug Evaluation ODE III**

# FACSIMILE TRANSMITTAL SHEET

**DATE: March 11, 2004**

| | |
|---|---|
| **To:** Edward D. Purich, Ph.D. | **From:** Ryan Barraco, B.A., B.S. |
| **Company:** ChiRhoClin, Inc. | Division of Division of Gastrointestinal & Coagulation Drug Products (DGCDP) |
| **Fax number:** 301-476-9529 | **Fax number:** 301-827-1305 |
| **Phone number:** 301-476-8388 | **Phone number:** 301-443-8017 |

**Subject:** NDA 21-256 – March 2, 2004 Amendment

**Total no. of pages including cover:** 2

**Comments:**

Dear Dr. Purich,

I have attached CMC comments concerning the March 2, 2004 amendment to NDA 21-256. If you have any other further questions, please call me at 301-443-8017. Thanks.

Ryan Barraco

**Document to be mailed:** ☐ **YES** ☒ **NO**

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(1). Regarding your request for an — expiratory date for the drug product, the Agency can grant only a — expiratory date according to the current 6-month stability data. However, a CBE-0 supplement to request an extension of the expiratory date to — could be submitted as soon as additional real-time — stability data are assembled and meet the release specifications (see Question #1 under "Stability" section, page 106 in the 3/2/04 amendment).

(2). In order to narrow the acceptance criteria for assay from — to — % of the label claim, you should commit to control manufacturing procedure in SOP to permit filling at target of — % of the label claim instead of — % when the new batches are manufactured. This change should reflect in the batch record (see Question #2 under "Stability" section, page 134 in the 3/2/04 amendment).

(3). Regarding the environment assessment, an incorrect regulation [21 CFR 25.24(c)] is cited in the response (page 138). Regulation [21 CFR 25.31(b)] should be cited.

APPEARS THIS WAY
ON ORIGINAL

2/23/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-256

**DISCIPLINE REVIEW LETTER**

ChiRhoClin, Inc.
Attention: Edward D. Purich, Ph.D.
Chief Executive Officer
4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129

Dear Dr. Purich:

Please refer to your June 14, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for synthetic human secretin for injection.

Please also refer to your October 10, 2003 resubmission, which constituted a complete response to our December 14, 2001 action letter.

Our review of the Chemistry, Manufacturing and Controls (CMC) section of your resubmission is complete, and we have identified the following deficiencies:

**DRUG SUBSTANCE:**

1. Please correct a number of statements in the response to Question 2.b.2 (page 1409 in Vol. B14B.8). For example,

   a.

   b.

   c.

**DRUG PRODUCT:**

**Regarding Composition and Components:**

1. A typo is noted in Table 2 on page 15 (Section 4.2.2 in Vol. 13.2). According to the batch record for Batch 0134589 (Attachment I in Vol. B14.2), 0.9% saline solution instead of — saline solution as indicated in Tablet 2 is utilized to compound human secretin formulation. Please correct this typo.

**Regarding Production Operation:**

1. Please clarify [redacted] (page 25, Section 4.2.5.4 in Vol. B14.2)

2. You stated on pages 18 and 25 (Section 4.2.4 in Vol. B14.2) that both Bell-More and [redacted] will perform the same tests, including visual and appearance, pH, [redacted] However, there is no mention on page 18 that [redacted] will perform tests, including [redacted] assay. Please clarify the kind of tests that [redacted] will conduct.

3. As stated in the Section of Manufacturing Method (page 23, Section 4.2.5.4 in Vol. B14.2), [redacted] are added. Please include this instruction [redacted] in the batch record.

4. [redacted] (see page 48, Section 3.2 of Attachment I in Vol. B14.2).

   Please experimentally determine the value [redacted]

5. Please provide the definition of [redacted] (page 117 in Attachment I of Vol. B14.2)." Moreover, explain how these values are calculated?

6. Please explain why the assay value for [redacted] (Lot 0134590) is outside the mean average [redacted] in comparison with other assay values [redacted] (page 216 in Attachment II of Vol. B14.2).

7. Include an instruction in the batch record describing how long the bottle containing human secretin needs to be equilibrated at room temperature prior to opening after taking it out of the freezer.

**Regarding Specifications for Drug Product:**

1. Please provide a typical HPLC chromatogram of the drug product using the [redacted]

2. Please explain why the standard curve is prepared with [redacted] concentration (range from [redacted] µg/mL) when the concentration of the prepared sample is [redacted] µg/mL (SOP [redacted] page 663, Section 4.4.2.2 in Vol. B14.4). Is this standard calibration curve utilized to determine the [redacted] in the drug product?

3. In the regulatory specifications, replace the word — with the word "Reconstitution", which is used throughout the ICH Q6A document (page 422, Section 4.2.6.1 in Vol. B14.3).

4. Regarding the specification for — ', tighten the acceptance criterion from — according to Batch Analysis Data provided on page 424 (Section 4.2.6.3 in Vol. B14.3).

**Regarding Method Validation:**

1. Please clarify the statements given in 6.1.3 and 6.1.4 (page 660 to 661 in Vol. B14.4).

2. There is no chromatogram presented in Appendix 10 (page 677, Section 4.4.3 in Vol. B14.4).

3. The peak shown on the chromatograms (Appendix 9, page 676, Section 4.4.3 in Vol. B14.4) is not that of — since the retention time is far from — as indicated in Appendices 7 and 8. What is this peak?

4. A typo was found on pages 597, 621, 643 (Vol. B14.4). The standard injection concentration should be 3.0 µg/mL instead of —.ıg/mL. Please correct it.

5. Since the drug formulation has been changed to include sodium chloride, revise the statement described under "Source of Samples" to read "The secretin, mannitol, cysteine hydrochloride, and sodium chloride content are 16 µg, 20 mg, 1.5 mg and 0.9 mg, respectively, for human vials" (see pages 595, 607, and 619 in Vol. B14.4).

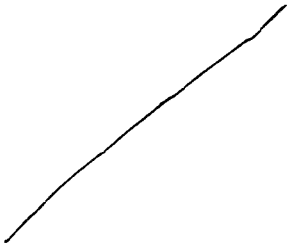
6. Since — provides — (page 665, Section 4.4.3 in vol. B14.4), please explain why the response factor and standard calibration curve for — could not be established with this reference material.

7. The bioassay data for human secretin in the drug product for are provided for (page 424, Section 4.2.6.3 in Vol. B14.3). Please clarify whether the cat bioassay has been validated. If yes, please submit the validation data. Moreover, include the bioassay method in the method validation package.

8. Please provide a complete, well-organized method validation package in triplicate. The package should include the specifications for the drug substance and the drug product, the composition and components of the drug product, samples (the drug substance and drug product), test methods as well as validation reports.

**Regarding Stability:**

1. Please provide a brief discussion and analysis of the data.

2. 
In the mean time, the Agency recommends widening the interim specification for the assay from — to — %. However, consider committing to narrowing the assay specification to — of the label claim when new batches are manufactured with a new filling target of — of the label claim.

3. Monitor — impurities (known or unknown) as well as degradation products during storage. Determine the amount of increase or decrease of these impurities and degradation products during storage. From these data, propose an acceptance criterion for individual impurities and degradation products as well as total impurities.

4. On page 2078 (Vol. B14.10), only responses to the questions are provided, however, there are no questions stated. Please provide the questions requested by the Agency.

**Regarding Environmental Assessment:**

1. In the "Environmental Assessment" section (page 552, Section 4.3 in Vol. B14.3), the incorrect regulation [21 CFR 25.31(e)] is cited for not preparing an environment assessment. In order to claim categorical exclusion from filing of an environmental assessment, cite an appropriate regulation to meet the requirements.

**Regarding Labeling:**

For the carton and vial labels, please make the following revisions:

1. The first sentence on the carton and vial labels should read, "Vial contains human secretin 16 mcg, L-cysteine hydrochloride — ng, mannitol 20 mg and sodium chloride 0.9 mg as a lyophilized powder."

2. Please change the name and address of the manufacturer for the drug product to Bell-More Laboratories, Hampstead, MD 21074-0179.

For the package insert, please make the following revisions:

Description Section:

1. Remove the word ' —— " Start the first sentence with "Human secretin is a gastrointestinal peptide hormone produced by cells in the duodenum in response to acidification. Human secretin (as the acetate) is a purified, synthetic peptide with an amino acid sequence identical to the naturally occurring hormone."

2. Revise the last sentence to read "(Trade name) contains 16 mcg of purified synthetic human secretin, 1.5 mg of L-cysteine hydrochloride, 20 mg of mannitol, and 0.9 mg of sodium chloride per vial."

How Supplied Section:

1. Since the trade name for human secretin has not been decided, replace the word ' —— ' in the first sentence with a trade name, which is acceptable to the Agency.

2. Since the manufacturing site for the drug product has been changed, revise the last paragraph to read:

   Manufactured for:
   ChiRhoClin, Inc.
   Burtonsville, MD 20866

   By:

   Bell-More Laboratories, Inc.
   Hampstead, MD 21074-0179

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

If you have any questions, call Ryan Barraco, Consumer Safety Officer, at (301) 443-8017.

Sincerely,

/S/

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
2/23/04 12:16:02 PM

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

# REQUEST FOR CONSULTATION

*Division/Office):*
**ammie Beam**
**Division of Medication Errors and Technical Support (DMETS), HFD-420**
**PKLN Rm. 6-34**

FROM:
Ryan Barraco, Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180
PKLN Rm. 6B-45
301-443-8017

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| 2/17/04 | | 21-256 | Correspondence | February 9, 2004 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| — | Standard | RS | March 18, 2004 |

NAME OF FIRM: ChiRhoClin. Inc.

**REASON FOR REQUEST**

**I. GENERAL**

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

**II. BIOMETRICS**

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

**III. BIOPHARMACEUTICS**

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

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

| ☐ CLINICAL | ☐ PRECLINICAL |
|---|---|

**COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:**
ChiRhoClin., Inc. resubmitted NDA 21-256 (submitted October 10, 2003, received October 10, 2003), and it was classified as a Class 2 resubmission. A discipline review letter was issued on January 12, 2004, which requested a new proprietary name (— and — were found unacceptable). The firm proposes the proprietary name, — for human synthetic secretin (correspondence dated February 9, 2004). Please revie this new proposed proprietary name. Please also review the updated package insert, immediate container, and carton labels (found in the October 10, 20( submission). We would appreciate your finalized review, submitted to the NDA via DFS, by March 18, 2004. Please call me with any questions.

**PDUFA DATE: April 10, 2004**

**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels and the February 9, 2004 correspondence

| SIGNATURE OF REQUESTER<br>Ryan Barraco, B.A., B.S. | METHOD OF DELIVERY (Check one)<br>☐ MAIL ☒ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER<br>Ryan Barraco, B.A., B.S. |

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/s/

Ryan Barraco
2/17/04 04:36:07 PM

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

# REQUEST FOR CONSULTATION

*(Division/Office)*:
aine Hu
Office of Medical Policy, Division of Drug Marketing, Advertising and Communication
HFD-42, Rm. 17B-17

FROM:
Ryan Barraco
Division of Gastrointestinal and Coagulation Drug Products
HFD-180, 827-0191

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| December 19, 2003 | | 21-256 | RS | October 10, 2003 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| —— (synthetic human secretin) Injection | Standard | | March 12, 2004 |

NAME OF FIRM: ChiRhoClin, Inc.

**REASON FOR REQUEST**

**I. GENERAL**

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

**II. BIOMETRICS**

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

**III. BIOPHARMACEUTICS**

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

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

- ☐ CLINICAL
- ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**
Please review the attached draft package insert, immediate container and carton label. We would appreciate your finalized review, submitte the NDA via DFS, by March 12, 2004. The PDUFA goal date is April 10, 2004. DDMAC's consult review dated September 18, 2001 has been included. Thanks.

cc: Original NDA
HFD-180/Div. Files
HFD-180/Barraco

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

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/s/

Ryan Barraco
12/22/03 09:32:41 AM

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

# REQUEST FOR CONSULTATION

TO *(Division/Office)*:
**Sammie Beam**
**Division of Medication Errors and Technical Support (DMETS), HFD-420**
**PKLN Rm. 6-34**

FROM:
Ryan Barraco, Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180
PKLN Rm. 6B-45
301-827-0191

| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| 12/18/03 | | 21-256 | NDA resubmission (Class 2) | October 10, 2003 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| [redacted] | Standard | RS | March 10, 2004 |

NAME OF FIRM: ChiRhoClin. Inc.

**REASON FOR REQUEST**

**I. GENERAL**

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

**II. BIOMETRICS**

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

**III. BIOPHARMACEUTICS**

- ☐ DISSOLUTION
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- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
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- ☐ 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, CONCERNS, and/or SPECIAL INSTRUCTIONS:**
ChiRhoClin., Inc. has resubmitted NDA 21-256 (submitted October 10, 2003, received October 10, 2003), and it has been classified as a Class 2 resubmission. The resubmission includes updated labeling and the firm has decided to use the proprietary name, [redacted] The firm was told that [redacted] was found unacceptable in a July 17, 2001, discipline review letter. They were again reminded of this in a phone call dated December 12, 200: however, wish that [redacted] be re-consulted. In efforts to be proactive, DGCDP asks that DMETS also re-review the name [redacted] which was found an acceptable name for this drug product on September 21, 2001. However, DGCDP identifies that NDA 21-136, SecreFlo was approved on April 4, 2002 Please also review the updated package insert, immediate container, and carton labels. All of the referenced material will be included in this consult reque We would appreciate your finalized review, submitted to the NDA via DFS, by March 10, 2004. Please call me with any questions.

**PDUFA DATE: April 10, 2004**

**ATTACHMENTS:** Draft Package Insert, Container and Carton Labels, all referenced letters and consults

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) |
|---|---|
| Ryan Barraco, B.A., B.S. | ☐ MAIL ☒ HAND |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER<br>Ryan Barraco, B.A., B.S. |

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/s/

Ryan Barraco
12/18/03 12:24:42 PM

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

# REQUEST FOR CONSULTATION

(Division/Office):
**dtn: Patricia Tuegel, HFD-805**
**PKLN Rm 18B08**
**5600 Fishers Lane**
**Rockville, MD 20857**

**Phone: (301) 827-7340**

FROM:
**Betsy Scroggs, Pharm. D.**
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products, HFD 180
Center for Drug Evaluation and Research
Food and Drug Administration
Tel: (301) 827-1250 Fax: (301) 827-1305
Email: scroggsb@cder.fda.gov

| DATE: November 13, 2003 | TYPE OF DOCUMENT<br>NDA: 21-256/N-000 AZ | DATE OF DOCUMENT<br>10-Oct-2003 | |
|---|---|---|---|
| NAME OF DRUG<br>—— (human secretin) | PRIORITY CONSIDERATION<br>High | CLASSIFICATION OF DRUG<br>GI Diagnostic Agent | DESIRED COMPLETION DATE<br>10-Feb-2003 |

NAME OF FIRM: ChiRhoClin

**REASON FOR REQUEST**

**I. GENERAL**

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

CLINICAL ☐ PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

HFD-180 requests a microbiology consult for submission NDA 21-256 N-000 AZ with a letter date of October 10, 2003 and a User Fee Goal Date of April 10, 2003. —— (synthetic human secretin) was approvable 14- December 2001. The firm has responded to the deficiencies listed in the Action letter and CMC Discipline review letter. HFD-180 will schedule a team meeting to determine if this is a complete response due to the complexity of the submission.
There are many items to cover, mostly chemistry; however it may also involve biopharmaceutics.
To note, the firm has changed its manufacturing site in this review cycle.
As a matter of reference, please note that this firm also markets the approved drug NDA 21-136 SecreFlo (synthetic secretin) with a supplement under review for a manufacturing site change with a pending microbiology consult. SecreFlo has been determined to be a medically necessary drug product and is expected to be in drug shortage this month.

| SIGNATURE OF REQUESTER: Betsy Scroggs, Pharm.D.<br>Consumer Safety Officer | METHOD OF DELIVERY (Check one)<br>☐ MAIL X HAND |
|---|---|
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/s/

Betsy Scroggs
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