



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

1/17/02

NDA 21-256

ChiRhoClin, Inc.  
Attention: Edward D. Purich, Ph.D.  
15500 Gallaudet Ave  
Silver Spring, MD 20905-4176

Dear Dr. Purich:

Please refer to the teleconference between representatives of your firm and FDA on December 5, 2001. The purpose of the teleconference was to summarize outstanding NDA deficiencies.

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

If you have any questions, call me at (301) 827-7310.

Sincerely,

*{See appended electronic signature page}*

Melodi McNeil  
Regulatory Health Project Manager  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF TELECONFERENCE MEETING MINUTES

**MEETING DATE:** December 5, 2001  
**TIME:** 10-10:30 AM  
**LOCATION:** Room 6B-45 (PKLN)  
**APPLICATION:** NDA 21-256; synthetic human secretin for injection  
**TYPE OF MEETING:** Review Status

**MEETING CHAIR:** Dr. Joyce Korvick, Deputy Division Director

**MEETING RECORDER:** Ms. Melodi McNeil, Regulatory Health Project Manager

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. Joyce Korvick, Deputy Division Director  
Dr. Liang Zhou, Chemistry Team Leader  
Dr. Art Shaw, Chemistry Reviewer  
Ms. Melodi McNeil, Regulatory Health Project Manager

### EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

#### ChiRhoClin, Inc.

Dr. Edward Purich, Chief Executive Officer  
Dr. Seymour Fein, Chairman

**BACKGROUND:** Pending NDA 21-256 provides for synthetic human secretin as a GI Diagnostic agent. Specifically, the applicant has proposed the following indications:

1. Diagnosis of pancreatic exocrine
2. Diagnosis of gastrinoma ( ) and
3. Facilitation of ( ) during ERCP

This application will be signed off at the Office level. The Division has completed all reviews and made a recommendation for regulatory action to the Office. Today's teleconference with the firm was arranged to give the firm advance notice of the outstanding deficiencies in the NDA, from the Division's perspective.

**MEETING OBJECTIVES:** To describe the remaining deficiencies in the NDA

### DISCUSSION POINTS:

1. Dr. Korvick indicated that that purpose of today's teleconference was to provide a general

overview of the outstanding deficiencies in the NDA. She noted that while substantial chemistry deficiencies remain to be addressed, the firm's proposed indications may be able to be approved from a clinical perspective.

2. CMC:

a. Background: A detailed CMC Discipline Review (DR) letter was issued on November 21, 2001. (The firm responded shortly thereafter, however, review of the firm's response will be deferred to the next cycle.) According to the NDA, \_\_\_\_\_ is the manufacturer that will be used to supply the drug substance for the marketed drug product. However, \_\_\_\_\_ is the manufacturer that supplied drug substance for the product used during drug development. The applicant has never manufactured drug product made with \_\_\_\_\_ drug substance.

b. Dr. Shaw said the detailed list of deficiencies contained in the DR letter could be summarized as the following significant approvability issues:

- i. The batch of \_\_\_\_\_ drug substance was manufactured under poorly controlled conditions.
- ii. According to the submitted batch record, drug product manufactured with \_\_\_\_\_ drug substance was also manufactured under poorly controlled conditions, as evidenced by \_\_\_\_\_.

Because of these concerns, there is insufficient information in the NDA to permit extrapolation from the drug product manufactured with \_\_\_\_\_ drug substance to the drug product that will be manufactured with \_\_\_\_\_ drug substance. Further, information about the \_\_\_\_\_ drug substance is contained in a DMF, which has been reviewed and found deficient. Dr. Shaw indicated that the way to address these concerns is to manufacture a batch of drug product made with \_\_\_\_\_ drug substance. However, \_\_\_\_\_ must satisfactorily respond to all of the deficiencies in the DMF before FDA can determine whether \_\_\_\_\_ must manufacture another batch of drug substance.

In response, the firm commented that, if needed, manufacture of a second batch of drug substance will be expensive. They said they do not want to incur this expense if other deficiencies in the NDA are ultimately not able to be resolved. Similarly, they said that if they must incur this expense, they would want to know as soon as possible. FDA reminded the firm that the \_\_\_\_\_ has not responded to the DMF deficiency letter issued September 14, 2001. FDA agreed to review any DMF submissions as soon as possible.

- iii. There is no stability-indicating assay for the drug product.

According to the firm, they have tried and failed to develop this assay, which was



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/s/

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Melodi McNeil  
12/21/01 10:31:30 AM

Joyce Korvick  
1/3/02 01:51:16 PM

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** February 12, 2002  
**TIME:** 1-2:30 P.M.  
**LOCATION:** Conference Room "L" (PKLN)  
**APPLICATION:** NDA 21-136; synthetic porcine secretin for injection  
NDA 21-209; synthetic porcine secretin for injection  
NDA 21-256; synthetic human secretin for injection

**TYPE OF MEETING:** Discussion of NDA Deficiencies

**MEETING CHAIR:** Dr. Liang Zhou, Chemistry Team Leader

**MEETING RECORDER:** Ms. Melodi McNeil, Regulatory Health Project Manager

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

#### Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. Joyce Korvick, Deputy Division Director  
Dr. Marcelo Barreiro, Medical Officer  
Dr. Liang Zhou, Chemistry Team Leader  
Dr. Art Shaw, Chemistry Reviewer  
Ms. Alice Kacuba, Regulatory Health Project Manager  
Ms. Melodi McNeil, Regulatory Health Project Manager

#### Division of New Drug Chemistry II (HFD-820)

Dr. Eric Duffy, Division Director

### EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

#### ChiRhoClin, Inc.

Dr. Edward Purich, Chief Executive Officer

Mr. Skip Purich, IS Manager

**BACKGROUND:** Pending NDAs 21-136 and 21-209 provide for synthetic porcine secretin for injection. The applicant has proposed the following indications:

1. Diagnosis of pancreatic exocrine (21-136)
2. Diagnosis (21-209) (These indications will be reworded to reflect the functional, rather than diagnostic, effect that was demonstrated in the clinical trial population.)

The third review cycle for both applications is ongoing. The NDAs have been found approvable in

NDA 21-136  
NDA 21-209  
NDA 21-256  
Page 2

two previous cycles, pending the resolution of multiple chemistry deficiencies. The user fee goal date for the current review cycle is April 9, 2002.

NDA 21-256 provides for synthetic human secretin for injection. Specifically, the applicant has proposed the following indications:

1. Diagnosis of pancreatic exocrine .
  2. Diagnosis of gastrinoma ( . . . ); and
  3. Facilitation of . . . papilla during ERCP . . .
- (These indications will be reworded to reflect the functional, rather than diagnostic, effect that was demonstrated in the clinical trial population.)

This NDA was approvable on December 14, 2001, pending the resolution of multiple chemistry deficiencies.

In a December 21, 2001 submission, the applicant (ChiRhoClin, Inc.) requested a meeting to discuss the deficiencies identified in the NDAs to date.

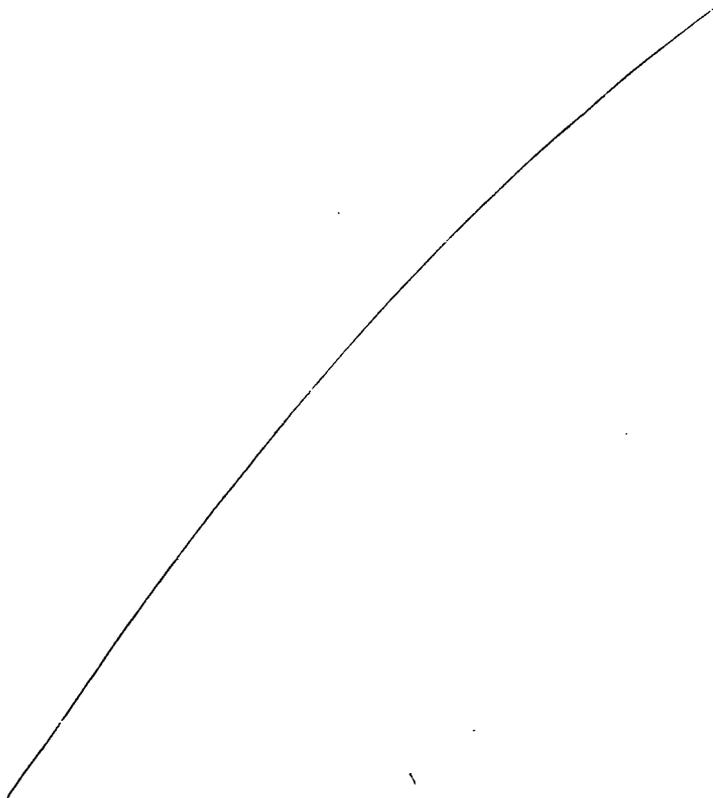
**MEETING OBJECTIVES:** To discuss the deficiencies that have been identified in the NDAs to date

**DISCUSSION POINTS:** The firm provided a number of specific questions for the Division to answer. The firm's questions are reproduced below in regular type. The Division's answers follow in bold type.

Regarding Synthetic Porcine Secretin:

1.

2.



Regarding Synthetic Human Secretin

1. Is \_\_\_\_\_ response to the DMF questions acceptable?

**FDA Response: Deficiencies have been conveyed to the DMF holder.**

2. Can ChiRhoClin proceed with manufacture of a parenteral batch of synthetic human secretin at \_\_\_\_\_ using \_\_\_\_\_ drug substance?

**FDA Response: As indicated in our January 29, 2002 letter, you may proceed with manufacture of a parenteral batch of synthetic human secretin at \_\_\_\_\_ using \_\_\_\_\_ drug substance.**

NDA 21-136  
NDA 21-209  
NDA 21-256  
Page 4

3. Besides the standard testing performed by — to release the drug product, are any additional tests required?

**FDA Response: See Comments conveyed in IR letter dated November 21, 2001.  
Responses will be reviewed when the NDA is resubmitted.**

4. Are the stability data sufficient to support a — expiration date?

**FDA Response: Available stability data are insufficient to support a — expiration date.**

5. Are there any additional recommendations related to the manufacture of the drug product by — and — required for this application?

**FDA Response: See comments in Appendix 1 concerning drug product manufacturing for Porcine Secretin.**

Appendix 1: [Requested information should be provided as an amendment to both pending NDAs. The two amendments (i.e., one to each NDA) should be identical.]

Regarding Synthetic Porcine Secretin:

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secret and/or

confidential

commercial

information

NDA 21-136  
NDA 21-209  
NDA 21-256  
Page 6

**CONCLUSIONS:** Division representatives noted that there are several items to be addressed in each of the NDAs before they can be approved. The provision of timely, complete, well-documented, and validated information will facilitate Division review.

Minutes Preparer: \_\_\_\_\_

/S/

Chair Concurrence: \_\_\_\_\_

/S/

Drafted by: mm/February 20, 2002  
Initialed by: AShaw 2/20/02  
LZhou 2/21/02  
EDuffy 2/26/02  
JKorvick 2/23/02  
VRaczkowski 2/26/02  
final: February 28, 2002

**MEETING MINUTES**

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/s/

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Melodi McNeil  
2/28/02 10:33:11 AM

Liang Zhou  
2/28/02 01:53:33 PM

**MEMORANDUM OF TELECONFERENCE MEETING MINUTES**

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**MEETING RECORDER:** Ms. Melodi McNeil, Regulatory Health Project Manager

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. Joyce Korvick, Deputy Division Director  
Dr. Liang Zhou, Chemistry Team Leader  
Dr. Art Shaw, Chemistry Reviewer  
Ms. Melodi McNeil, Regulatory Health Project Manager

**EXTERNAL CONSTITUENT ATTENDEES AND TITLES:**

ChiRhoClin, Inc.

Dr. Edward Purich, Chief Executive Officer  
Dr. Seymour Fein, Chairman

**BACKGROUND:** Pending NDA 21-256 provides for synthetic human secretin as a GI Diagnostic agent. Specifically, the applicant has proposed the following indications:

1. Diagnosis of pancreatic exocrine —
2. Diagnosis of gastrinoma — ; and
3. Facilitation — papilla during ERCP . —

This application will be signed off at the Office level. The Division has completed all reviews and made a recommendation for regulatory action to the Office. Today's teleconference with the firm was arranged to give the firm advance notice of the outstanding deficiencies in the NDA, from the Division's perspective.

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In response, the firm commented that, if needed, manufacture of a second batch of drug substance will be expensive. They said they do not want to incur this expense if other deficiencies in the NDA are ultimately not able to be resolved. Similarly, they said that if they must incur this expense, they would want to know as soon as possible. FDA reminded the firm that the \_\_\_\_\_ not responded to the DMF deficiency letter issued September 14, 2001. FDA agreed to review any DMF submissions as soon as possible.

- iii. There is no stability-indicating assay for the drug product.

According to the firm, they have tried and failed to develop this assay, which was originally requested more than a year ago. FDA reiterated the importance of the requested assay and said that if the firm could not develop it, full, detailed reports of the development efforts must be submitted.

**CONCLUSIONS:** The Division's reviews have been completed. From the Division's perspective, substantial CMC deficiencies remain. The Division asked the firm to provide timely, complete submissions in response to the Division's previous letters and the issues raised in today's teleconference.

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/s/

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Melodi McNeil  
1/7/02 10:17:42 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-256

1/29/02

ChiRhoClin, Inc.  
Attention: Edward D. Purich, Ph.D.  
15500 Gallaudet Ave  
Silver Spring, MD 20905-4176

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).

We recently reviewed DMF — held by — manufacturer of synthetic human secretin drug substance. Remaining deficiencies will be conveyed directly to the DMF holder. However, effective immediately, it is acceptable for drug product to be manufactured using drug substance from —

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal & Coagulation Drug  
Products, HFD-180  
DNDC 2, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/  
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Liang Zhou

1/29/02 04:33:41 PM



Office of Orphan Products Development (HF-35)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

April 30, 2002

ChiRhoClin, Incorporated  
15500 Gallaudet Avenue  
Silver Spring, MD 20905-4176

Attention: Edward D. Purich, PhD  
President and Chief Executive Officer

Re: Designation Request # \_\_\_\_\_

Dear Dr. Purich:

Reference is made to your letter of February 13, 2002. We also refer to our notification letters dated March 7, 2000, granting orphan-drug designation to synthetic human secretin (Designation request # \_\_\_\_\_ and synthetic porcine secretin (Designation request # \_\_\_\_\_ both for use in conjunction with diagnostic procedures for pancreatic disorders to increase pancreatic fluid secretion.

We have reviewed the information submitted in your letter. Pursuant to 21 CFR 316.26, we agree to amend the orphan-drug designation as follows:

1. Designation request # \_\_\_\_\_ Synthetic human secretin is indicated for use in conjunction with diagnostic, therapeutic, or combined diagnostic/therapeutic procedures for pancreatic disorders to increase pancreatic fluid secretion.
2. Designation request # \_\_\_\_\_ Synthetic porcine secretin is indicated for use in conjunction with diagnostic, therapeutic, or combined diagnostic/therapeutic procedures for pancreatic disorders to increase pancreatic fluid secretion.

We would like to bring to your attention that, as defined in § 316.3(b)(13)(ii)(A), the two drugs, synthetic porcine secretin and synthetic human secretin, are considered the same two drugs. While the two drugs differ structurally by two amino acids, these differences are considered minor differences in amino acid sequence since there is no evidence to suggest that their human pharmacologic activities can be distinguished. In fact, in your

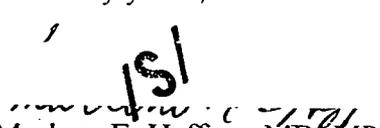
letter of February 13, 2002, you made reference to the "identical pharmacologic effect" of these two drugs.

Since marketing applications (NDA # 21-136 and NDA # 21-209 of synthetic porcine secretin (Secreflo™) have been approved for indications for which orphan-drug designations were granted, the Food and Drug Administration will not approve other marketing applications for the same drug and the same uses before the expiration of seven years from the date of such approval (see § 316.31(a)), you may give consent for marketing application of synthetic human secretin to gain approval for the same indications. In such case, both drugs will share the same orphan-drug exclusive approval.

It should be noted that for synthetic human secretin to receive its own orphan-drug exclusive approval for the same indication, it must be shown to be clinically superior to synthetic porcine secretin under the terms of § 316.3(b)(3).

Should you have any questions, please contact Mr. Jeff Fritsch, RPh, in our Office at (301) 827-0989.

Sincerely yours,

  
Marlene E. Haffner, MD, MPH  
Rear Admiral, United States Public Health Service  
Director, Office of Orphan Products Development

cc:

HF-35/OP File # —

HF-35/OP File # —

HF-35/Chron

HF-35/TNguyen

JFritsch 4/15/02

AMENDMENT TO INDICATION



NDA 21-256

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 new drug application (NDA) for synthetic human secretin lyophilized sterile powder.

We also refer to your submission dated October 10, 2003 in which you provided a complete response to our December 14, 2001 action letter.

As discussed in a telephone conversation dated March 25, 2004 between Dr. Seymour Fein, Chairman, and Ryan Barraco, Consumer Safety Officer, of this Division, we are requesting your response to a letter dated April 30, 2002, from the Office of Orphan Products Development. The letter stated that:

as defined in § 316.3(b)(13)(ii)(A), the two drugs, synthetic porcine secretin and synthetic human secretin, are considered the same two drugs. While the two drugs differ structurally by two amino acids, these differences are considered minor differences in amino acid sequence since there is no evidence to suggest that their human pharmacologic activities can be distinguished. In fact, in your letter of February 13, 2002, you made reference to the 'identical pharmacologic effect' of these two drugs.

Since marketing applications (NDA # 21-136 and NDA # 21-209 of synthetic porcine secretin (SecreFlo<sup>TM</sup>) have been approved for indications for which orphan-drug designations were granted, the Food and Drug Administration will not approve other marketing applications for the same drug and the same uses before the expiration of seven years from the date of such approval (see § 316.31(a)), you may give consent for marketing application of synthetic human secretin to gain approval for the same indications. In such case, both drugs will share the same orphan-drug exclusive approval.

It should be noted that for synthetic human secretin to receive its own orphan-drug exclusive approval for the same indication, it must be shown to be clinically superior to synthetic porcine secretin under the terms of § 316.3 (b)(3).

Please promptly respond to this April 30, 2002, letter. If you have any questions, please call Ryan Barraco at 301-443-8017.

Sincerely,

~~S~~  
{*See appended electronic signature page*}

Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

FOOD AND DRUG ADMINISTRATION  
DIVISIONS OF GASTROINTESTINAL  
AND COAGULATION DRUG PRODUCTS  
DOCUMENT CONTROL ROOM 6B-24  
5600 FISHERS LANE  
ROCKVILLE, MARYLAND 20857

DATE: 12/14/01



TO:

Name: E. Purich  
Fax No: (301) 384-1565  
Phone No:  
Location: Ch. RhoClin

FROM:

Name: M. McNeil  
Fax No: (301) 443-9285  
Phone No: (301) 827-7310  
Location: FDA, Division of  
Gastrointestinal and  
Coagulation Drug Products

5 page(s), total

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Comments:

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

DATE: December 14, 2001

FROM: Florence Houn MD MPH

SUBJECT: Office Director Memo

TO: NDA 21-256. — (synthetic human secretin) for Injection by ChiRhoClin, Inc.

This memo documents my concurrence with the Division of Gastrointestinal and Coagulation Drug Products to issue ChiRhoClin, Inc. an approvable letter for their application of — for three indications: to stimulate pancreatic secretions, bicarbonate, and gastrin to aid in the diagnosis of pancreatic exocrine dysfunction and gastrinoma, and the identification of the ampulla of Vater during endoscopic retrograde cholangio-pancreatography. Two major outstanding issues remain with the application that must be addressed prior to approval: satisfactory resolution of chemistry and manufacturing deficiencies, and appropriate labeling. The deficiencies for chemistry are well outlined in the approvable letter. They pertain to the need for adequate information on the manufacturing of the drug product as the actual final drug product manufacturer differs from what is stated in the drug marketing application compared to the manufacturer of drug for the clinical trials. Initially the medical officer and the team leader felt there were deficiencies related to a cannulation indication. They were concerned about unblinding due to administration of the high level of drug causing the endoscopist to see pancreatic outpouring of fluid and that this effect lasts for 60 minutes, making the 5 minute interval between drug administration and attempts to cannulate an insufficient time period for washout. They expressed desires for a new protocol be developed to address these trial design issues and clinical data be gathered. However, in my discussion with Ms. Bronwyn Collier and the acting division director and deputy division director, it appears that by using a functional indication approach

— there is sufficient information. In reference to the — indication, the very problems with the study design and unblinding are the active physiologic properties of the drug. Therefore, a functional indication means that the NDA supplied clinical data that the drug product produced the intended physiological activity in test subjects. This memo will then focus on my thinking about the evidence for efficacy presented in the NDA for the functional indication of stimulation of the pancreas and labeling that may be needed.

**Evidence for Efficacy**

The Statistical Team has appropriately pointed out that the data to support indications for diagnosis of pancreatic exocrine dysfunction and gastrinoma are not adequate. The studies CRC 98-9 (for diagnosis of pancreatic exocrine dysfunction) and CRC 99-8 (for diagnosis of gastrinoma) between them contained about one dozen patients who had known diagnoses. Study 98-2 uses an unapproved secretin compound in 12 patients and could be viewed as supportive. These patients were not the intended population for the tests (we don't anticipate — be used in already diagnosed patients). It is unclear how the test will perform in a population with symptoms suggesting the disease but without a clinical diagnosis. Also, the Statistical Team raises the concern that given the spectrum of disease for pancreatic exocrine dysfunction and gastrinoma, can the test perform adequately. Finally, the clinical data do not show diagnostic accuracy in the intended use population. What is presented is that for a limited number of patients with known diagnoses, the test produced confirmation of the diagnoses. The data also show that for these patients, the drug product produced expected physiologic responses of the pancreas. There is a plausible mechanism why this hormone should produce the biological expected results. Given the orphan status of this test, I feel that labeling should describe the clinical testing to show that data on this product is from patients with known diagnoses. I also feel that the indications as proposed by the company (to diagnose pancreatic exocrine insufficiency, gastrinoma, — are not reflective of the

data and the indications should be changed to say that the drug product produces the specific physiologic responses observed. Two remaining concerns are that the population tested is not the "undiagnosed" population (the intended population of use) and the numbers in the trials are small. I feel that the issue of intended use population not tested should be in the label to alert clinicians to this fact. I also feel that the small numbers are commensurate with our view that this drug is an orphan product and trials in larger populations may not be feasible. Finally, the identification of the ampulla through observation of the pancreas secretions was done in a large number of patients. The exact numbers of patients can be included in the clinical trials section so prescribers are aware of limits of the trial data. This product must be manufactured in a manner to ensure purity and quality. Human secretin has known chemical and physical properties. The clinical data presented demonstrate predicted physiologic activity.

Labeling

Some labeling suggestions would include:

Clinical Trials Section would describe the actual studies, describe the population studied, provide the numbers of patients studied, and state the sensitivity and specificity of the product is not known. The label could also state there may be false-negatives and false-positives with \_\_\_\_\_

Indications Section would provide for a functional indication, such as, \_\_\_\_\_ stimulates pancreatic secretions and pancreatic bicarbonate output, and increases serum gastrin levels. These physiologic responses to \_\_\_\_\_ can be used to assist in the diagnosis of exocrine pancreatic dysfunction and gastrinoma and identification of the ampulla of Vater during ERCP.

I've discussed these thoughts with the division's acting director and deputy director and the NDA's project manager. The action letter reflects these issues.

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/s/

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Florence Houn  
12/14/01 11:06:48 AM  
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**MEMORANDUM**

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

DATE: 12/12/01

TO: Florence Houn, MD  
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: ChinRhoClin

SUBSTANCE: — (synthetic human secretin) for Injection  
(lyophilized sterile powder)  
Chemical & Therapeutic Class: Type 1, GI Diagnostic  
User Fee Goal Date: December 14, 2001

**I. Background:**

The subject of this application is the injectable synthetic human secretin (sHS) product manufactured by ChinRhoClin. 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. ChinRhoClin has both a synthetic porcine secretin (sPS) and synthetic human secretin (sHS) product in development. The FDA granted the sPS product an approvable status in 2000 for the diagnosis of pancreatic exocrine dysfunction and gastrinoma, pending the resolution of chemistry and manufacturing issues. Currently sPS can be obtained for patient use through an IND mechanism.

ChinRhoClin 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: 0.2  $\mu$ g/Kg B<sub>wt</sub>);
- diagnosis of gastrinoma (dose: 0.4  $\mu$ g/Kg B<sub>wt</sub>);
- facilitation of ————— r papilla during ERCP —————  
(dose: 0.2  $\mu$ g /Kg B<sub>wt</sub>).

## II. Discipline review summary and commentary:

- A. **OPDRA** : Review by the nomenclature committee recommended approval of the tradename
- B. **Chemistry**: The specific amino acid sequence (27 amino acid) of human secretin is known, therefore sHS should consist of the identical amino acid sequence. Literature that describes the sequence of human secretin was not submitted by the applicant, and incomplete data was supplied which confirms sHS is identical to that sequence. In addition, the generic name of synthetic human secretin has not been used before and does not have USAN (US Adopted Name) or CAS (Chemical Abstracts Service) number which establishes this name.

A chemistry "discipline review memo" was sent to the applicant on 11/21/01. The major issues which remain to be resolved include CMC issues for drug product, development of an assay for detecting impurities, stability data and responses to deficiencies noted in the DMF. manufactured the drug substance and product utilized in the clinical studies. The applicant does not intend to use this laboratory for the manufacture of the marketed product, but rather will manufacture both the drug substance and drug product. did produce a drug substance that was biologically similar to that made by No batches of drug product were made by, using drug substance made by. A summary of the specific chemistry deficiencies that make this product approvable can be found in the chemistry review "remarks/comments" section.

- 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.
- 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 pharmacokinetic 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<sub>0-∞</sub>. 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.
- E. **Clinical: Efficacy /Safety**:  
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 pancreatic secretion, is approvable, pending additional clinical studies.

The current study is inadequate (CRC98-4). However, if one further explores the reason that the study failed, one 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 unblinded to the study assignment. Thus, if the indication requested was to facilitate the identification of the ampulla 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.

**Recommendations:**

NDA 21-256 is approvable due to the extensive list of Chemistry, Manufacturing, and Controls deficiencies surrounding .

The Division finds the following indications approvable:

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.
3. Stimulate the secretion of gastrin 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 in 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.

The most important issue to resolve prior to an approval of this NDA is to provide a synthetic drug product that has established specifications for purity and stability. Overall, assurance of potency for this drug product is paramount to its approval, given proposed indications.

S

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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Joyce Korvick  
12/14/01 10:12:37 AM  
MEDICAL OFFICER

12/13/01

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEMORANDUM

From: Marcelo A. Barreiro, MD, MSc  
Medical Reviewer

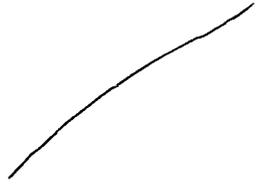
To: Hugo Gallo-Torres, MD, PhD  
Medical Team Leader

Re: 21-256 (Synthetic Human Secretin, sHS)  
28 November, 2001 Telephone Call to ChiRhoClin, Inc

As discussed with Dr. Gallo-Torres, this reviewer contacted Dr. Edward D. Purich, CEO of ChiRhoClin Inc., sponsor of the sHS NDA, to clarify some issues related to pediatric use of sHS during the clinical trials.

In their submission, ChiRhoClin Inc, states that sHS has been used in children without specifying the number or providing any other details of the results:

Package insert:



New Drug Application. Vol 2, page 000027, 2.3, Foreign Marketing History:

“...the number of patients who receive bPS (biological porcine secretin) each year in the US has been under — This includes up to — children per year receiving secretin for diagnosis of pancreatic function when malabsorption or cystic fibrosis is suspected. The annual use in Canada is approximately — of the US.

There have been no spontaneous adverse reports on bPS for many years.”

Dr. Purich stated that sHS has been used in children in CRC 98-4 (Open label, non-comparative, single arm, multicenter study for the routine clinical use of sHS as a diagnostic agent — which is still in progress. He didn't have detailed information about the pediatric patients studied in that clinical trial.

He volunteered that sHS had been used in the Autism trials and that the information had been published: NEJM – Sandler et al. 341 (24):1801.

On that note we hang up at 9:29 AM.

cc:

HFD-103/FHoun

HFD-180/VRaczkowski

HFD-180/JKkorvick

HFD-180/HGallo-Torres

HFD-180/MBarreiro

HFD-180/MMcNeil

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Marcelo Barreiro  
12/13/01 04:32:09 PM  
MEDICAL OFFICER

Hugo Gallo Torres  
12/14/01 02:18:18 PM  
MEDICAL OFFICER

12/12/01

# NDA 21-256

## Injection 16 µg

### CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: ChiRhoClin, Silver Spring MD

Indication: Diagnosis of exocrine pancreatic dysfunction  
 Diagnosis of \_\_\_\_\_  
 Facilitation of \_\_\_\_\_ papilla during  
 ERCP; \_\_\_\_\_

EER Status: unacceptable

Consults: Microbiology – acceptable 11/6/01  
 Biopharm – acceptable 11/14/01  
 OPDRA – acceptable 9/21/01

#### Introduction

This NDA was originally submitted on 3/16/00 and was refused to file 5/11/00. The NDA was re-submitted 6/14/01. Note that there is no established name (USAN) as yet. A substantive DR letter for CMC issues was issued 8/8/01. The active drug substance is a synthetic 27mer peptide.

The **drug substance** is proposed to be manufactured by \_\_\_\_\_, and the process and controls are described in DMF \_\_\_\_\_ which was found inadequate 9/14/01. Note that no drug product has been manufactured from this source and only one batch of drug substance has been manufactured. Clinical supplies were manufactured at \_\_\_\_\_ Synthesis is \_\_\_\_\_

\_\_\_\_\_ The impurity profiles have been shown to be comparable. The \_\_\_\_\_ drug substance is actually more pure. A satisfactory EER will be needed for \_\_\_\_\_

#### Discussion

Deficiency comments have been sent to the DMF holder and we await a response.

#### Conclusion

The drug substance manufacturing is unsatisfactory.

The **drug product** is a lyophilized formulation with manitol and cysteine HCL manufactured by \_\_\_\_\_ and is a single presentation of vials of 16 µg. Product is manufactured at \_\_\_\_\_ The manufacturing process \_\_\_\_\_ and the applicant has been asked to identify

correct the manufacturing problem(s). Additional deficiencies have been sent in the 8/8/01 DR letter.

The container, carton and insert **labeling** was not reviewed in the review cycle.

**Discussion**

Deficiency comments have been sent in the 8/8/01 DR letter and we await a response.

**Conclusion**

The drug product manufacturing is unsatisfactory.

**Over-All Conclusion**

From a CMC perspective the application is recommended for an approvable action.

Eric P Duffy, PhD  
Director, DNDC II/ONDC

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/s/

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Eric Duffy  
12/12/01 03:13:23 PM  
CHEMIST



NDA 21-256

**DISCIPLINE REVIEW LETTER**

ChiRhoClin, Inc.  
Attention: Edward D. Purich, Ph.D.  
15500 Gallaudet Ave  
Silver Spring, MD 20905-4176

11/21/01

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).

We also refer to your submissions dated July 16, August 10, and September 26, 2001.

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

1. Provide a USAN and a CAS number for the drug substance.
2. DMF \_\_\_\_\_ was found deficient and the holder notified in a letter dated September 14, 2001.
3. Regarding the drug substance manufactured by \_\_\_\_\_
  - a. Regarding the Characterization:
    - 1) Explain where "Appendix H" and "Appendix J" can be found in the application (see Page 132 of the September 26, 2001 submission)
    - 2) Provide experiments to characterize the identity of the drug substance, including the following:
      - a) \_\_\_\_\_
      - b) \_\_\_\_\_
      - c) \_\_\_\_\_
      - d) \_\_\_\_\_
      - e) \_\_\_\_\_
    - 3) Provide data or literature references to support the assignment of the proposed structure as human secretin.
    - 4) Regarding the assignment of the
      - a) Provide data to unambiguously assign the

b)

c) Provide data to demonstrate

b. Regarding the manufacturing process at

[

3) Provide the following information regarding

]

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

- 2) Regarding the box label: Change the word "secretin" to "human secretin."  
Revise the amounts of L-cysteine hydrochloride and mannitol to reflect the actual amounts.
- 3) Regarding the package insert:
  - a) Revise the "Description" in the package insert to remove all references to "secretin" and "porcine secretin." All references should be to "human secretin," including any references to literature.
  - b) Provide stability studies to determine the light sensitivity of the drug product or include a statement on the label "Protect from light."

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 Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,



Liang Zhou, Ph.D.  
Chemistry Team Leader for the  
Division of Gastrointestinal & Coagulation Drug  
Products, HFD-180  
DNDC 2, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Liang Zhou  
11/21/01 02:30:31 PM

No postmarketing commitments were requested in review cycle 1.

1/5  
11/20/01

APPEARS THIS WAY  
ON ORIGINAL



NDA 21-136  
NDA 21-209  
NDA 21-256

11/16/01

ChiRhoClin, Inc.  
Attention: Edward D. Purich, Ph.D.  
15500 Gallaudet Ave  
Silver Spring, MD 20905-4176

Dear Dr. Purich:

We received your November 2, 2001 correspondence on November 5, 2001 requesting a meeting to discuss what corrective actions may be required of \_\_\_\_\_ drug substance manufacturer for the NDAs cited above, to address the deficiencies identified during a recent manufacturing inspection at that facility. We considered your request and concluded the meeting is premature.

We have the following comments and recommendations:

Regarding NDA 21-256 (synthetic human secretin for injection):

1. You should resolve the issues specified in the FDA Form 483 with the appropriate FDA District Office. The District Office and/or the Office of Compliance may seek input from our division on this matter, and if so, we will facilitate that communication.
2. We have completed our review of DMF \_\_\_\_\_ held by \_\_\_\_\_ and submitted in support of the NDA. Deficiencies were conveyed to the holder in a letter dated September 14, 2001, however, to date there has been no response to our letter.
3. The chemistry review of this NDA is ongoing. We anticipate that any deficiencies found as a result of that review will be sent to you in writing by late November 2001.
4. Prior to the December 14, 2001 user fee goal date, we may contact you for a teleconference to convey conceptual disagreements and/or to seek clarification on certain aspects of the NDA.
5. Otherwise, we advise that you wait until after we take an action on the NDA to request a meeting on this NDA.

NDA 21-136  
NDA 21-209  
NDA 21-256  
Page 2

Regarding NDAs 21-136 and 21-209 (synthetic porcine secretin for injection):

If you disagree with our decision, you may discuss the matter with Melodi McNeil, Regulatory Project Manager, at (301) 827-7310. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fnl.htm>.

Sincerely,

{See appended electronic signature page}

Victor F. C. Raczowski, M.D., M.Sc.  
Acting Director  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Victor Raczkowski  
11/16/01 01:14:18 PM

9/21/01

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED: 08/16/01**      **DUE DATE: 09/30/01**      **OPDRA CONSULT #: 01-0183**

**TO:**  
Lilia Talarico, M.D.  
Director, Division of Gastro-Intestinal and Coagulation Drug Products  
(HFD-180)

**THROUGH:**  
Melodi McNeil  
Project Manager  
(HFD-180)

**PRODUCT NAME:** — (synthetic human secretin for injection)  
**NDA #:** 21-256

**MANUFACTURER:**  
ChiRhoClin, Inc.

**SAFETY EVALUATOR:** Hye-Joo Kim, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products, OPDRA conducted a review of the proposed name, — to determine the potential for confusion with approved proprietary and generic names as well as pending names. In addition, the Division requested us to review the sponsor's comments on our previous recommendation to change dosing to clinical units from micrograms.

**OPDRA RECOMMENDATION:** OPDRA has no objection to the use of the proprietary name, — In addition, we no longer object to the use of microgram-dosing. (See review for details.)

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

|S|

|S|

Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3246  
Fax: (301) 480-8173

Martin Himmel, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B-32  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE REVIEWED:** September 14, 2001  
**NDA#:** 21-256  
**NAME OF DRUG:** — (synthetic human secretin for injection)  
**NDA HOLDER:** ChiRhoClin, Inc.

**I. INTRODUCTION:**

This consult is in response to a August 16, 2001 request, by the Division of Gastrointestinal and Coagulation Drug Products, OPDRA conducted a review of the proposed name, — to determine the potential for confusion with approved proprietary and generic names as well as pending names. In addition, the Division requested us to review the sponsor's comments on our previous recommendation to change dosing to clinical units from micrograms. The container labels, the carton labeling, and the package insert were previously reviewed in our September 12, 2001 consult (00-0177-1).

The sponsor, ChiRhoClin, originally submitted the proposed name, — OPDRA completed a Proprietary Name Review for this product on September 20, 2000 and did not recommend the use of the name, — (see OPDRA consult 00-0177).

**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 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 OPDRA conducted a search of several standard published drug product reference texts<sup>1,2,3</sup> as well as several FDA databases<sup>4</sup> for existing drug names which sound-alike or look-

<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

<sup>2</sup> American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

alike — to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of Thomson and Thomson and the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5,6</sup>. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies consisting of written prescription studies and a 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 OPDRA 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. This group is composed of OPDRA medication errors prevention staff and representation from the Division of Drug Marketing and Advertising 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. Five products were identified in the Expert Panel Discussion that was thought to have potential for confusion with — These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Product Name	Generic name; strength	Usual dose	Observation
—	Synthetic human secretin for injection; 16 mcg	<u>Test dose:</u> 0.2 mcg for potential allergic reaction <u>Pancreatic function testing:</u> 0.2 mcg/kg by intravenous injection over 1 minute <u>Diagnosis of gastrinoma:</u> 0.4 mcg/kg by intravenous injection over 1 minute	
Secretin-Ferring <i>(Discontinued 7/99 per manufacturer)</i>	Porcine secretin for injection; 75 CU	<u>Test dose:</u> 0.1-1 CU <u>Pancreatic function testing:</u> 1 CU/kg by intravenous injection over 1 minute. <u>Diagnosis of gastrinoma:</u> 2 CU/kg by intravenous injection over 1 minute.	*LA/SA
—	Synthetic porcine secretin for injection; 16 mcg	<u>Test dose:</u> 0.2 mcg for potential allergic reaction <u>Pancreatic function testing:</u> 0.2 mcg/kg by intravenous injection over 1 minute <u>Diagnosis of gastrinoma:</u> 0.4 mcg/kg by intravenous injection over 1 minute	*LA/SA
Carafate	<b>Sucralfate;</b> Suspension: 1 g/10 mL Tablets: 1 g	1 g po QID.	*SA
Zanaflex	Tizanidine; Tablets: 2 mg and 4 mg	A single dose of 8 mg, may repeat q 6-8 hours, to a maximum of 3 doses in 24 hours.	*SA
Ocuflox	Ofloxacin; Ophthalmic solution 0.3 %	<u>Bacterial Conjunctivitis:</u> Day 1 and 2: 1-2 gtt. Q 2-4 hours, Day 3-7: 1-2 gtt. QID <u>Bacterial Corneal Ulcer:</u> Day 1 and 2: 1-2 gtt q 30 min., while awake. Day 3-7: 1-2 gtt q 1 hour, while awake. Day 7-9: 1-2 gtt QID	*SA

\*LA = Look-alike  
\*SA = Sound-alike

<sup>4</sup> Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

<sup>5</sup> Data provided by Thomson and Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com).

<sup>6</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

2. DDMAC – no objections

B. PRESCRIPTION ANALYSIS STUDIES

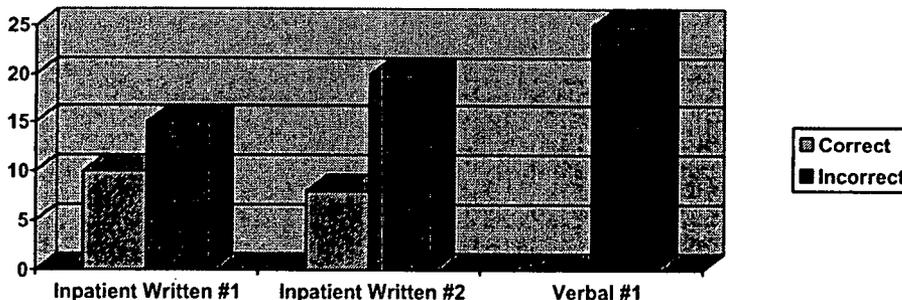
1. Methodology:

The studies conducted by OPDRA involved 116 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Secratix with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Written prescriptions, consisting of (known/unknown) drug products and a prescription for Secratix were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, verbal 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 the prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Inpatient #1: ↑, <u>Secratix</u> 12 mcg IV over 1 minute.	Inpatient #1: Increase, <u>Secratix</u> 12 mcg IV over 1 minute
Inpatient #2: ↑: <u>Secratix</u> 12 mcg IV over 1 minute.	

2. Results:

Study	# of Participants	# of Responses	<u>Secratix</u> Response	Other Responses
Inpatient Written #1	39	25 (64 %)	10 (40 %)	15 (60 %)
Inpatient Written #2	39	28 (72 %)	8 (29 %)	20 (71 %)
Verbal	38	25 (66 %)	0 (0 %)	25 (100 %)
Total	116	78 (67 %)	18 (23 %)	60 (77 %)



Since Secratix is a diagnostic agent and would not be dispensed in an outpatient setting, written studies, which normally consist of inpatient and outpatient prescriptions, were conducted with only inpatient prescriptions. Both studies consisted of the same drug order, but two different handwriting samples were utilized.

Among participants in the two written prescription studies, 35 of 53 (66 %) participants interpreted the name incorrectly. However, most of the incorrect interpretations were misspelled variations of the proprietary name and none of the incorrect responses were of marketed products. Six (6) participants interpreted the name as *Secratiux*, five (5) participants interpreted the name as Secratix and four (4)

participants interpreted the name as *Sicuflux*. Other interpretations include, /

Among the verbal prescription study participants, 25 of 25 (100 %) participants interpreted the name incorrectly. *One participant interpreted the name as Ciproflox, which is similar to an approved established name, ciprofloxacin.* Other interpretations were phonetic variations of the proprietary name. Seven participants interpreted the name as *Cecoflex*. Other interpretations include *Cecaflux, Cicaflex, Circoflex, Cecaflex, Cicoflex, Cekoflex, Cecoflox, Fecoflex, Cycloflox,* and

### C. SAFETY EVALUATOR RISK ASSESSMENT

1. In reviewing the proprietary name, — the expert panel identified Secretin-Ferring, —, sucralfate, Zanaflex, and Ocuflux. *Of these products, Secretin products were considered by the OPDRA expert panel to be most significant. We conducted prescription studies to simulate the prescription ordering process in order to detect potential medication errors. There was a suggestion that — could be confused with ciprofloxacin, an established name of Cipro. One respondent from the verbal study provided ciproflox as an interpretation.* Although there are limitations to the predictive value of these studies, primarily due to a small sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the U.S. population. Other misinterpretations did not overlap with any other currently approved drug names. The majority of the incorrect interpretations of the written and the verbal studies were misspelled/phonetic variations of the proposed name, —

One respondent from the verbal study interpreted the name as *Ciproflox, a name similar to ciprofloxacin.* However, — and ciprofloxacin differ in strength, dose, and dosing interval. Cipro is supplied as tablets (100 mg, 250 mg, 500 mg, and 750 mg), oral suspension (5% and 10%), otic solution, and injection (200 mg and 400 mg). Cipro products are usually dosed twice daily. — is only available as 16 mcg lyophilized powder and needs to be reconstituted. In addition, — is given over 1 minute during a *diagnostic procedure*. Given the above differences in strength, dose, and dosing interval in combination with the lack of convincing sound-alike potential, there is insufficient evidence at this time to conclude that the proposed drug would be confused with ciprofloxacin.

The proposed name, — and the currently marketed product, sucralfate, — according to the expert panel. However, there is a low risk of confusion between — and sucralfate, because these two products share no commonalities other than similar names. Sucralfate is an established name for the approved product, Carafate. Sucralfate is indicated in the treatment and maintenance therapy of duodenal ulcer. It is available as 1 g tablets and 1 g/10 mL oral suspension and the usual dose is 1 g four times daily. — is available as 16 mcg lyophilized powder and needs to be reconstituted. In addition, — is given over 1 minute during a *diagnostic procedure*.

The proposed proprietary names, — and the currently available name, Zanaflex, — according to the expert panel, because: — However, the — differ enough to distinguish one name from another. In addition, — and Zanaflex differ in dosage form, strength, and dose. Zanaflex, which contains tizanidine, is a short-acting drug for the management of spasticity. It is available as 4 mg and 8 mg tablets. The usual dose is a single dose of 8 mg, which may be repeated q 6-8 hours.

The expert panel also mentioned Ocuflux as a sound-alike name to the proposed name, —, because the suffixes “ — ” and “flox” sound similar. However, the prefixes “Ocu” and “ — ” differ enough to

distinguish one name from another. In addition, \_\_\_\_\_ and Ocuflax differ in dosage form, strength, and dose. Ocuflax, which contains ofloxacin, is indicated for the treatment of bacterial conjunctivitis and corneal ulcers. It is available as 5% otic solution.

The primary concern regarding the proposed name is that \_\_\_\_\_ sounds and looks similar to the "Secretin" products. OPDRA previously reviewed the name, \_\_\_\_\_ which contains synthetic porcine secretin, in August 2000 and the name was found to be objectionable (OPDRA consult #00-0160). Secretin-Ferring, which contains biologically derived porcine secretin, has been discontinued from the market in July 1999. Therefore, the risk of confusion with the proposed name, \_\_\_\_\_ is not significant.

*Given the above findings, we do not object to the use of the proprietary name, \_\_\_\_\_*

2. In our previous consult (00-0177), OPDRA expressed safety concerns regarding the dosing of the proposed product. Synthetic human secretin (\_\_\_\_\_ is dosed in micrograms and not in clinical units (CU), which was used in Secretin-Ferring. We were concerned that introducing a new dosing unit may cause confusion for health practitioners who are familiar with Secretin-Ferring. After reviewing the sponsor's response, we no longer recommend clinical units (CU) for the following reasons:
  - a. The biologically derived porcine secretin, such as Secretin-Ferring, has been discontinued from the United States market since July 1999. Therefore, ChiRhoClin products, synthetic porcine secretin and synthetic human secretin, have been available for investigation use. The sponsor has conducted all clinical studies using microgram dosing and these studies have been published in medical journals. According to the sponsor, "for the past four years, physicians have not had difficulty using 0.2 mcg/kg or 0.4 mcg/kg instead of 1 or 2 CU/kg." Since, the medical community is familiar with the microgram-dosing; we agree with the sponsor that changing the "units would be confusing to the medical community."
  - b. The Adverse Event Reporting System (AERS) was searched using the search terms, *secretin%*, and \_\_\_\_\_ % for any medication error reports of the drug. *The search results did not reveal any medication error reports for secretin products.*

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

See consult number 00-0177-1, which was completed on September 13, 2001.

**IV. RECOMMENDATIONS:**

OPDRA has no objection to the use of the proprietary name, \_\_\_\_\_

OPDRA 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 Hye-Joo Kim at 301-827-0925.

/s/

\_\_\_\_\_  
Hye-Joo Kim, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

/s/

\_\_\_\_\_  
Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

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/s/

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Hye-Joo Kim  
9/21/01 01:49:34 PM  
PHARMACIST

Jerry Phillips  
9/21/01 01:56:15 PM  
DIRECTOR

Martin Himmel  
9/21/01 02:13:03 PM  
MEDICAL OFFICER

9/14/01

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED: 8/03/01**      **DUE DATE: 11/14/01**      **OPDRA CONSULT #: 00-0177-1**

**TO:**  
Lilia Talarico, M.D.  
Director, Division of Gastro-Intestinal and Coagulation Drug Products  
(HFD-180)

**THROUGH:**  
Melodi McNeil  
Project Manager  
(HFD-180)

**PRODUCT NAME:** Synthetic Human Secretin for Injection  
**NDA #:** 21-256

**MANUFACTURER:**  
ChiRhoClin, Inc.

**SAFETY EVALUATOR:** Hye-Joo Kim, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), OPDRA reviewed the proposed container label, carton labeling, and package insert of synthetic human secretin for possible interventions that may help minimize medication errors.

**OPDRA RECOMMENDATION:** OPDRA recommends the implementation of the proposed labeling in conjunction with the labeling revisions outlined in the review in order to minimize the potential for medication errors.

/S/

/S/

Jerry Phillips, R.Ph.  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3246  
Fax: (301) 480-8173

Martin Himmel, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B-32  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE REVIEWED:** September 12, 2001  
**NDA#:** 21-256  
**NAME OF DRUG:** Synthetic Human Secretin for Injection  
**NDA HOLDER:** ChiRhoClin, Inc.

**I. INTRODUCTION:**

This consult is in response to a August 3, 2001 request, by the Division of Gastrointestinal and Coagulation Drug Products, to re-review the container label, carton labeling and package insert for possible interventions in minimizing medication errors. OPDRA originally reviewed the container label, carton labeling and package insert in our October 2000 consult (# 00-0177) under the proprietary name, \_\_\_\_\_ OPDRA found the name, \_\_\_\_\_ unacceptable. The sponsor proposed another proprietary name, \_\_\_\_\_ for this product. The name, \_\_\_\_\_ will be reviewed and submitted to your Division (consult # 01-183) in the near future.

**PRODUCT INFORMATION**

Synthetic human secretin 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 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. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

In the review of the container label, carton labeling, and the package insert of synthetic human secretin, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has identified the following areas of possible improvement, which might minimize potential user error.

**A. CONTAINER LABEL**

1. We recommend revising the statement, "Caution: Federal law prohibits dispensing without prescription" to "Rx Only" per FDA Modernization Act of 1997. Revising this statement would also increase available label space.
2. We recommend adding the strength, 16 mcg, on the front of the label, below the proprietary and established names.

3. We recommend revising the "contains secretin 16 mcg.." statement by changing "secretin" to "synthetic human secretin".
4. The established name should be revised to reflect that this is a lyophilized dosage form. In accordance with the USP, the name should include "for Injection." We also recommend adding the parenthesis around the established name as follows:

(Synthetic Human Secretin for Injection)

#### B. CARTON LABELING

1. We recommend that the reconstitution instructions and the expression of the strength (*2 mcg/mL after reconstitution*) be included on the carton, as there is sufficient label space.
2. Since the same manufacturer has proposed both the synthetic human and porcine secretin products, we recommend that the labeling for these two drugs appear distinctively different in order to prevent confusion between these two drug products.
3. We recommend adding the statement, "For Intravenous Use Only", on the front of the carton labeling.
4. See comments under CONTAINER LABEL.

#### C. PACKAGE INSERT

##### 1. General Comment

- a. Based on our postmarketing experience with medication error reports, we recommend the expression of the strength of "µg" be changed to "mcg" *throughout* the package insert.
- b. Please delete terminal zero when specifying quantity of Sodium Chloride Injection USP to be used for reconstitution. Specifically, "8.0 mL" should be designated as "8 mL". Including terminal zeros increases the risk of 10-fold dosing errors occurring. See also "Dosage and Administration" for this same correction.
- c. The *INDICATION* section is listed twice in the insert. We recommend deleting the first *INDICATION* section that is located above the *DESCRIPTION* section.

##### 2. Dosage and Administration

- a. \_\_\_\_\_
- b. The statement, \_\_\_\_\_ is unclear.  
Please specify how long the proposed product is stable after the reconstitution.
- c. \_\_\_\_\_

3. How Supplied

In the statement, "Synthetic human secretin is supplied as a lyophilized sterile powder in 10 mL vials containing 16 ug.", delete "in 10 mL". This information is not necessary and may be confusing to the staff preparing a product with 8 mL of diluent, as synthetic human secretin is supplied as a powder, not a liquid.

**IV. RECOMMENDATIONS:**

OPDRA recommends the implementation of the proposed labeling in conjunction with the labeling revisions outlined above in order to prevent the potential for medication errors. This review supersedes our original OPDRA consult number 00-177.

OPDRA 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 Hye-Joo Kim at 301-827-0925.

/s/

---

Hye-Joo Kim, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

/s/

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Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

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/s/

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Hye-Joo Kim  
9/14/01 09:24:42 AM  
PHARMACIST

Jerry Phillips  
9/14/01 09:27:06 AM  
DIRECTOR

Martin Himmel  
9/14/01 02:46:01 PM  
MEDICAL OFFICER

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Marci C. Kiester  
9/18/01 02:58:28 PM  
UNKNOWN

## MEMORANDUM OF TELECON

DATE: September 13, 2001

APPLICATION NUMBER: NDA 21-256, Synthetic Human Secretin for Injection

**BETWEEN:**

Name: Edward D. Purich, Ph.D., Chief Executive Officer  
Phone: (301) 384-1554  
Representing: ChiRhoClin, Inc.

**AND**

Name: Brian Strongin, R.Ph., M.B.A., Regulatory Health Project Manager  
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Response to August 10, 2001 Information Request Letter

### Background

NDA 21-256 for Synthetic Human Secretin, submitted March 16, 2000, provides for the following indications: (1) diagnostic use in pancreatic dysfunction; (2) (3) diagnosis of gastrinoma; and, (4) the facilitation of papilla during ERCP. A refuse-to-file letter for all indications, citing clinical deficiencies, was sent May 11, 2000. The sponsor submitted a June 14, 2001 resubmission requesting approval for indications #1, #3, and #4 only. An information request letter was sent August 8, 2001 and included pharmacology/toxicology, clinical, statistical, CMC, and biopharmaceutics requests.

### Today's Call

I asked Dr. Purich for an estimate of when his response to the August 8 letter would be submitted. He replied that they were working on the response and it would be submitted toward the week of September 17, 2001. The call was then concluded.

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/s/

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Brian Strongin  
9/13/01 03:48:57 PM  
CSO

**Wilson, Helen A**

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**From:** Neal Sweeney 301-827-7340 FAX 301-827-3084 [SWEENEYN@cder.fda.gov]  
**nt:** Wednesday, September 12, 2001 2:23 PM  
**o:** stronginb  
**Cc:** mcneilm; wilsonh; Neal Sweeney  
**Subject:** Human Secretin Team Meeting  
  
**Sensitivity:** Confidential

Brian,

I cannot attend this afternoon's Human Secretin team meeting. Thus far I have no approval issues, as the applicant has cited DMF [redacted] which was previously reviewed in support of NDAs 21-136 and 21-209. I expect to have the microbiology review completed by mid-October.

-Neal Sweeney  
Microbiology Reviewer

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## MEMORANDUM OF TELECON

DATE: August 30, 2001

APPLICATION NUMBER: NDA 21-256, Synthetic Human Secretin for Injection

BETWEEN:

Name: Dr. Edward Purich, Chief Executive Officer

Phone: (301) 384-1554

Representing: ChiRhoClin, Inc.

AND

Name: Ms. Melodi McNeil, Regulatory Health Project Manager  
Dr. Art Shaw, Review Chemist  
Dr. Liang Zhou, Chemistry Team Leader  
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: CMC Information Requests

BACKGROUND: Pending NDA 21-256 is currently under review in the Division. It proposes marketing approval of synthetic human secretin for injection as a GI diagnostic. The purpose of today's teleconference was to convey the CMC information requests listed below.

TODAY'S PHONE CALL: Dr. Shaw said he could not locate the following items in the application and asked that the firm submit them as soon as possible:

1. A full physical and chemical characterization of the drug substance (see the March 24, 2000 letter for NDA 21-236). This characterization should include, but not necessarily be limited to, solubility (in a number of solvents), stability (with a number of treatments, such as acid, base, oxidation), isoelectric pH (theoretical and experimental), and solution pH. (Alternatively, provide data demonstrating that this characterization cannot be done.)
2. A comparison between drug substances manufactured at \_\_\_\_\_ and \_\_\_\_\_
3. Results of experiments measuring the limit of quantitation and limit of detection for \_\_\_\_\_ (drug substance degradants).

The call was then concluded.

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\_\_\_\_\_  
Melodi McNeil  
Regulatory Health Project Manager

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/s/

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Melodi McNeil  
11/27/01 04:08:34 PM  
CSO

## MEMORANDUM OF TELECON

DATE August 20, 2001

NDA NUMBER: 21-256

BETWEEN: Edward Purich, Ph.D.

Representing ChiRhoClin  
Phone Number 301-989-0049

AND

Name: Arthur B. Shaw, Ph.D.  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: I called Dr. Purich to request some information that is missing from this NDA. I also told him we would be calling him next Monday, August 27, 2001 to discuss review issues, specifically related to the assay of the drug product.

The missing information requested was:

1. Pages 63 and 64 were copied poorly in the submission. He will send corrected pages.
2. I asked for the specifications for the solvents and reagents used by \_\_\_\_\_ the synthesis.
3. I asked for a clarification of the \_\_\_\_\_  
Specifically I asked for the page number for the batch records for the \_\_\_\_\_  
and for any missing \_\_\_\_\_ records. He said that would take some time to obtain from \_\_\_\_\_ but that he would obtain that information.

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TELECON

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/s/

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Arthur B. Shaw  
8/20/01 04:05:38 PM  
CHEMIST



NDA 21-256

**INFORMATION REQUEST LETTER**

ChiRhoClin, Inc.  
Attention: Edward D. Purich, Ph.D.  
15500 Gallaudet Ave  
Silver Spring, MD 20905-4176

8/10/01

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.

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

1. Pharmacology/Toxicology:

Provide information on any other preclinical toxicology studies (of which you have knowledge), using your drug product.

2. Clinical:

Provide an integrated summary of safety for the entire database of synthetic human secretin including the current NDA and any IND or NDA studies. This summary should include blood pressure data. Alternatively, please tell us where these data can be located in the June 14, 2001 resubmission by referencing a specific volume and page number.

3. Clinical Statistical:

- a. Please provide data sets (refer to the guideline entitled, "Regulatory Submissions in Electronic Format: New Drug Applications [see [www.fda.gov/cder/guidance/index.htm](http://www.fda.gov/cder/guidance/index.htm)]) on the following demographic and efficacy variables, separately for each of the three studies **CRC98-1**, **CRC98-2**, and **CRC99-9**:

PATNO – Patient number  
STUDYN - Study number  
TRT – Treatment  
PERD – Period for crossover design  
GEND – Gender  
RACE  
AGE

WEGT – Weight

HEIGT - Height

V\_B – Baseline volume of pancreatic fluid (mL)

BC\_B – Baseline bicarbonate concentration (mEq/L)

V\_15 - Volume of pancreatic fluid (mL) for 0 - 15 minutes

BC\_15 – Bicarbonate concentration (mEq/L) for 0 – 15 minutes

V\_30 - Volume of pancreatic fluid (mL) for 15 - 30 minutes

BC\_30 – Bicarbonate concentration (mEq/L) for 15 - 30 minutes

V\_45 - Volume of pancreatic fluid (mL) for 30 - 45 minutes

BC\_45 – Bicarbonate concentration (mEq/L) for 30 – 45 minutes

V\_60 - Volume of pancreatic fluid (mL) for 45 - 60 minutes

BC\_60 – Bicarbonate concentration (mEq/L) for 45 - 60 minutes

V\_1\_60 - Volume of pancreatic fluid (mL) for 1 - 60 minutes

BC\_1\_60 – Bicarbonate concentration (mEq/L) for 1 - 60 minutes

B\_TBC – Total bicarbonate baseline adjusted (mEq) for 0 – 60 minutes

TBC - Total bicarbonate (mEq) for 0 – 60 minutes

- b. Please provide the programs used to perform the statistical efficacy analyses described in Volume 29, using data sets described in point “a” (above) separately for each of the three studies **CRC98-1**, **CRC98-2**, and **CRC99-9**. The programs provided should be able to read data from “a” (above) and recreate the analysis results contained in pages 430 to 533, pages 568 to 612, and pages 620 to 741 in Volume 29 of the June 14, 2001 submission. Please add additional variables if needed.
  - c. Please provide data sets on the efficacy variables listed in Table 2, page 550, in Volume 29, along with their program for studies **CRC99-8** and **CRC97-2**. Leave one space between two adjacent variables and provide a text description for each variable on the data diskettes. The submitted programs should be able to read data from the submitted data file and recreate the analysis results contained in pages 547 and 548 in Volume 29 of the June 14, 2001 submission.
  - d. Please provide data sets on the efficacy variables listed in pages 748 and 749, in Volume 29, along with its program for study **CRC98-4**. Provide a text description for each variable on the data sets. The programs provided should be able to read data from the submitted data file and recreate the analysis results contained in pages from 750 to 789 in Volume 29 of the June 14, 2001 submission.
4. Chemistry, Manufacturing, and Controls:
- a. Please revise the form FDA 356h to include all referenced DMFs.
  - b. Add impurity specifications to the drug product.
  - c. Submit the validated stability assay.

5. Biopharmaceutics:

You have submitted stability data for samples in plasma considering the susceptibility of secretin to \_\_\_\_\_ degradation. However, synthetic human secretin, like any other secretin, is expected to \_\_\_\_\_ This \_\_\_\_\_ could affect the amount of hormone administered or assayed. You have included L-cysteine HCl in the product formulation, which \_\_\_\_\_ however no data were provided to support this claim. Please either provide these data, or provide the location in your resubmission by referencing a specific volume and page number.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, RN, MSN  
Chief, Project Management Staff  
Division of Gastrointestinal & Coagulation Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/

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Melodi McNeil  
8/8/01 11:35:19 AM  
Signed for J. DuBeau.