cc:
NDA 21-136
HFD-180/Div.Files
HFD-180/L.Goldkind
A.Shaw
T.Chakraborti
HFD-715/W.J.Chen
HFD-870/A.Sancho

Drafted by: BKS/July 27, 1999
R/d init: LT/July 27, 1999
Final: BKS/July 27, 1999
Filename: minutes/21136907.0

12 Page(s) Withheld

D.F.

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 18, 1998

Time: 3PM – 5PM

Location: Parklawn Building, Conference Room "O"

Application: IND 54,196 for Synthetic Porcine Secretin

Type of Meeting: Pre-NDA

Meeting Chair: Lilia Talarico, M.D.

Meeting Recorder: Brian Strongin

FDA Attendees, Titles, and Office/Division:

The Division of Gastrointestinal and Coagulation Drug Products

Lilia Talarico, M.D.	Director
Hugo Gallo-Torres, M.D., Ph.D.	Team Leader, Medical
John Senior, M.D.	Medical Officer
Thomas Holzbach, M.D.	Medical Officer
Eric Duffy, Ph.D.	Team Leader; Chemistry, Manufacturing and Controls
Art Shaw, Ph.D.	Review Chemist
Jasti Choudary, B.V.Sc., Ph.D.	Team Leader; Pharmacology and Toxicology
Tim Robison, Ph.D.	Review Pharmacologist

Division of Biometrics II

A.J. Sankoh, Ph.D.	Acting Team Leader, Biometrics

Division of Pharmaceutical Evaluation II

David Lee, Ph.D.	Team Leader, Biopharmaceutics

Office of Orphan Products Development

Michael Dreis	Senior Reviewing Pharmacist

Office of the Commissioner, Office of Health Affairs

Freddie Ann Hoffman, M.D.	Deputy Director

External Constituent Attendees and Titles:

Seymour Fein, M.D.	Chairman, ChiRhoClin, Inc.
Edward Purich	CEO. ChiRhoClin, Inc.

Background:

IND 54,196 was submitted September 12, 1997 to investigate synthetic porcine secretin , as a diagnostic agent for pancreatic exocrine , and

Secretin extracted from porcine intestine has been approved since 1981 for the diagnosis of pancreatic exocrine disease and Zollinger-Ellison Syndrome and as an adjunct in obtaining desquamated pancreatic cells for cytopathologic examination. The submission included three draft protocols. The first, Protocol CRC97-1, was for a Phase I study entitled, "A Double-Blind, Placebo Controlled, Randomized, Four-Treatment Latin Square Crossover, Dose-Response, Pharmacodynamic Study of Intravenous Synthetic Porcine Secretin Administration in Normal Healthy Subjects". The second, Protocol CRC97-2 entitled, "Synthetic Porcine Secretin Treatment IND Protocol" is a Phase II/III study of synthetic porcine secretin The third, Protocol CRC97-3, is a proposed patient study to evaluate the use of synthetic porcine secretin for the prevention of post-ERCP pancreatitis.

Meeting Objectives:

1. to review and discuss the planned synthetic porcine secretin NDA in terms of the adequacy of the CMC, Pharm-Tox, and clinical sections

2. to review and discuss the preferred formatting of individual reports and sections of the document as well as the overall NDA

3. to establish the preferred mechanics of interaction and communication between ChiRhoClin and FDA to facilitate the NDA review

Discussion Points:

1. The firm briefly reviewed the amino acid sequencing, formulation, biological and chemical assays, completed and planned toxicology studies, proposed indications, the relationship between the biologically derived and synthetic porcine secretins, and the clinical studies to be submitted in support of the NDA. The firm explained that the NDA

2.

3. The firm's questions included in the background package were discussed.

Decisions Reached:

The firm's questions are italicized below, followed by the Agency's responses.

Chemistry, Manufacturing, and Controls

1. *has synthesized the 27 amino-acid peptide, porcine secretin, utilizing rocedures in accordance with the FDA guidance (CDER/CBER "Guidance for Industry for the submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances") as defined in Section 2. The purification procedures are in complete compliance with section 2 of the guidance. The testing procedures of the final product are in accordance with section 4 of the document and this should assure the identity and purity of the final peptide. A detailed description is contained in part 2 of this document with the complete documentation provided in IND 54,196, Submission 002. ChiRhoClin intends to provide the entire submission contained in IND 54,196 as the complete documentation to the NDA for the drug substance. Does the FDA agree that this is fully adequate?*

   Based on the information presented, if the Guidance is followed, the planned submission appears to be adequate. It is not our practice at this time to perform as thorough and complete a review of IND submissions as performed for NDA submissions. Complete information must be submitted to the NDA, not referenced from the IND. Dr. Shaw stated his preference for this information to be submitted to the NDA rather than referenced in a drug master file.

2. *Inc. synthesized porcine secretin in complete compliance with current Good Manufacturing Procedures. They are continuing to plan improvements in the purity of the bulk drug (currently and develop methods to characterize impurities, which represent less than of the total. As part of the cGMP procedures they are monitoring the stability of the bulk drug substance when stored at -20°C. Does the FDA desire to provide input for this on going effort as part of NDA approval process or as a condition for approval?*

The Division will work with you on drug substance manufacturing and scale-up issues if requested. The importance of characterizing as well as quantifying impurities present in the drug substance is emphasized.

3. *Based on its experience with synthesizing peptides, including porcine secretin, , expects its procedures to be able to Does the FDA agree that this synthetic procedure for porcine secretin can be ? Will similar support documentation, as provided for this NDA, be adequate to characterize .he synthesis of porcine secretin?*

You must provide a demonstration that the drug substance synthesis is

4. *Based on the intention to submit to the NDA the complete batch production records, purification, and testing procedures contained in IND 54,196 for the porcine secretin drug substance, does the FDA agree that this portion of the NDA is complete?*

See the response to question #1.

5. *Does the FDA have any additional comments associated with the porcine secretin drug substance?*

The drug substance manufacturing and testing methods, and the impurity profiles for the development through clinical batches should be compared, and the differences highlighted. We recommend following the appropriate Guidances.

6. *manufactured the porcine secretin in strict compliance with cGMP. The IND 54,196 contains the batch production records, testing procedures and results. These documents will be submitted to the NDA to support the manufacture of the parenteral porcine secretin product. Does the FDA have any questions or criticisms of this document? Is it fully adequate for NDA approval?*

See the response to question #1.

7. *[redacted] has conducted additional support studies for porcine secretin that included, validation of the HPLC assay for porcine secretin; [redacted] study for porcine secretin; Recovery study; and Stability study (on going) for the final product. Does the FDA agree that these studies and their results should be submitted to the NDA?*

With the exception of the current Good Manufacturing Practices (cGMP) validation studies (i.e., [redacted] study for porcine secretin), the listed studies should be submitted to the NDA. It is unnecessary to submit cGMP validation studies to the NDA.

8. *ChiRhoClin has validated an HPLC assay for porcine secretin and the biological cat assay that is currently the release assay for the biologically sourced porcine secretin. While the HPLC assay is quite useful for the high purity synthetic porcine product, it is unable to deal with the porcine intestinal peptides and proteins found in the currently approved biologically sourced product. It is the intention of ChiRhoClin to utilize the HPLC assay as the release assay for synthetic porcine secretin. Does the FDA agree?*

At this time, the biological cat assay is necessary in conjunction with the HPLC assay. Since secretin is a peptide product with the potential for a secondary structure, it is important to include the bioassay. We recommend that a more discriminating method be developed.

9. *The parenteral formulation for synthetic porcine secretin contains the active drug in the [redacted] (Mannitol and Cysteine). These excipients are common to many parenteral products and have been utilized in QC release procedures to evaluate component materials, and for the evaluation of production equipment. [redacted] has utilized these excipients in studies to test [redacted] in compliance with FDA requirements for [redacted]. Included in these studies are [redacted] has utilized the results of these studies to [redacted] has agreed to provide the "Right of Reference" to its DMF that contains the results of these studies. [redacted]'s also indicated that they may be willing to provide the relevant test results for inclusion in the NDA. Will the "Right to Reference" [redacted] DMF be sufficient for these studies or would the FDA prefer the studies be included in the NDA?*

Studies demonstrating compatibility of materials with [redacted] should be submitted in the NDA. It will also be necessary to demonstrate [redacted] This compatibility is necessary for the maintenance of a constant, consistent formulation and is an important characteristic of a well designed manufacturing process.

Non-clinical Pharmacology and Toxicology Section

1. *Acute toxicology studies at 50 to 100 fold the human dose of synthetic porcine secretin in mice and rabbits have been completed and filed to the IND.*

ChiRhoClin believes these two studies fully satisfy the required toxicology testing for the NDA and for approval of the single dose diagnostic indications. Does the FDA share this assessment?

No. The Agency's requirements for Pre-clinical data submitted in support of a NDA are often more stringent than the requirement for data submitted in support of an IND.

Based upon the guidance entitled, "Single Dose Acute Toxicity Testing for Pharmaceuticals" (Federal Register Notice Volume 61, Number 166, August 26, 1996), your acute toxicity studies in mice and rabbits submitted February 21, 1998 were inadequate to serve as primary safety data in support of single dose studies in humans for the following reasons: dose-response relationships and pharmacokinetics were not assessed, and clinical pathology (hematology, blood chemistry, urinalysis, etc.) and histopathology parameters were not monitored at an early time and at termination. In addition, the number of animals employed in the rabbit experiment was inadequate and compliance with Good Laboratory Practices and Quality Assurance regulations was not indicated.

Preclinical toxicology studies required to support the proposed NDA should include a two-week repeat intravenous dose toxicity study in a rodent and a nonrodent species. The studies should employ at least three doses. Dose selection should be based on acute toxicity testing and such that the high dose should evince some toxicity. It is recommended that preliminary studies be conducted to assess potential dose-limiting problems, and adjustments be made if necessary. All toxicological parameters, i.e., clinical signs, body weight, food consumption, mortality, hematology, blood chemistry, urinalysis, organ weights, gross pathology and histopathology, etc. should be completely assessed. The study should comply with GLP regulations and quality assurance. We recommend consulting the ICH Guidance for Industry entitled, "S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (July 1997) and "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" (November 1997).

2. *Multiple cat-bioassay experiments on the bulk active substance and finished product of synthetic porcine secretin in comparison to the biologically derived porcine secretin have been completed and filed to the IND. The assay has been fully validated.*

ChiRhoClin believes these studies fully satisfy the requirements for NDA approval. Since synthetic porcine secretin is a pure peptide product, ChiRhoClin

believes that the cat bioassay will not be a required test for the commercial product. Does the FDA agree that the HPLC assay should be used as the release assay?

See the response to CMC question #8.

3. *ChiRhoClin does not believe there are any other requirements or issues in the non-clinical pharmacology and toxicology areas for the planned NDA. Does the FDA agree?*

See the response to Pharm/Tox question #1.

Clinical Section

1. *The clinical program for synthetic porcine secretin consists of the volunteer subject study (CRC97-1), the chronic pancreatitis patient study (CRC98-1), and the ERCP study (CRC97-3) for additional safety data.*

ChiRhoClin believes these studies establish the diagnostic efficacy, safety and dosing guidelines for synthetic porcine secretin for the diagnostic indications and with the published literature on porcine secretin, which provided the basis for approval of the biologically derived drug, fully satisfy the requirements for NDA approval. Does the FDA concur with this assessment?

Any decision regarding the approvability of an application is based on the data for your product submitted in the NDA. It is premature at this time to make any conclusions regarding approvability. Since efficacy for the proposed NDA is to be supported by a small database consisting of only 24 patients in two studies, it is possible that more support may be needed. It may be necessary to submit clinical data, including data regarding the sensitivity and specificity, in support of the efficacy of your product for each requested indication. If literature is provided in support of efficacy, it must be from studies using your product or bioequivalence between the product used and your product must be demonstrated. Source documents from the referenced studies must be provided as well.

Literature for studies utilizing the porcine derived product may be submitted as background information, but cannot serve as the basis for approval.

Since the safety data from Study CRC 97-3 are blinded, it will be impossible to determine if adverse reactions are due to synthetic porcine secretin, a disease state, or a complication of ERCP. It may, therefore, be necessary to use a conservative approach in the evaluation of that data and attribute all adverse reactions to synthetic porcine secretin. It is acceptable to develop a stopping rule based on safety parameters and to use a data safety monitoring board to review blinded safety data.

2. *Since the two pharmacodynamic studies contain a total of 24 subjects, ChiRhoClin plans to provide the Case Report Forms of each subject. What additional listings will the FDA require?*

Please clarify if these studies are pharmacodynamic studies or pharmacokinetic studies as well. In the latter case, we need to see plasma concentration versus time data and other conventional parameters to fully characterize the pharmacokinetic profile of the drug. It appears that the parameters of total volume, bicarbonate concentration, and bicarbonate output are adequate to characterize the pharmacodynamic profile of the drug.

3. *The ERCP study's demographics and AEs will be provided for safety. Does the FDA want a particular format for those listings?*

Please follow the recommendations stated in the guidance entitled, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" dated July 1988.

Human Pharmacokinetics and Bioavailability Section

1. *Human pharmacokinetics for porcine secretin (biologically derived and synthetic) are provided by published papers submitted to the IND.*

ChiRhoClin believes these published data fully satisfy the pharmacokinetic requirements for NDA approval of synthetic porcine secretin. Since the final product is a solution, which is administered via intravenous bolus and infusion, no bioequivalence problem is expected for this formulation. Therefore, characterization of the pharmacokinetic profile after intravenous administration should be sufficiently documented by the published papers. Does the FDA agree with this conclusion?

No. The submitted literature are not pharmacokinetic studies. Studies CRC 97-1 and 98-1 will be reviewed as pharmacodynamic studies. It is necessary to demonstrate that your drug product has the same pharmacokinetic profile as the approved drug product. Please refer to 21 CFR 320.24(b)(1)(i) for additional requirements or provide justification for a waiver per section 320.22.

Minutes Preparer: LSI 12/15/98

Chair Concurrence: LSI 12-15-98

Attachments/Handouts

cc:
IND 54,196
HFD-180/Division File
HFD-180/Meeting Minutes File
HFD-180/CSO
HFD-180/Reviewers & Attendees

Draft: BKS/December 14, 1998
R/d Init: LT/December 15, 1998
Final: BKS/December 15, 1998
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MEETING MINUTES

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CONSULTATION RESPONSE

Division of Medication Errors and Technical Support
Office of Drug Safety
(ODS; HFD-400)

DATE RECEIVED:	DUE DATE:	ODS CONSULT #:
February 25, 2002	April 5, 2002	02-0028

TO: Victor Raczkowski, M.D.
Acting Director, Division of Gastro-Intestinal and Coagulation Drug Products
(HFD-180)

THROUGH: Alice Kacuba
Project Manager
(HFD-180)

PRODUCT NAME:	MANUFACTURER:
SecreFlo (synthetic porcine secretin for injection) 16 mcg/vial NDA #: **21-136** and **21-209**	ChiRhoClin, Inc.

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

SUMMARY: In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, SecreFlo, to determine the potential for confusion with approved proprietary and established names as well as pending names.

METS RECOMMENDATION: DMETS has no objections to the use of the proposed proprietary name SecreFlo provided that ***only one name***, SecreFlo (NDA 21-136 and 21-209) **or** — (NDA 21-256), is approved. The acceptability of the proposed proprietary name SecreFlo depends on which application, SecroFlo or — receives approval first, as these two proprietary names may not coexist due to their similarities. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

DMETS 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, labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
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/S/

Jerry Phillips, RPh
Associate Director
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Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 7, 2002

NDA: 21-136 and 21-209

NAME OF DRUG: SecreFlo (synthetic porcine 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 Gastro-Intestinal and Coagulation Drug Products for assessment of the proposed proprietary drug name, SecreFlo, regarding potential name confusion with other proprietary and/or established drug names.

SecreFlo is the *third* proposed proprietary name for this product. DMETS previously reviewed the name, [redacted] on January 18, 2000, and had *no objections* to the use of the name (OPDRA consult 99-104). However, according to the Division of Gastrointestinal and Coagulation Drug Products, the applicant decided to pursue the proprietary name. [redacted] instead of [redacted] At the request of the Division, DMETS conducted a review of the proprietary name on August 12, 2000, and did not recommend the use of the name [redacted] (OPDRA consult 00-160).

PRODUCT INFORMATION

SecreFlo (synthetic porcine secretin for injection) is indicated for use as a diagnostic agent for the diagnosis of pancreatic exocrine dysfunction and gastrinoma. It is also used to facilitate the identification of the ampulla of vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP). Patients suffering from acute pancreatitis should not receive SecreFlo until the acute episode has subsided. SecroFlo should be prepared immediately prior to use. The contents of a vial (16 mcg of powder) are dissolved in 8 mLs of Sodium Chloride Injection, USP, to yield a concentration of 2 mcg/mL. An intravenous test dose of 0.2 mcg should be administered to screen for a potential allergic reaction. The recommended dose for exocrine pancreas function testing and for the identification of the ampulla of Vater and acessorry papilla during ERCP is 0.2 mcg/kg of body weight by intravenous injection over 1 minute. The recommended dose in the diagnosis of gastrinoma is 0.4 mcg/kg of body weight by intravenous injection over 1 minute.

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 that sound alike or look alike to "SecreFlo" 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 trademark electronic search system[4] (TESS) was conducted.
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 inpatient prescription studies 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 "SecreFlo". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Three product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with SecreFlo. These products are listed in Table 1 along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

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

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
SecreFlo	Synthetic Porcine Secretin for Injection 16 mcg	*Exocrine pancreas function testing and identification of ampulla of Vater and accessory papilla during ERCP:* 0.2 mcg/kg by IV injection over 1 minute. *Diagnosis of gastrinoma:* 0.4 mcg/kg by IV injection over 1 minute.	
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.	L/A

[1] MICROMEDEX Healthcare Intranet Series, 2002, 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), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002)
[2] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=searchss&state=3hec6f.1.1
[5] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Cipro	Ciprofloxacin, Tablets: 100 mg, 250 mg, 500 mg, 750 mg Oral suspension: 5 mg/100 mL, 10 mg/100 mL Injection: 200 mg and 400 mg	Dose and duration vary according to type and severity of infection.	S/A
— *** *NDA status pending*	Synthetic human secretin for injection 16 mcg	*Pancreatic function testing:* 0.2 mcg/kg by intravenous injection over 1 minute *Diagnosis of gastrinoma:* 0.4 mcg/kg by intravenous injection over 1 minute	S/A, L/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
*** **NOTE: This review contains proprietary and confidential information that should not be released to the public.**

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of SecreFlo with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the name. These studies employed 112 health care professionals comprised of pharmacists, physicians, and nurses. This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff members wrote two inpatient order prescriptions, each consisting of a combination of marketed and unapproved drug products and a prescription for SecreFlo (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one DMETS staff member recorded a verbal inpatient prescription that was then delivered to a random sample of the participating health care professionals via telephone voicemail. 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.

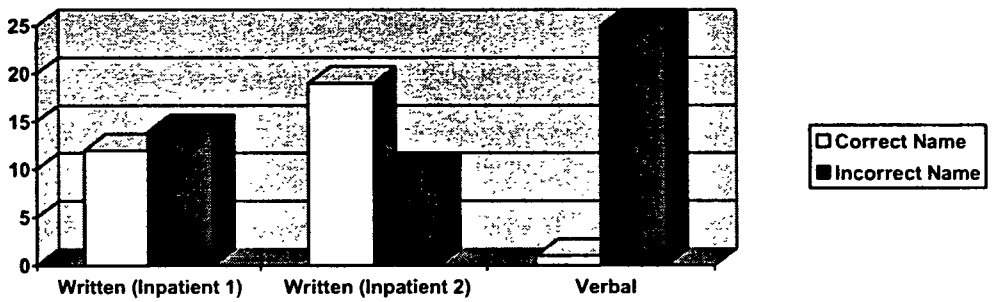
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient 1 RX: Then Ogive Secreflo 0.2 mcg IV, if no rxn give additional 24 mcg IV over 1 minute	SecreFlo Give SecreFlo 0.2 mcg IV, if no rxn, give additional 24 mcg IV over 1 minute
Inpatient 2 RX: give Secreflo 0.2 mcg IV, if no rxn give additional 24 mcg IV over 1 minute	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted SecreFlo	Incorrectly Interpreted
Written: Inpatient 1	38	26 (68%)	12 (46%)	14 (54%)
Inpatient 2	40	29 (73%)	19 (66%)	10 (34%)
Verbal	34	26 (76%)	1 (4%)	25 (96%)
Total	112	81 (72%)	32 (40%)	49 (60%)



Among the verbal inpatient SecreFlo prescriptions, 25 of 26 (96%) respondents interpreted the name incorrectly. Many of the incorrect name interpretations were misspelled variations of "SecreFlo". Incorrect interpretations included Secreflow, Cecaflow, Sequeflow, Secroflo, Secraflo, Cecloflow, Cikroflo, Sigoflo, Cecroflow, Cecraflow, Secuflo, Cicoflow, and Secraflow.

When examining the interpretations from the written inpatient prescriptions, 24 of 68 (35%) respondents interpreted the name incorrectly. Common incorrect responses were Secroflo, Sacriflo, Sacroflo, Sacreflo, Secrefto, Secretio, Secrefio, Secrefio, Ecrefio, Serefto, and Secretro, Secriflo. One respondent interpreted the proposed proprietary name as —— which is very similar to the proposed proprietary name —— (NDA 21-256)*** .

***** NOTE: This review contains proprietary and confidential information that should not be released to the public.**

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "SecreFlo", the primary concerns raised by the Expert Panel were related to two sound-alike, look-alike names that already exist in the U.S. marketplace and one that is currently under review by the Division. The products considered having the greatest potential for name confusion with SecreFlo were Cipro, Zanaflex and — NDA 21-256).

DMETS conducted prescription studies to simulate the prescription ordering process. One respondent from the written inpatient study (Inpatient 1 Rx) interpreted the name as — This interpretation, — , is very similar to the proposed proprietary name — (NDA 21-256). Other misinterpretations did not overlap with any 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, SecreFlo.

— s the proposed proprietary name for a gastrointestinal peptide hormone containing synthetic human secretin. Synthetic human secretin is indicated for diagnosis of pancreatic exocrine — and gastrinoma —), and for the facilitation of — 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. SecreFlo and — . not only sound similar, the drug names look similar when scripted (see sample below) varying only in the — In addition, these drug products have the same indication, strength, dosing regimen, dosage form, reconstitution directions and both will be stored in the freezer. Furthermore, the labeling and packaging of these two products may appear similar since they will be manufactured by the same company. *DMETS reviewed — (OPDRA consult 01-0183) on September 14, 2001, and did not object to the name. However, to date, the status of the — application has not been determined by the Division. The acceptability of the proposed proprietary name SecreFlo depends on which application, SecroFlo or — receives approval first, as these two proprietary names may not coexist due to their similarities.* ***Therefore, DMETS has no objections to the proposed proprietary name SecreFlo provided that only one name, SecreFlo or — is approved.***

Cipro is broad spectrum antimicrobial agent indicated in the treatment of infections caused by susceptible strains of designated microorganisms. Although SecreFlo and Cipro sound similar, the drug names do not look similar when scripted. SecreFlo and Cipro differ in strength, dosage, 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. SecreFlo is only available as 16 mcg lyophilized powder and needs to reconstituted. In addition, SecreFlo is given over 1 minute during a *diagnostic procedure.* Given the above differences in strength, dosage, dosing interval and the lack of convincing sound-alike potential, there is insufficient evidence at this time to conclude that the proposed drug would be confused with Cipro.

Zanaflex (tizanidine hydrochloride tablets) is a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important. Although SecreFlo and Zanaflex may look similar when scripted, the drug names do not sound similar. SecreFlo and Zanaflex differ in strength, dosage, and dosing interval. Zanaflex is supplied as 2 mg and 4 mg tablets and is dosed every 6 to 8 hours. SecreFlo is only available as 16 mcg lyophilized powder and needs to reconstituted. In addition, SecreFlo is given over 1 minute during a *diagnostic procedure.* Given the above differences in strength, dosage, dosing interval, and the lack of convincing look-alike potential, there is insufficient evidence at this time to conclude that the proposed drug would be confused with Zanaflex.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft container label, draft carton and draft package insert labeling for SecreFlo, DMETS has attempted to focus on safety issues relating to possible medication errors. The following labeling and packaging recommendations were provided in the proprietary name review for [redacted] (OPDRA consult # 00-0160). However, the labeling and packaging recommendations were not addressed in the current submission.

A. CONTAINER LABEL

[redacted]

B. CARTON LABELING

[redacted]

C. PACKAGE INSERT

1. General Comment

Based on our post-marketing experience with medication error reports, we recommend the expression of the strength of "µg" be changed to "mcg" *throughout* the package insert.

2. Dosage and Administration

The insert states that a *test dose* should be given because of a *potential allergic reaction* to secretin. However, this information is listed in the *WARNINGS* section and is not repeated in the *DOSAGE AND ADMINISTRATION* section. We recommend that this information should also be included in the *DOSAGE* section of the package insert.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the proposed proprietary name SecreFlo provided that ***only one name***, SecreFlo (NDA 21-136 and 21-209) ***or*** — NDA 21-256), is approved. The acceptability of the proposed proprietary name SecreFlo depends on which application, SecroFlo or — receives approval first, as these two proprietary names may not coexist due to their similarities.

DMETS 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, labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

B. DMETS recommends implementation of the above labeling revisions to minimize user error.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

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

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
3/21/02 03:42:58 PM
PHARMACIST

Carol Holquist
3/22/02 07:23:34 AM
PHARMACIST

Jerry Phillips
3/25/02 09:23:21 AM
DIRECTOR

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

DATE RECEIVED: 5/ 19/ 2000	DUE DATE: 8/ 24/ 2000	OPDRA CONSULT #: 00-0160

TO:

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

THROUGH:

Brian Strongin
Project Manager
(HFD-180)

PRODUCT NAME: — (synthetic porcine secretin for injection)

MANUFACTURER: ChiRhoClin, Inc.

NDA #: 21-136, 21-209

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name. — We recommend that the Division of Gastro-Intestinal and Coagulation Drug Products consider making a request to the manufacturer to submit a new proprietary name for review.

LSL 8/29/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

LSL 8/30/00

Peter Honig, MD
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-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE REVIEWED: August 11, 2000

NDA#: 21-136, 21-209

NAME OF DRUG: — (synthetic porcine secretin for injection)

NDA HOLDER: ChiRhoClin, Inc.

I. INTRODUCTION:

This consult is in response to a May 18, 2000 request, by the Division of Gastrointestinal and Coagulation Drug Products, to review the proposed proprietary drug name, —, regarding potential name confusion with other proprietary/generic drug names. *Revised* container labels and carton labeling were also submitted for review of possible interventions in minimizing medication errors.

— is the *second* proposed proprietary name for this product. OPDRA previously reviewed the name. —, on January 18, 2000, and had *no objections* to the use of the name. However, according to the Division of Gastrointestinal and Coagulation Drug Products, the applicant decided to pursue the proprietary name, — instead of —

PRODUCT INFORMATION

— contains synthetic porcine secretin, a gastrointestinal peptide hormone, as an acetate salt. The primary action is to increase the volume and bicarbonate content of secreted pancreatic juices. — is indicated for use as a diagnostic agent for the assessment of exocrine pancreatic function to diagnose causes of pancreatic dysfunction, — is also indicated for use in diagnosis of gastrinoma (Zollinger-Ellison Syndrome). —

The usual dosage requires an intravenous test dose of 0.2 mcg for potential allergic reaction, and if no allergic reaction is noted, a dose of 0.2 mcg/kg or 0.4 mcg/kg by intravenous injection over 1 minute is recommended for pancreatic function testing or diagnosis of gastrinoma, respectively. — is supplied as a lyophilized sterile powder for reconstitution. Each vial contains 16 mcg of Secretin, and is to be stored at –20°C (freezer).

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound-alike or look-

[1] 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).
[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

alike [redacted] 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[5]. 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, [redacted] 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. The panel discussed the following sound-alike/look-alike drug names:

Product Name	Generic name; strength	Usual dose	Observation
[redacted]	**Synthetic porcine secretin for injection; 2mcg/ mL**	**Test dose: 0.2 mcg for potential allergic reaction** **Pancreatic function testing: 0.2 mcg/kg by intravenous injection over 1 minute** **Diagnosis of gastrinoma: 0.4 mcg/kg by intravenous injection over 1 minute**	
Secretin-Ferring ***(Discontinued 7/99 per manufacturer)***	Porcine secretin for injection; 10 CU/mL	Test dose: 0.1-1 CU Pancreatic function testing & procedure for obtaining desquamated pancreatic cells for cytopathology: 1 CU/kg by intravenous injection over 1 minute. Diagnosis of gastrinoma: 2 CU/kg by intravenous injection over 1 minute.	*LA SA
Neupogen	Filgrastim injection (recombinant granulocyte colony stimulating factor [G-CSF]); 300 mcg/ mL, 480 mcg/ 1.6 mL	Cancer Patients Receiving Myelosuppressive Chemotherapy: 5 mcg/kg/day as single daily injection by SC bolus injection, by short IV infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion. Cancer Patients Receiving Bone Marrow Transplant: 10 mcg/kg/day given as an IV infusion of 4 or 24 hours, or as a continuous 24-hour SC infusion. Peripheral Blood Progenitor Cell Collection and Therapy in Cancer Patients: 10 mcg/kg/day SC, either as a bolus or a continuous infusion Congenital Neutropenia: 6 mcg/kg BID SC QD. Idiopathic or Cyclic Neutropenia: 5 mcg/kg as a single injection SC every day.	*LA

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] 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.
[5] WWW location http://www.uspto.gov/tmdb/index.html.

Respigam	Respiratory syncytial virus immune globulin intravenous (RSV-IGIV); 10 mg/mL	Maximum total dosage per monthly infusion is 750 mg/kg as follows: 1-15 min - 1.5 mL/kg/hr 15-30 min – 3 mL/kg/hr 30 min to end of infusion – 5 mL/kg/hr	*LA
Epogen	Epoetin alfa injection; 2000 Units/mL, 3000 Units/mL, 4000 Units/mL, 10,000 Units/mL , 20,000 Units/mL	Chronic Renal Failure Patients: starting dose of 50 to 100 Units/kg TIW as IV or SC injection. Zidovudine-treated HIV-infected Patients: Starting Dose: For patients with serum erythropoietin levels </= 500 mUnits/mL who are receiving a dose of zidovudine </= 4200 mg/week, the recommended starting dose of EPOGEN® is 100 Units/kg as an IV or SC injection TIW for 8 weeks. Cancer Patients on Chemotherapy: recommended starting dose is 150 Units/ kg SC TIW. Surgery Patients: recommended dose is 300 Units/kg/day SC for 10 days before surgery, on the day of surgery, and for 4 days after surgery. An alternate dose schedule is 600 Units/kg SC in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.	*LA

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

A number of sound-alike and/or look-alike product names were identified in the OPDRA focus group including Secretin-Ferring, Respigam, Neupogen, and Epogen. *Of these products,* Secretin-Ferring was considered by the OPDRA expert panel to be most significant. In addition, since the proposed proprietary name is lengthy, , the panel expressed concerns regarding the possible use of either ' . in reference to the drug.

2. DDMAC – no issues

B. PRESCRIPTION ANALYSIS STUDIES

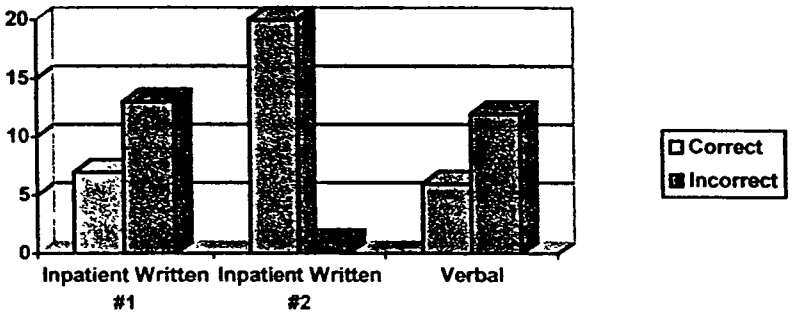
1. Methodology:

The studies conducted by OPDRA involved ninety-one health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of . 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 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 either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Inpatient #1: 0.2 mcg IV, if no rxn, give additional 24 mcg over 1 minute	*Inpatient:* give . 0.2 micrograms IV, if no reaction, then give additional 24 micrograms over 1 minute
Inpatient #2: 0.2 mcg IV, if no reaction, give additional 24 mcg over 1 minute	

2. Results:

Study	# of Participants	# of Responses	— Response	Other Responses
Inpatient Written #1	30	20 (66.7 %)	7 (35 %)	13 (65 %)
Inpatient Written #2	30	21 (70 %)	20 (95.2 %)	1 (4.8 %)
Verbal	31	18 (58.1 %)	6 (33.3 %)	12 (66.7 %)
Total	91	59 (64.8 %)	33 (55.9 %)	26 (44.1 %)



Since — 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. One of the written studies was conducted with the prescribed drug as — instead of — since there is a possibility that physicians would abbreviate the drug name and use only — when writing the prescriptions, and because — is a familiar term.

Among participants in the two written prescription studies, twenty-seven (51.2 %) out of forty-one study participants interpreted the name correctly. The majority of the respondents provided misspelled variations of the drug name. According to the *written study #1* results, four (4) study participants interpreted the name as —. Other interpretations include: *Senetin-Kipijen, Sevetin-Raph,* — *Sevetin-Replijen, Rephjen, and* —. In this study, the drug name, — was used, but two participants responded back with their interpretation of only the — part of the name. In the *written study #2*, only one participant misinterpreted the name as *Ryligen.*

Among verbal prescription study participants, six out of eighteen (33.3 %) participants interpreted the name correctly. Most of the name interpretations were phonetic variations of the proprietary name; 5 study participants interpreted the name as —; 2 study participants interpreted the name as — other interpretations include — *and Neupogen.* In this particular study, it is noteworthy that five participants interpreted the name to be — and one participant interpreted the "— part of the name as *Neupogen.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, — the expert panel identified *Secretin-Ferring* as *most problematic with the potential for name confusion.* However, according to the manufacturer of Secretin-Ferring, this product was *discontinued in July 1999.* Since this product is not currently available, the risk of confusing these two products is not significant.

However, since the proposed drug name consists of the — — there are three issues that need to be addressed as follows:

Of these three sound-alike and look-alike products, Neupogen was actually confused for the proposed product in the verbal study. This positive finding between "Neupogen" and — is significant given the small sample size of the study. Moreover, these two *injectable* drugs are similar in that they are both dosed based on the weight of the individual patient and are prescribed in micrograms. *However, given the limited uses of the proposed drug, these similarities do not necessarily out-weigh the differences between these two drugs.* In addition to the differences listed above, these two drugs differ in that the actual prescribed doses would be substantially larger for Neupogen, and the doses would be not be given on a one-time basis like — The strengths of these two drugs are also different.

In our prescription studies thirty-three out of fifty-nine participants correctly interpreted — Although there are limitations to the predictive value of these studies due to their sample size, the majority of the incorrect interpretations were misspelled/phonetic variations of the drug name..

Given the above findings, the primary safety concern for name confusion involves the approval of human secretin and the likelihood of other secretin formulations becoming available on the market. Although human secretin has not yet been approved, it is possible that this product or other secretin products could be available in the future. Although there is precedence of using the term, ' — followed by the name of the — in the proprietary name, other Secretin products were not available when Secretin-Ferring was on the market. In light of these findings, the use of the proprietary name, — — is not recommended at this time.

In addition to the proprietary name, there are safety concerns regarding the dosing of the proposed product. — is dosed in micrograms and not in clinical units (CU), which is used in Secretin-Ferring. Although the package insert provides the equivalency between CU and mcg, introducing a new dosing unit may cause confusion for health practitioners who are familiar with Secretin-Ferring.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

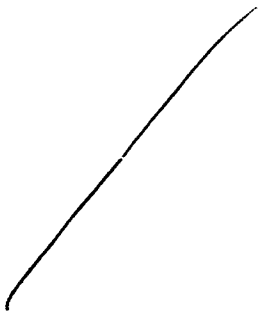
In the review of the *revised* container label, carton labeling, and the package insert of — OPDRA has attempted to focus on safety issues relating to possible medication errors. Our initial label/labeling recommendations are listed in OPDRA consult # 99-104.

A. CONTAINER LABEL

1. We recommend that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10 (g) (2). In addition, we recommend that both the established and proprietary names appear more prominent on the label so that they are more easily readable.

2. 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.

B. CARTON LABELING



C. PACKAGE INSERT

1. General Comment

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.

2. Dosage and Administration

The insert states that a *test dose* should be given because of a *potential allergic reaction* to secretin. However, this information is listed in the *WARNINGS* section and is not repeated in the *DOSAGE AND ADMINISTRATION* section. We recommend that this information should also be included in the *DOSAGE* section of the package insert.

IV. RECOMMENDATIONS:

A. OPDRA does not recommend the use of the proprietary name.

B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

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 Sammie Beam at 301-827-3161.

/S/

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 8/29/2000

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

CC:

NDA: 21-136 & 21-209
Office Files
HFD-180; DivFiles; Brian Strongin, Project Manager
HFD-180; Lilia Talarico, Division Director
HFD-042, Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Mary Dempsey, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Mac Lumpkin, Deputy Center Director for Review Management (Electronic Only)

JAN 19 2000

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

DATE SENT: December 3, 1999	**DUE DATE:** January 15, 2000	**OPDRA CONSULT #:** 99-104

TO: Lilia Talarico, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

PRODUCT NAME: [redacted] (synthetic porcine secretin) **NDA #:** 21-136, 21-209	**MANUFACTURER:** ChiRhoClin, Inc. Silver Spring, MD 20905

CASE REPORT NUMBER(S): Not applicable.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180). OPDRA conducted a review of the proposed proprietary name [redacted] to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA does not object to the use of the name [redacted]. We also have made recommendations for labeling revisions to minimize potential errors with the use of this product.

/S/ 1/18/2000

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

/S/ 1/19/00

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 13, 2000

NDA NUMBER: 21-136, 21-209

NAME OF DRUG: — (synthetic porcine secretin)

NDA HOLDER: ChiRhoClin, Inc.
Silver Spring, MD 20905

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) for assessment of the tradename —

— is indicated for diagnostic use in pancreatic dysfunction, —
—, in suspected gastrinoma —, and for the facilitation of
— during ERCP. A test dose of 0.2 mcg is administered intravenously. If no allergic reaction occurs, a dose of 0.2 mcg or 0.4 mcg per kilogram of body weight is administered, depending upon which diagnostic exam is being performed. This product is supplied as a 16-mcg vial of sterile powder for reconstitution and is to be stored in a freezer.

II. SAFETY AND RISK ASSESSMENT

A. Product name search, product availability and dosing comparison, and focus group

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to — to a degree where potential confusion between drug names

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[i] MICROMEDEX Healthcare Intranet Series, 1999, 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, 1999).

[ii] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

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

[iv] 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.

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[v]. An internal focus group discussion was conducted to review all findings from the searches.

A number of product names were identified in the OPDRA focus group that were thought to have potential for confusion. These products included Prozac, Prilosec, Posicor, Percocet, Lorcet, and Proscar. However, these products were considered unlikely sources of confusion, given the differences in dosage forms and usual dosing versus —

B. Handwritten and verbal analysis of proposed name

A study was conducted within FDA employing a total of 46 health care professionals to evaluate potential errors in handwritten and verbal communications of the name — This exercise was conducted in an attempt to simulate usual clinical practice settings. One of the following prescriptions was communicated per each study participant. Each reviewer was then requested to provide an interpretation of this prescription via email.

HANDWRITTEN INPATIENT ORDER (n=23)	VERBAL INPATIENT ORDER (n=23)
For ERCP: — 0.2 mcg IV test If no reaction, give 13 mcg IV over 1 minute. Send with patient Benadryl 50mg IV, Solu-Cortef 100mg IV.	For ERCP, giv — 0.2 mcg IV test If no reaction, give 13 mcg IV over 1 minute. Send with patient Benadryl 50mg IV and Solu-Cortef 100mg IV.

Results of this exercise are provided in Tables 1 and 2 (see Attachment 1). A low response to these surveys occurred, presumably due to holiday absences among participants. We received responses from 14 (61%) of those surveyed with verbal prescriptions and 7 (30%) of those surveyed with written prescriptions. Fifty-percent (50%) of verbal respondents provided misspelled variations of the drug name, which were generally phonetic variations of the name, and 50% provided the proper spelling of — All written respondents provided the proper spelling of —

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the draft labeling for —, OPDRA has attempted to focus on safety issues relating to potential medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and medical officer.

We reviewed the draft product labeling for — and identified several labeling, packaging, and safety concerns.

A. CONTAINER LABELING (16 mcg vial)

[v] WWW location http://www.uspto.gov/tmdb/index.html.

B. CARTON LABELING (16 mcg vial)

C. PACKAGE INSERT

1. DESCRIPTION

   a. Delete — when specifying quantity of Sodium Chloride Injection USP to be used for reconstitution. Specifically, ' — " should be designated as "8 mL". Including — See also "Dosage and Administration" for this same correction.

2. HOW SUPPLIED

   a. In the statement, "Synthetic porcine secretin is supplied as a lyophilized sterile powder in — vials containing 16 µg.", 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 — is supplied as a powder, not a liquid.

   b. Revise statement "Caution: Federal law prohibits dispensing without prescription" to "Rx only" per the FDA Modernization Act of 1997.

IV. DISCUSSION

In reviewing this proprietary name, several names were identified that were sound-alike and look-alike names but were considered unlikely to be confused with — with consideration of dosage forms and usual dosing of these products. This finding was supported by written and verbal prescription surveys that were conducted, though a low response rate to these surveys occurred.

V. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name —

B. OPDRA recommends the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

LSI

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

LSI 1/18/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

Attachment 1: Responses to prescription surveys

Table 1: Verbal Prescriptions

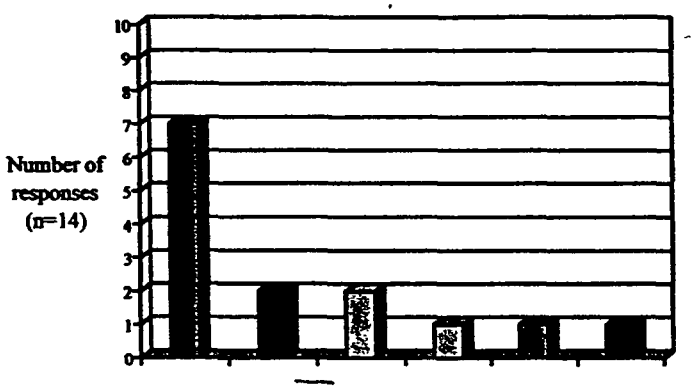
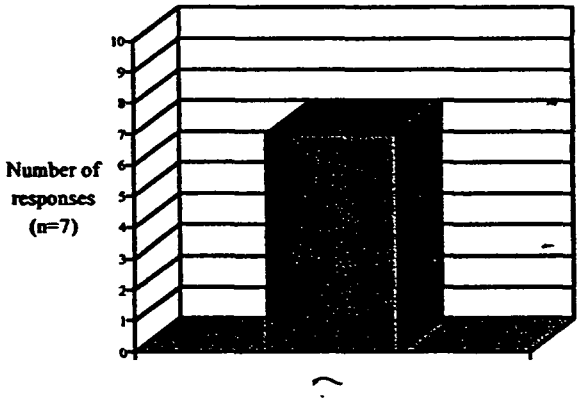


Table 2: Written Prescriptions



cc: NDA 21-136, 21-209
HFD-180; Division Files/Brian Strongin, Project Manager
HFD-180; Lilia Talarico, Division Director
HFD-400; Toni Piazza-Hepp, Team Leader, OPDRA
HFD-400; Ann Corken, Safety Evaluator, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 4, 2002

To: Edward D. Purich, Ph.D. CEO	**From:** Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager AK
Company: ChiRhoClin, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 301-384-1565	**Fax number:** 301-443-9285
Phone number: 301-384-1554	**Phone number:** (301) 827-1602 or 7310

Subject: NDA 21-136 & NDA 21-209

Total no. of pages including cover: 15

Comments: Attached is the approval letter for NDA 21-136 and 21-209.

Document to be mailed: ☑ YES ☐ NO

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 3, 2002

To: Edward D. Purich, Ph.D. CEO	**From:** Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager
Company: ChiRhoClin, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 301-384-1565	**Fax number:** 301-443-9285
Phone number: 301-384-1554	**Phone number:** (301) 827-1602 or 7310

Subject: NDA 21-136 & NDA 21-209

Total no. of pages including cover: 2

Comments: After reviewing your submission dated April 3, 2002, we request that the following labeling revisions be made:

1. Delete

2. In line 119, revise as follows: "

As this is a small change, you can make the change and send to me by fax at 301-443-9285.

1 Draft Labeling Page(s) Withheld

****
*** TX REPORT ***
****

TRANSMISSION OK

JOB NO.	0221
DESTINATION ADDRESS	913013841565
PSWD/SUBADDRESS	
DESTINATION ID	
ST. TIME	03/09 07:33
USAGE T	02'08
PGS.	7
RESULT	OK

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

FACSIMILE TRANSMITTAL SHEET

DATE: 3-8-02

To: Edward D. Purich, Ph.D. CEO	**From:** Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager [/S] Division of Gastrointestinal and Coagulation Drug Products
Company: ChiRhoClin, Inc.	
Fax number: 301-384-1565	**Fax number:** 301-443-9285
Phone number: 301-384-1554	**Phone number:** (301) 827-1602 or 7310

Subject: NDA 21-136 & NDA 21-209

Total no. of pages including cover: 6

Comments: Attached is a Discipline Review letter for the Secretin NDAs. I will call on Monday, 3-11-02 to set up a t-con between ChiRhoClin and the Division to further discuss this letter.

Document to be mailed: ☑ YES ☐ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-136
NDA 21-209

DISCIPLINE REVIEW LETTER

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

Dear Dr. Purich:

Please refer to your May 14 and August 17, 1999 new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SecreFlo (synthetic porcine secretin) for Injection.

We also refer to your submission dated March 1, 2002.

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

1. Regarding the Drug substance

   a. Provide an established name with an approved name from the USAN Council.

   b. Provide a complete set of your specifications for the drug substance, including specific references to all tests performed by you and including the following recommended acceptance criteria:

Porcine secretin
Total Impurities
impurity

The format for the drug substance specifications provided by can serve as a model.

   c. Provide a complete and clear description of each assay (including assay(s) for secretin purity and impurity levels) in a separate, uniquely numbered SOP.

2. Regarding the Drug Product:

a. Amend the specification for the drug product to ensure adequate testing for identity, strength, quality, and purity. Each test method, including assay(s) for secretin purity and impurity levels, should be completely and clearly described in a separate, uniquely numbered SOP.

In particular (see Finished Product release Specifications, Page 58 of the March 1, 2002 submission)

i. Include a test for "Appearance after reconstitution".

ii. Change the test for "Composite mean" to "Assay" or "Secretin Content", with the units listed as "% Label Claim".

iii. Specify the particular — method for all tests, including "Assay" and "Content Uniformity".

iv. Change the acceptance criterion for reconstitution time to —

b. Change the acceptance criteria for secretin content in the drug product to of — of label claim., using assays — for the following reasons.

i. The manufacturing procedure should be sufficiently controlled to permit filling at a target of 100% of label claim. Overage is permitted in the formulation to allow for losses during processing but the vials are filled based upon assay values tc — of label claim in each vial. Variations in the volume filled should be sufficiently controlled to permit consistent fill of the target volume.

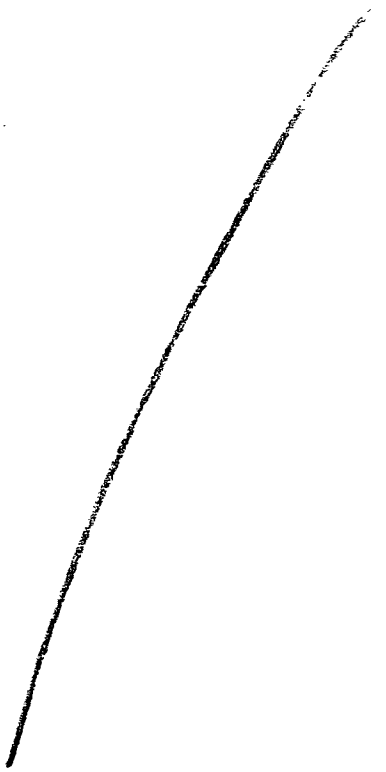
ii. The amount of secretin in the vial should be sufficiently well-controlled to permit accurate dosing for all indications. A flat dose-response curve has not been demonstrated for all indications.

iii. The existence of monographs for other products with broader acceptance criteria is not a sufficient precedent. Each drug product must be evaluated on the basis of its own properties and current analytical technology.

c. Set the expiration date to — , since the expiration date is set based on the stability data only, rather than considerations of supply.

d. You may submit a CBE-0 supplement for the extension of the expiry dating when additional stability data for Lot CBL 1100-7 is available.

1 Page(s) Withheld



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 Alice Kacuba, RN, MSN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

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

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
3/8/02 04:32:26 PM

APPEARS THIS WAY
ON ORIGINAL

21-209 4-3-02

ChiRhoClin, Inc.
301-384-1554
FAX 301-384-1565
edpurich@compuserve.com
www.chirhoclin.com

facsimile transmittal

To:	Alice Kacuba, RN, MSN, RAC	Fax:	301-443-9285
From:	E. Purich, Ph.D. S. Fein, MD J. Purich, RN M. Doerr, BA S. Purich, BA	Date:	04/03/02
Re:	PI-NDA 21-136 & 21-209	Pages:	11
CC:			

X Urgent X For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Please find the labeling change as you requested.

Attached:

1. Single page with the requested change
2. The entire PI with the requested change.

If you have any questions, please do not hesitate to contact me.

APPEARS THIS WAY
ON ORIGINAL

9 Draft Labeling Page(s) Withheld

Kacuba, Alice

From: Chen, Wen Jen
Sent: Friday, March 15, 2002 10:09 AM
To: Kacuba, Alice
Cc: Permutt, Thomas J; Chen, Wen Jen
Subject: Labeling comments on Secretin

Hi Alice:

From the attached file, please find the comments and recommendations which Tom agreed on the Secretin labeling package. If you have any questions please let me know.

Wen-Jen.

secretnl.doc

APPEARS THIS WAY
ON ORIGINAL

Kacuba, Alice

From: Roy, Sandip K
nt: Monday, March 11, 2002 4:22 PM
Kacuba, Alice
: Doddapaneni, Suresh
Subject: SecreFlo label

Alice,

Please find SecreFlo label attached.

21-136-label.doc

Sandip

APPEARS THIS WAY
ON ORIGINAL

The PK profile for SecreFlo™ was evaluated in 12 normal subjects. After intravenous bolus administration of 0.4 μg/kg, SecreFlo™ concentration rapidly declines to baseline secretin levels within 60 to 90 minutes in most of the normal volunteers studied. The elimination half-life of SecreFlo™ is 27 minutes. The clearance of SecreFlo™ is 487 ± 136 mL/minute and the volume of distribution is about 2 liter.

3 Page(s) Withheld

Printed by Brian Strongin

Electronic Mail Message

.tivity: COMPANY CONFIDENTIAL

Date: 11-Jul-2000 02:34pm
From: Brian Strongin
STRONGINB
Dept: HFD-180 PKLN 6B45
Tel No: 301-827-7310 FAX 301-443-9285

D: Khairy Malek (MALEKK)

C: Lawrence Goldkind (GOLDKINDL)
C: Hugo Gallo Torres (GALLOTORRESH)
C: Steven Aurecchia (AURECCHIA)
bject: Request for an Audit for NDA 21-136

)A 21-136 for — (synthetic porcine secretin for
ıjection) was submitted May 14, 1999 for the following indications: (1)
ıagnosis of pancreatic exocrine —
(3)
.agnosis of gastrinoma —); and (4)
ıcilitation of — during ERCP. On July 22,
)99 indications #3 and #4 were refused to file. An informal conference
ıs held with the firm September 14, 1999 during which they requested
ıat indication #3 be filed over protest. On October 28, 1999 NDA
?1-209 was administratively created for the diagnosis of gastrinoma
ıdication. Approvable letters were sent March 24, 2000 for NDA 21-136
ıd May 17, 2000 for NDA 21-209.

: the Medical Officer's request (Dr. Larry Goldkind) I sent a Request
)r Audit for NDA 21-209 June 22, 2000. I faxed it again today. Dr.
·ind would like one site from NDA 21-136 audited in addition to Dr.
— site for NDA 21-209.

IDICATION: Diagnosis of pancreatic exocrine

:VOTAL PROTOCOL NUMBER: CRC 98-1

'UDY TITLE: A Randomized, Crossover Study Evaluating Synthetic Porcine
:cretin and Biologically Derived Porcine Secretin for the Assessment of
:ocrine Pancreas Function In Patients with a Diagnosis of Chronic
ıncreatitis

ıvestigator's Name and Address:

/

ımber of Subjects Reported by the Sponsor: 12

IDICATION: Diagnosis of pancreatic exocrine —

VOTAL PROTOCOL NUMBER: CRC 98-2

'UDY TITLE: A Randomized, Crossover Study Evaluating Synthetic Porcine
·cretin and Synthetic Human Secretin for the Assessment of Exocrine
ıncreas Function In Patients with a Diagnosis of Chronic Pancreatitis

· tigator's Name and Address:

/

lumber of Subjects Reported by the Sponsor: 12

'ou need anymore information, please contact me.

Application # 21-209 Drug Name: SecreFlo (secretin) for Injection

Applicant: ChiRhoClin, Inc. Chem./Ther. Type: 3P

CSO/PM: ~~Brian Strongin, Melodi McNeil~~, Alice Kacuba Phone: 7-7310 HFD-180

Original Application Date: August 17, 1999 Original Receipt Date: August 17, 1999

CURRENT USER FEE GOAL DATE: April 9, 2002 Date Table of Contents Completed: 4-4-02

Section A: Administrative Information

Tab A-1	Action Letter(s) Current Action: ____AP_____ *4-02-02 , 11-28-00 AE, 5-16-00 AE*	X
Tab A-2	Phase 4 Commitments:	
	a. Copy of applicants communication committing to Phase 4	X
	b. Agency Correspondence requesting Phase 4 Commitments	X cmc DR
Tab A-3	FDA revised Labels & Labeling and Reviews: (Separate each version/cycle with a colored sheet)	
	a. Package Insert	X
	b. Immediate Container and Carton Labels	X
Tab A-4	Original Proposed Labeling ...*[2-14-02; 8-17-02]*.....	X
Tab A-5	Foreign Labeling:	
	a. Foreign Marketing History.....	N/A
	b. Foreign Labeling and Review(s)	N/A
Tab A-6	Labeling and Nomenclature Committee's Tradename Review ..... *[3-25-02, SecreFlo; 8-29-00, —— , 1-19-00, —*	X
Tab A-7	Summary Memoranda (e.g., Division Director, Group Leader, Office)	X
Tab A-8	Copy of Patent Statement	X
	Exclusivity Checklist (and any requests for exclusivity)	X
	Debarment Statements	X
Tab A-9	Correspondences, Faxes, & Telecons	X
Tab A-10	Minutes of Meetings:	
	a. End-of-Phase II meeting	N/A
	b. Pre-NDA meeting(s) .....*[11-18-98]*.....	X
	c. Filing meeting .....*[7-27-99]*.....	X
	d. Other meetings .*[9-14-99 Informal conference following a Refuse to File; 2-12-02 NDA deficiencies (cmc)]*.....	X
Tab A-11	Advisory Committee Meeting:	
	a. Questions Considered by the committee	N/A
	b. List of Attendees	N/A
	c. 24 hour alert memorandum	N/A
Tab A-12	Project Management Administrative Information (optional).....	X

Application # 21-209 Drug Name: SecreFlo (secretin) for Injection

Section B:	Clinical Information	X (completed), N/A (not applicable), or Comment
Tab B-1	Clinical Reviews and Memoranda ....*[6-16-00; 5-16-00]*.....	X
Tab B-2	Safety Update Reviews .....*[2-5-02]*.....	X
Tab B-3	Pediatric Page	X
Tab B-4	Statistical (Clinical) Review and Memoranda ...*[1-31-00]*.....	X
Tab B-5	Biopharmaceutics Review and Memoranda ..*[11-28-00, 2-10-00]*...	X
Tab B-6	Abuse Liability Review	N/A
Tab B-7	DSI Audits .....*[9-15-00]*.....	X
Tab B-8	Summary of Efficacy (from the summary volume of the application)	X
Tab B-9	Summary of Safety (from the summary volume of the application)	X

Section C:	Chemistry, Manufacturing, and Controls (CMC) Information	X (completed), N/A (not applicable), or Comment
Tab C-1	CMC Reviews and Memoranda ...*[4-3-02, 3-7-02, 3-4-02, 11-28-00, 2-4-00]*.....	X
Tab C-2	DMF Reviews .... [# — 2-7-00; # — 2-27-99].....	X
Tab C-3	EA Reviews/FONSI	N/A
Tab C-4	Micro Review (validation of sterilization) ..*[11-28-00, 2-2-00]*	X
Tab C-5	Statistical Review of drug stability ....*[2-13-02]*.....	X
Tab C-6	Inspection of facilities => Decision:_*Acceptable*__ Date:__*3-5-02*__	X
Tab C-7	Methods Validation Information	Not sent out yet

Section D:	Pharmacology/Toxicology Information	X (completed), N/A (not applicable), or Comment
Tab D-1	Pharmacology/Toxicology Reviews and Memoranda ..*[3-5-02; 11-5-99]*....	X
Tab D-2	Carcinogenicity Review (statistical)	N/A
Tab D-3	CAC/Executive Committee Report	N/A

ADDITIONAL NOTES:

See the memorandum dated October 25, 1999 from Brian Strongin, Project Manager, to Peggy Hair, of the Central Document Room for the administrative history of the creation of this application. This document can be found under "Tab A-12, Project Management".

Division of Gastrointestinal and Coagulation Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: 21-136

Name of Drug: Synthetic Porcine Secretin

Sponsor: ChiRhoClin, Inc.

JUN 17 1999

Material Reviewed

Submission Date: May 14, 1999

Receipt Date: May 25, 1999

Filing Date: July 22, 1999

User-Fee Goal Dates: March 23, 2000 (10-Month)
May 23, 2000 (12-Month)

Proposed Indication: 1. Diagnosis of pancreatic exocrine
2.
3. Diagnosis of gastrinoma (
4. Facilitation during ERCP

Other Background Information: NDA 18-290 for Secretin-Ferring, sponsored by Ferring Laboratories, Incorporated, is extracted from porcine duodenum and was approved May 29, 1981. It is labeled for the diagnosis of pancreatic exocrine disease, as an adjunct in obtaining desquamated pancreatic cells for cytopathologic examination, and for the diagnosis of gastrinoma (Zollinger-Ellison Syndrome). On April 26, 1999 Ferring Laboratories issued a "Dear Doctor" letter advising that they will cease manufacture of Secretin-Ferring in June 1999.

Review

PART I: OVERALL FORMATTING[a]

	Y	N	COMMENTS (list volume & page number)
1. Cover Letter (original signature)	Y		Volume 1, First page, unnumbered
2. Form FDA 356h (original signature)	Y		Volume 1, pages 1-2
a. Reference to DMF(s) & Other Applications	Y		INDs 54,196; and referenced. No DMFs referenced on Form FDA 356h. LOA for DMF Volume 4, page 1418.

NDA 21-236
Synthetic Porcine Secretin

3. Patent Information & Certification	Y		Volume 1, page 4
4. Debarment Certification	Y		Volume 1, page 3
5. Financial Disclosure		N	Requested from firm 6/17/99
6. Comprehensive Index	Y		Volume 1, pages 5-10; beginning of each volume
7. Pagination	Y		Entire NDA is paginated consecutively
8. Summary Volume	Y		Volume 1
9. Review Volumes		N	Micro review volumes were not sent. CMC Volumes 2-4 requested 6/17/99.
10. Labeling (PI, container, & carton labels)			
a. unannotated PI		N	Requested from firm 6/17/99
b. annotated PI	Y		Volume 1, pages 11-22; Volume 6, pages 2366-2409
c. immediate container		N	Requested from firm 6/17/99
d. carton		N	Requested from firm 6/17/99
e. foreign labeling (English translation)		N	N/A. Not approved in any country.
11. Foreign Marketing History	Y		Volume 1, page 25; Volume 13, page 4460
12. Case Report Tabulations (CRT, paper or electronic, by individual patient data listing or demographic)	Y		Volume 15
13. Case Report Forms (paper or electronic, for deaths and dropouts due to adverse events)	Y		Volumes 16-18

PART II: SUMMARY[b]

	Y	N	COMMENTS (list volume and page number)
1. Pharmacologic Class, Scientific Rationale, Intended Use & Potential Clinical Benefits	Y		Volume 1, page 23
2. Summary of Each Technical Section	Y		
a. Chemistry, Manufacturing, and Controls	Y		Volume 1, pages 26-51
b. Nonclinical Pharmacology/Toxicology	Y		Volume 1, pages 52-56
c. Human Pharmacokinetics & Bioavailability	Y		Volume 1, pages 57-144
d. Microbiology		N	Not Applicable
e. Clinical Data & Results of Statistical Analysis	Y		Volume 1, pages 146-350
3. Discussion of Benefit/Risk Relationship & Proposed Post	Y		Volume 1, pages 351-352

Marketing Studies			
4. Summary of Safety	Y		Volume 1, page 350
5. Summary of Efficacy		N	ISE only, Volume 13, page 4764

PART III: CLINICAL/STATISTICAL SECTIONS[c]

	Y	N	COMMENTS (list volume & page numbers
1. List of Investigators	Y		Volume 10, page 3202
2. Controlled Clinical Studies	Y		
a. Table of all studies	Y		"Overview of Clinical Studies", Volume 10, pages 32203-3204
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	Y		CRC 98-1 Synopsis: Volume 11, pages 3521-3524, 3526-3529 Protocol: Volume 11, pages 3564-3589 Related Publications: Volume 1, pages 164-349; Volume 11, pages 4462-4763 List of Investigators: Volume 11, page 3536 Integrated Clinical/Statistical Report: Volume 11, pages 3530-3757 CRC 98-2 Synopsis: Volume 11, pages 3759-3762 Protocol: Volume 11, pages 3797-3822 Related Publications: Same as CRC98-1 List of Investigators: Volume 11, Page 3769 Integrated Clinical/Statistical Report: Volume 11, pages 3758-3990 CRC 97-3 Synopsis: Volume 12, pages 3992-3993 Protocol: Volume 12, pages 4027-4058 Related Publications: Same as CRC98-1 List of Investigators: Volume 12, page 4001 Integrated Clinical/Statistical Report: Volume 12, pages 3991-4278
c. Optional overall summary & evaluation of data from controlled clinical studies	Y		See ISE

3. Integrated Summary of Efficacy (ISE)	Y		Volume 13, pages 4764-4765
4. Integrated Summary of Safety (ISS)	Y		Volume 13, pages 4766-4767
5. Drug Abuse & Overdosage Information	Y		Volume 13, pages 4768
6. Integrated Summary of Benefits & Risks of the Drug	Y		Volume 13, pages 4769-4770
7. Gender/Race/Age Safety & Efficacy Analysis Studies		N	We will discuss the need for this presentation at the filing meeting.

PART IV: MISCELLANEOUS

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		N	A Pediatric Assessment is required because of the new indication requested. The firm will be notified in the acknowledgment letter.
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 97		N	Requested from the firm 6/17/99
b. Stability data in SAS data set format		N	We will discuss the need for this at the filing meeting.
c. Efficacy data in SAS data set format		N	We will discuss the need for this at the filing meeting.
d. Biopharmacological information & study summaries in MS WORD 97		N	We will discuss the need for this at the filing meeting.
e. Animal tumorigenicity study data in SAS data set format		N	Not applicable
3. User-Fee Payment Receipt	Y		Volume 1, unnumbered page after the cover letter

[a] "GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (February 1987)
[B] "GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (February 1987)
[C] "GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (July 1988)

Conclusions

From an administrative standpoint, this application is fileable. In a June 17, 1999 telephone conversation between Dr. Edward Purich of ChiRhoClin and Brian Strongin of the Division, the firm was asked to submit the following items as soon as possible:

1. a completed financial disclosure form;
2. microbiology review copies of Volumes 2, 3 and 4;

Request for Audit

DATE: June 22, 2000

TO: David Lepay, M.D., Director, DSI/HFD-45
Khairy Malek, M.D. GCPD Reviewer/HFD-45

FROM: Lilia Talarico, M.D., Director, HFD-180 /s/ 6-22-00

SUBJECT: Request for Clinical Inspections for NDA 21-209; [redacted]™ (synthetic porcine secretin for injection)

In support of the above mentioned NDA, the sponsor (ChiRhoClin, Inc.) has submitted the results of the following pivotal protocols for the indication identified below:

Indication: Diagnosis of gastrinoma [redacted]

Pivotal Protocol #: CRC 99-8 and CRC 97-2

Study Title: A Randomized, Controlled, Crossover Study Evaluating Synthetic Porcine Secretin, Synthetic Human Secretin, and Biologically Derived Porcine Secretin for the Diagnosis of Gastrinoma. Pooled Analysis of CRC 99-8 and CRC 97-2 (with 2-Way Crossover Amendment) Studies

Investigator's Names and Addresses:

[redacted]

We have discussed this application informally with Antoine El-Hage, M.D. who suggested that we submit this request for audit.

We request the inspections be performed and the Inspection Summary Results be provided by

August 4, 2000. We intend to make a regulatory decision on this application by August 16, 2000. One issue of particular importance is verification of the total number of patients enrolled at each center.

Should you require any additional information, please contact Brian Strongin, Regulatory Project Manager at (301) 827-7310.

cc:
NDA 21-209
HFD-180/Div.File
HFD-180/B.Strongin

3 Page(s) Withheld

297 Page(s) Withheld