CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-136/S001

Trade Name: SecreFlo Injection

Generic Name: (secretin)

Sponsor: ChiRhoClin, Inc.

Approval Date: November 1, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136/S001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136/S001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-136/S-001

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

Dear Dr. Purich:

Please refer to your supplemental new drug application dated May 1, 2002, received May 3, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SecreFlo™ (secretin) Injection.

We acknowledge receipt of your submissions dated June 19 and October 24 and 25, 2002.

This supplemental new drug application provides for the use of SecreFlo (secretin) Injection for use in secretin stimulation testing for: Stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangio-pancreatography (ERCP).

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-136/S-001." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you

submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Alice Kacuba, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Joyce Korvick
11/1/02 03:18:23 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136/S001

LABELING

SecreFlo™
Secretin for Injection

DESCRIPTION

SecreFlo™ (secretin) is a pure sterile, nonpyrogenic, lyophilized white cake powder acetate salt of secretin, a peptide hormone. Secretin has an amino acid sequence identical to the naturally occurring porcine secretin consisting of 27 amino acids. Secretin is chemically defined as follows:

Molecular Weight 3055.5
Empirical Formula: $C_{130}H_{220}N_{44}O_{41}$

Structural Formula:
H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

SecreFlo™ contains 16 mcg of purified secretin, 15 mg of L-cysteine hydrochloride, and 20 mg of mannitol per vial. When reconstituted in 8 mL of Sodium Chloride Injection USP, each mL of solution contains 2 mcg secretin for intravenous use. The pH of the reconstituted solution has a range of 3-6.5.

CLINICAL PHARMACOLGY

The primary action of SecreFlo™ is to increase the volume and bicarbonate content of secreted pancreatic juices. The standard unit of activity used for SecreFlo™ is the clinical unit defined by Jorpes & Mutt in 1966.[1] In the validated cat bioassay, which was used to define and quantitate the biological activity of secretin and as the release test for the biologically derived porcine secretin product, SecreFlo™ demonstrates a potency of approximately 5000 clinical units (CU) per milligram of peptide as opposed to 3000 CU per mg for biologically derived porcine secretin. As a pure peptide drug product, SecreFlo™ dosing is expressed by weight in micrograms. The relationship of micrograms of secretin to biological activity is 0.2 mcg = 1 CU.

Pharmacokinetics:

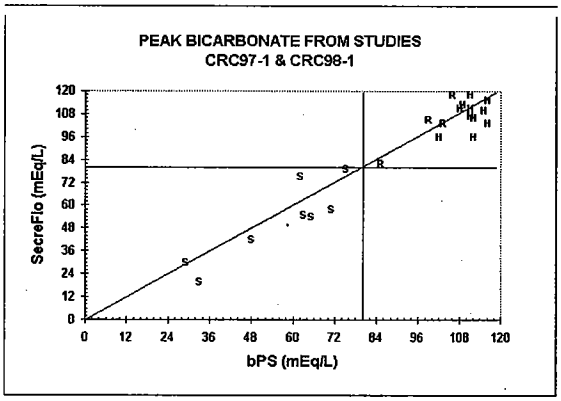
The PK profile for SecreFlo™ was evaluated in 12 normal subjects. After intravenous bolus administration of 0.4 mcg/kg, SecreFlo™ concentration rapidly declines to baseline secretin levels within 60 to 90 minutes in most of the normal volunteers studied. The elimination half-life of SecreFlo™ is 27 minutes.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

CLINICAL STUDIES

To stimulate pancreatic secretions, including bicarbonate, to aid in the diagnosis of exocrine pancreas dysfunction:

SecreFlo™ administered intravenously stimulates the exocrine pancreas to secrete pancreatic juice, which can assist in the diagnosis of exocrine pancreas dysfunction. Normal ranges for pancreatic secretory response to intravenous secretin in patients with defined pancreatic diseases have been shown to vary. One source of variation is related to the inter-investigator differences in operative technique. Two small studies (CRC 97-1 and CRC 98-1) examined the relationship of peak bicarbonate concentration observed in three groups of patients: normal healthy subjects; patients with chronic pancreatitis; patients with a past medical history of chronic pancreatitis and abnormal secretin stimulation test results but with sufficient recovery of exocrine panereas function to have currently normal test results (Figure 1). SecreFlo™ was compared to biologically derived porcine secretin (bPS). All 12 normal subjects had peak bicarbonate concentrations > 80 mEq/L while all patients with chronic pancreatitis had peak bicarbonate concentrations < 80 mEq/L.

Figure 1



S = Sick patients
R = Recovered patients
H = Healthy patients

The values obtained for Figure 1 were performed by investigators skilled in performing secretin stimulation testing and are to be taken only as guidelines. These results should not be generalized to results of secretin stimulation testing conducted in other laboratories. However, a volume response of less than 2.0 mL/kg/hr, bicarbonate concentration of less than 80 mEq/L, and bicarbonate output of less than 0.2 mEq/kg/hr are consistent with impaired pancreatic function.

A physician or institution planning to perform secretin stimulation testing for diagnosis of pancreatic disease should begin by assessing enough normal subjects (> 5) to develop proficiency in proper techniques and to generate normal response ranges for the commonly assessed parameters of pancreatic exocrine response to SecreFlo™.

In three crossover studies (CRC 98-1, CRC 98-2, and CRC 99-9) evaluating 21 different patients with a documented history of chronic pancreatitis, SecreFlo™ was compared to biologically derived secretin (bPS). All of the patients, treated with either drug, had peak concentrations of < 80 mEq/L.

Proper technique for carrying out secretin stimulation testing is described in DOSAGE AND ADMINISTRATION.

Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma:

SecreFlo™ administered intravenously stimulates gastrin release in patients with gastrinoma whereas only small changes in serum gastrin concentrations occur in normal subjects and patients with peptic ulcer disease. Deveney et al, 1977[(2)] established secretin stimulation testing as an aid in the diagnosis of gastrinoma by using discriminant analysis. An increase from basal levels of ≥ 110 pg/mL was the optimal point separating positive and negative tests. This gastrin response is the basis for the use of secretin as a provocative test in the evaluation of patients in whom gastrinoma is a diagnosis consideration.

In two crossover studies, eight patients with tissue confirmed gastrinoma received SecreFlo™. Results of serum gastrin concentrations were compared with those for biologically derived porcine secretin. Serum gastrin concentrations exceeded 110 pg/mL from basal levels in all patients for both drugs tested.

Correlation with clinical data and additional diagnostic modalities should be utilized when considering the diagnosis of gastrinoma.

Proper technique for carrying out secretin stimulation testing is described in DOSAGE AND ADMINISTRATION.

Facilitation of identification of the ampulla of Vater and the accessory papilla during ERCP to assist in cannulation of the pancreatic ducts:

In a randomized, placebo controlled crossover study in 31 patients with pancreas divisum undergoing ERCP, SecreFlo™ administration at a dose of 0.2 mcg/kg resulted in 25 of 28 successful cannulations of the minor duct compared to 1 of 16 for placebo.

INDICATIONS AND USAGE

SecreFlo™ is indicated for use in secretin stimulation testing for:
(1) Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction.
(2) Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma, and
(3) Stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangio-pancreatography (ERCP).

CONTRAINDICATIONS

Patients suffering from acute pancreatitis should not receive SecreFlo™ until the acute episode has subsided.

WARNINGS

Because of a potential allergic reaction to secretin, patients should receive an intravenous test dose of 0.2 mcg (0.1 mL). If no allergic reaction is noted after one minute, the recommended dose for the specific indication (see DOSAGE AND ADMINISTRATION) may be injected slowly over 1 minute. A test dose is especially important in patients with a history of atopic allergy and/or asthma. Appropriate measures for the treatment of

acute hypersensitivity reactions should be immediately available. No allergic reactions were observed after the test dose or full dose of SecreFlo™ in over 556 patients.

PRECAUTIONS

General: Patients who have undergone vagotomy, or are receiving anticholinergic agents at the time of secretin stimulation testing, or who have inflammatory bowel disease may be hyporesponsive to secretin stimulation. This response does not indicate pancreatic disease. A greater than normal volume response to secretin stimulation, which may mask coexisting pancreatic disease, is occasionally encountered in patients with alcoholic or other liver disease.

Drug/Laboratory Test Interaction:

The concomitant use of anticholinergic agents may make patients hyporesponsive, i.e. may produce a false positive result.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of secretin. Studies to evaluate its potential for impairment of fertility or its mutagenic potential have not been performed.

Pregnancy, Teratogenic Effects, Pregnancy Category C: Animal reproduction studies have not been conducted with secretin. It is also not known whether secretin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Secretin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether porcine secretin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when secretin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Among the 556 patients who have received SecreFlo™ in clinical trials 16% were 65 years of age or older and 12% were 75 years of age or older. Dosing was identical to the overall population of patients. No overall differences in safety, pharmacological response, or diagnostic effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and the younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Occasional mild adverse events have been noted in association with the use of SecreFlo™ in clinical studies of over 957 patients and 24 volunteer subjects.

TABLE 4
ADVERSE EVENTS

Event	**SecreFlo™ N = 981 Incidence (Patients)**
Abdominal cramps	2 (2)
Abdominal discomfort	7 (7)
Bleeding – sphincterectomy	6 (6)
Bleeding – upper GI 2° to endoscopic abrasion	2 (2)
Bloating	1 (1)
Bradycardia (mild)	2 (2)
Burning in stomach	3 (2)
Decreased blood pressure	6 (5)
Diaphoresis	6 (4)
Diarrhea	1 (1)
Endoscopic perforation of pancreatic duct	2 (2)
Fatigue	1 (1)
Fever	1 (1)
Flushing	6 (5)
Headache	2 (2)
Hot Sensation	1 (1)
Hunger Pangs	1 (1)
Leukocytoplastic Vasculitis	1 (1)
Lightheaded	3 (2)
Nausea	8 (8)
Numbness/Tingling in extremities	2 (1)
Pallor	1 (1)
Possible seizure	1 (1)
Rash – abdominal	1 (1)
Thready pulse	1 (1)
Transient low O^2 saturation	1 (1)
Transient respiratory distress	2 (2)
Urticaria 2° contrast material (prior to secretin administration)	1 (1)
Vomiting	1 (1)
Total patients with AEs (%)	73 (7.4)

OVERDOSAGE

A single intravenous dose of 20 mcg/kg of secretin was not lethal to mice or rabbits.

DOSAGE AND ADMINISTRATION

Dissolve the contents of the vial of SecreFlo™ in 8 mL of Sodium Chloride Injection USP, to yield a concentration of 2 mcg/mL. Shake vigorously to ensure dissolution. Use immediately after reconstitution. Discard any unused portion after reconstitution.

The reconstituted drug product should be inspected visually prior to administration. If particulate matter or discoloration is seen, the product should be discarded.

Dosage

SECRETIN STIMULATION TESTING:

1. TO STIMULATE PANCREATIC SECRETIONS, INCLUDING BICARBONATE, TO AID IN THE DIAGNOSIS OF EXOCRINE PANCREAS DYSFUNCTION: 0.2 mcg/kg body weight by intravenous injection over 1 minute.

2. STIMULATION OF GASTRIN SECRETION TO AID IN THE DIAGNOSIS OF GASTRINOMA: 0.4 mcg/kg body weight by intravenous injection over 1 minute.

3. FACILITATION OF THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ERCP to aid in cannulation of the pancreatic ducts: 0.2 mcg/kg body weight by intravenous injection over 1 minute.

Administration

SECRETIN STIMULATION TESTING:
1. TO STIMULATE PANCREATIC SECRETIONS, INCLUDING BICARBONATE, TO AID IN THE DIAGNOSIS OF EXOCRINE PANCREAS DYSFUNCTION: A radiopaque, double-lumen tube is passed through the mouth following a 12-15 hour fast. Under fluoroscopic control, the opening of the proximal lumen of the tube is placed in the gastric antrum and the opening of the distal lumen just beyond the papilla of Vater. The positioning of the tube must be confirmed and the tube secured prior to secretin testing. Intermittent negative pressure of 25-40 mmHg is applied to both lumens and maintained throughout the test. When duodenal contents have a pH of $\geq$ 6.0, a baseline sample of duodenal fluids is collected for a 10 minute period. A test dose of SecreFlo™ 0.2 mcg (0.1 mL) is injected intravenously to test of possible allergies. After one minute, if there are no untoward reactions, SecreFlo™ at a dose of 0.2 mcg/kg of body weight is injected intravenously over 1 minute. Duodenal fluid is collected for 60 minutes thereafter. The aspirate is divided into four collection periods of fifteen minutes each. The duodenal lumen of the tube is cleared with an injection of air after collection of each sample. Wide variation in volume of the aspirate is indicative of incomplete aspiration. Each sample of duodenal fluid is to be chilled and subsequently analyzed for volume

and bicarbonate concentration. Exocrine pancreas dysfunction typically associated with chronic pancreatitis is indicated if the peak bicarbonate concentration for any sample is <80 mEq/L.

2. STIMULATON OF GASTRIN TO AID IN THE DIAGNOSIS OF GASTRINOMA: The patient should have fasted for at least 12 hours prior to beginning the test. Before injecting SecreFlo™, two blood samples are drawn for determination of fasting serum gastrin levels (baseline values). Subsequently, a test dose of SecreFlo™ 0.2 mcg (0.1 mL) is injected intravenously, to test for possible allergies. If no untoward reactions, 0.4 mcg/kg of SecreFlo™ is administered intravenously over 1 minute; post-injection blood samples are collected after 1, 2, 5, 10, and 30 minutes for determination of serum gastrin concentrations.

Gastrinoma is strongly suspected in patients who show an increase in serum gastrin concentration of more than 110 pg per mL over basal levels on any of the post injection samples.

3. FACILITATION OF THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ERCP: When difficulty is encountered by the endoscopist in identifying the ampulla of Vater or in identifying the accessory papilla in patients with pancreas divisum, administration of secretin at a dose of 0.2 mcg/kg of body weight intravenously over 1½ minute will results in visible excretion of pancreatic fluid from the orifices of these papillae enabling their identification and facilitating cannulation.

HOW SUPPLIED

SecreFlo™ is supplied as a lyophilized sterile powder in vials containing 16 mcg secretin.

STORAGE: The unreconstituted product should be stored at -20°C (freezer).

RX only

References

1. Jorpes, E. and Mutt V.
On the biological assay of secretin. The reference standard.
Acta Physiol Scand 66 (1966) 316-325.

2. Deveney, C.W., et al.
Use of Calcium and Secretin in the Diagnosis of Gastrinoma (Zollinger-Ellison Syndrome).
Annals of Internal Medicine 87 (1977) 680-686.

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April 2002

sNDAChiRhoClinPI0101

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136/S001

MEDICAL REVIEW

CLINICAL REVIEW

Medical Officer Review of NDA 21-136 SE-001: SecreFlo™ (synthetic porcine secretin)

Date Submitted: 1 May 2002
Date Received: 3 May 2002
Date Assigned: 3 June 2002
Date Completed: 25 September 2002

Applicant: ChiRhoClin, Inc.
15500 Gallaudet Avenue
Silver Sprint, MD 20905
Contact person: Edward D. Purich, Ph.D.

Drug:
Proprietary Name - SecreFlo
Generic Name - Synthetic Porcine Secretin
Molecular Weight - 3055.5
Molecular formula - $C_{130}H_{220}N_{44}O_{41}$
Molecular structure – H-His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_3

Drug Class: Pancreatic polypeptide secretagogue

Formulation: 16 mcg of purified secretin, 15 mg of L-cysteine hydrochloride and 20 mg of mannitol combined with 8 ml of Sodium chloride forming a reconstituted solution of 2 mcg of secretin

Route of Administration: Intravenous

Table of Contents

Clinical Review for NDA 21-136

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This medical officer recommends approval of SecreFlo for the indication to facilitate identification of the ampulla of vater and accessory papilla during endoscopic retrograde cholangiopancreatography. This is a single dose regimen which is being recommended for approval. ChiRhoClin, Inc. has submitted a Supplemental New Drug Application (sNDA) for the drug SecreFlo (synthetic porcine secretin). The applicant is requesting a new indication for stimulation of pancreatic secretions to facilitate the identification the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP). SecreFlo was previously approved on April 4, 2002 for two clinical indications (evaluation of exocrine pancreas dysfunction, and diagnosis of gastrinoma.).

The applicant's submission demonstrates a favorable risk/benefit profile for this indication. This is based on the clinical study CRC-97 (amended), submitted in support for this sNDA. This study shows statistically significant increases in success rates for cannulation of the pancreatic duct during ERCP when SecreFlo is used versus placebo. The side effect profile is acceptable with no serious or life-threatening adverse events that were related to the study drug.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

[ ]

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Secretin is a naturally occurring hormone that stimulates the pancreas to secrete bicarbonate and other pancreatic juices through the pancreatic duct. In 1981, the FDA approved biologically derived porcine secretin for use in diagnosis of pancreatic disease. Because the biological preparation had significant amounts of impurities, research was done to produce synthetic secretin.

ERCP is an endoscopic procedure where by the physician places an endoscope orally, advances it to the duodenum, and attempts to cannulate the pancreatic duct. It is typically performed with the patient under conscious sedation, and is indicated for patients with

cholangitis, cholelithiasis or some other biliary tree process. Because it can be a tedious and difficult procedure, some physicians over the years have given secretin to stimulate the pancreas. This would cause the pancreas to secrete bicarbonate producing a spurt of fluids that the endoscopist could use as a guide to the ampulla of Vater and thus facilitate cannulation. Initially, this was off label use of biologically derived porcine secretin. In December 2001, the agency issued an approvable letter to ChiRhoClin's synthetic human secretin for the indication of stimulation of exocrine pancreas secretions to facilitate the cannulation of the pancreatic duct. This is the same indication ChiRhoClin is seeking for synthetic porcine secretin. The study design for this sNDA is identical to the one that led to the approval of synthetic human secretin for this indication.

The applicant's submission relies on a singe trial designated as CRC97-2. This was a multi-center randomized, double blinded, placebo controlled, crossover study involving 31 patients with pancreas divisum. The objective of the study was to obtain pivotal efficacy and safety data in standard clinical use for cannulation in patients with pancreas divisum during ERCP. The primary endpoint of the trial was successful cannulation of the pancreatic duct.

Initially, the study had an untreated control in which the patients underwent ERCP and cannulation was attempted without the patients receiving either placebo or the study drug. Patients who were not successfully cannulated were then randomized to receive placebo or SecreFlo. Each patient received placebo or 0.2 mcg/kg of the study drug intravenously over 1 minute and cannulation was again attempted. The patient and endoscopist were blinded to what whether placebo or study drug was adminstered. The endoscopist had 3 minutes to identify the minor papilla and orifice and 5 minutes to successfully cannulate the duct. Those patients who were not successfully cannulated went on to receive either placebo or the study drug (based on what they already had received). The primary endpoint of the study was successful cannulation of the pancreatic duct. The secondary endpoint was the measured time for cannulation attempts for sPS (synthetic porcine secretin) and placebo.

B. Efficacy

Thirty-one patients enrolled at 4 study centers. The patients underwent the ERCP and the endoscopist attempted cannulation without the patients receiving any therapy. This was the untreated control phase of the trial. Two of the 31 patients were successfully cannulated as untreated controls. As per the protocol of the study, these two patients were not randomized and did not enter the placebo/treatment phase of the study. Thus, 29 patients were randomized to receive placebo or SecreFlo. Thirteen patients received placebo in the initial phase, and of these only 1 was successfully cannulated. This patient did not go on the second phase to receive the study drug. Sixteen patients received SecreFlo in the initial phase, 13 of which underwent successful cannulation. The 12 patients who received placebo initially and were not cannulated then received SecreFlo. All 12 patients subsequently had successful cannulations. The 3 patients who received SecreFlo initially but were not successful cannulated received placebo. None of these 3 had successful cannulations.

Overall, the applicant demonstrated the efficacy of SecreFlo. For the randomized population, 86% (25/29) of the patients who received SecreFlo had successful cannulations versus 3% (1/29) of the patients who received placebo. The difference is statistically significant. There are methodologic flaws in two aspects of the trial. First, there was no true blinding of the operator. The very physiologic effect of the secretin prevented this. Once the

patient received the SecreFlo the endoscopist would see the secretion of bicarbonate from the pancreatic duct. Secondly, it was not a true crossover study. Only 15 of 31 patients received both placebo and the study drug. This again was due to the physiologic nature of secretin. Those that were randomized to SecreFlo first had a successful cannulation 81% of the time and thus did not go on to the placebo arm of the trial. These flaws were noted with the review of synthetic human secretin, which had the same study design. At that time synthetic human secretin was granted approval based on a functional indication approach. This data demonstrates that the drug has the intended physiologic effect.

C. Safety

Overall, the sponsor has demonstrated that SecreFlo is safe in adults when given as a single intravenous dose. There were no deaths or serious adverse events in the Study 97-2. No patients had to discontinue the medication because of the study drug. For the safety analysis, the applicant included patients from Study CRC 97-2 as well as patients from other approved NDA's for SecreFlo. A total of 981 patients were analyzed. Among all patients, adverse events were experienced by 7.4%. The most common events out of 981 patients analyzed were as follows:

- abdominal discomfort (7 patients)
- flushing (5 patients)
- nausea (8 patients)
- diaphoresis (5 patients)
- decreased blood pressure (5 patients)

These adverse events were not serious, all were self limiting and did not require hospitalization. It is unclear whether they are related to SecreFlo in light of the fact that these patients also were receiving sedation for their ERCP. Three patients did have serious adverse events. These included the following

- One patient suffered upper GI bleeding secondary to endoscopic abrasion
- One patient experienced mild nausea and vomiting which resulted in a brief hospitalization for rehydration
- One patient with known seizure disorder suffered a seizure. Phenytoin levels were subtheraputic.

None of these adverse events were thought to be secondary to SecreFlo. There are no documented drug-drug interactions with this product. In summary, SecreFlo has a favorable side effect profile in particular when it is considered that many of the adverse events may be related to the sedation taken when patients underwent ERCP.

D. Dosing

The applicant's study used a dose of 0.2 mcg/kg body weight given intravenously over 1 minute. The biologic activity of secretin is measured quantitatively by the validated cat bioasssay devised by Jorpes and Mutt in 1966. They defined the standard unit of activity as a clinical unit (CU). Based on this measure SecreFlo has a potency of 5000 clinical units per milligram of peptide. 0.2 mcg of SecreFlo is equivalent to 1 CU. The applicant did not provide data to establish a dose-toxicity relationship. This dose regimen is safe and efficacious, however,

C. Special Populations

There were too few patients to draw any conclusions in regards to efficacy differences based on gender, age or ethnicity. There were 8 males and 23 females. What is known about the biologic activity of secretin suggests that this hormone has identical action in males and females. The age range was 21-76 years of age. The majority of patients were Caucasian - 90%(28/31). Three subjects were black, no Asians or other races included. Because of the paucity of data, no firm conclusion can be stated regarding efficacy of SecreFlo in different age or ethnic groups. Secretin is a naturally occurring hormone, and porcine secretin has a great homology with the human secretin. In the long history of research dealing with both man-made and naturally occurring secretin, there has been no evidence of dissimilar effects in different racial groups or sex. These facts make it unlikely that SecreFlo has differences based on ethnicity and gender.

This study did not include any pediatric patients. The applicant submitted a request for pediatric waiver reasoning that there would be limited applicability in the pediatric population reasoning that ERCP procedures are performed almost exclusively in adults. There is limited safety data in pediatric patients predominantly [redacted] attempting to demonstrate efficacy of secretin in autistic children.

SecreFlo is Pregnancy Category C. It is not known whether secretin causes any fetal harm when given to pregnant patients. It is also unknown if porcine secretin is secreted in breast milk of nursing mothers. Further study is needed whether this medication can be used safely in pregnant or breastfeeding women.

In addition, there is sparse data relating to patients with renal and hepatic insufficiency. It is unclear the ideal dose or if any special precautions are necessary in this population.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

ClinRhoClin, Inc. has submitted a Supplemental New Drug Application (sNDA) for synthetic porcine secretin with a trade name of SecreFlo. The applicant's proposed new indication is to facilitate the identification of the ampulla of vater and minor papilla during endoscopic retrograde cholangio-pancretography (ERCP) procedures in which such identification and therefore cannulation is difficult.

SecreFlo was previously approved for evaluation of exocrine pancreas dysfunction and diagnosis of gastrinoma on April 4, 2002. SecreFlo is a peptide hormone with the identical amino acid sequence to naturally occurring porcine secretin. Its primary action is to increase the volume and bicarbonate content of secreted pancreatic juices. The applicant's proposed dose is 0.2 mcg/kg body weight by intravenous injection given over 1 minute. They are currently seeking an indication for adult use only.

B. State of Armamentarium for Indication(s)

Currently synthetic human secretin (under the trade name of ——— is indicated for facilitation of cannulation of the ampulla of vater and minor duct during ERCP ——— is also manufactured by ClinRhoClin and was judged approvable in December of 2001. The study design in the SecreFlo application is identical to the study that was done for ——— which led to approvable status for this indication pending resolution of chemistry issues.

C. Important Milestones in Product Development

Secretin was discovered by Bayliss and Starling in 1902. They demonstrated that an extract from the gastrointestinal mucosa of pigs could stimulate secretion in the pancreas of canines. This led to the conceptualization of the hormones in physiology. The hormone was first purified and extracted from porcine duodenum by Jorpes and Mutt in 1961. This resulted in the sequencing of the 27 amino acids that comprise secretin. A decade later, the Karolinska Instistute in Stockholm, Sweden produced the most purified form of secretin up to that time. In 1977, the manufacture of biologically derived secretin (bPS) was transferred to Kabi Diagnosit. Secretin Kabi (NDA 18-290) was approved by the FDA in 1981. In 1989, Ferring assumed production of bPS. It was approved for diagnosis of pancreatic exocrine disease, as adjunct in obtaining pancreatic cytology and diagnosis of gastrinoma. Ferring discontinued production of bPS in June 1999 due to lack of demand. On November 18, 1998 a Pre-NDA meeting was held with ChiRhoClin to discuss there application for a synthetic human secretin (sHS) and synthetic porcine secretin (sPS). On May 14, 1999, ChiRhoClin submitted NDA 21-136 for sPS. This submission consisted of four indications:

- For diagnostic use in pancreatic exocrine function
- (———————)
- Diagnosis of gastrinoma
- Facilitation of pancreatic duct cannulation during ERCP

For the latter two indications the clinical trials were judged not to contain meaningful clinical information and the Agency refused to file the application. Eventually this NDA was approved for the two other indications (evaluation of exocrine pancreas dysfunction, and diagnosis of gastrinoma) on April 4, 2002. In response to the agencies request for a controlled trial ChiRhoClin conducted a study to evaluate sPS effectiveness in facilitating the cannulation of the ampulla of vater and minor papilla during ERCP procedures.

D. Other Relevant Information

Currently SecreFlo is not approved abroad. It is approved in the United States for two indications:

- Stimulation of pancreatic secretions, including bicarbonate to aid in the diagnosis of pancreatic exocrine dysfunction.
- Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma

This sNDA is seeking a third indication "stimulation of pancreatic secretions to facilitate the identification of the ampulla of vater and accessory papilla during endoscopic retrograde cholangiopancreatography." This indication has been made approvable in its counterpart synthetic human secretin pending chemistry issues.

E. Important Issues with Pharmacologically Related Agents

Biologically derived porcine secretin (bPS) has been available in the U.S. since 1981 through several manufacturers. According to ChiRhoClin, the annual use of bPS in the U.S. had been form [redacted] vials. Biologically derived porcine secretin was also available in Canada where its use was estimated to be approximately [redacted] that of the U.S. These preparations contained [redacted] of impurities. It was suspected these impurities were biologically active with clinical effects seen when given to healthy volunteers most notably transient drops in blood pressure and elevations in serum Gastrin. Another concern with bPS has been contaminants of animal pathogens.

The high percentage of impurities and possibility of contaminants in bPS led to the development of synthetic secretin. Human synthetic secretin is also manufactured by ChiRhoClin and was given approvable letter in December 2001 fcr the identical indication that the applicant is seeking for synthetic porcine secretin. The secretin hormone has a significant homology across species. The porcine hormone differs form the human secretin only in that the amino acids aspartamine and serine in positions 15 and 16 are replaced by glutamine and glycine.

There have not been any safety issues that have arisen with synthetic human secretin to this date.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Dr. Wen-Jen Chen conducted the Statistical Review. He concluded that from a statistical perspective the sponsor's data supports efficacy. His review stated that although there were some potential for bias in the study design, the rate for successful cannulation when using SecreFlo was from a statistical standpoint significantly higher than placebo.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

No pharmacokinetic data was submitted with this sNDA, however, the applicant did reference their previous submission from May 6, 1999 for SecreFlo. Based on data from 12 healthy volunteers the elimination half-life of SecreFlo is 2.7 minutes. The volume of distribution is about 2 liters and the clearance is 487 +/- 136mL/minute. Protein binding in humans is thought to be 40%. The secretin levels return to baseline within 60-90 minutes after infusion with SecreFlo.

B. Pharmacodynamics

SecreFlo increases the volume and bicarbonate content of secreted pancreatic juices. The biologic activity of secretin is measured quantitatively by the validated cat bioasssay devised by Jorpes and Mutt in 1966. They defined the standard unit of activity as a clinical unit (CU). Based on this measure SecreFlo has a potency of 5000 clinical units per milligram of peptide. 0.2 mcg of SecreFlo is equivalent to 1 CU.

IV. Description of Clinical Data and Sources

A. Overall Data

This sNDA consisted of 15 volumes consisted of 615 pages. The data was presented from a single clinical trial that included 31 patients. The applicant also cross-referenced their previous submission for SecreFlo from 1999.

B. Tables Listing the Clinical Trials

The pertinent information about the clinical trial is as follows:

STUDY NAME	DESIGN	# PATIENTS ENROLLED	DOSAGE	LOCATION
CRC-97-2	Randomized, Double-blind, cross-over, placebo controlled	31	0.2 micrograms/kg intravenous bolus over 60 seconds	4 different centers in the United States

C. Postmarketing Experience

Since SecreFlo was only recently approved, no postmarketing data was supplied with this application.

D. Literature Review

The applicant did not submit a literature review with this sNDA. The previous submission for SecreFlo NDA 21-136 did contain a literature review and this was referenced as listed in the appendix.

V. Clinical Review Methods

A. How the Review was Conducted

The applicant's proposal for a new indication was based on a single clinical trial CRC-97-2 was reviewed in detail. In regards to efficacy, this study was the sole source of information. For the safety evaluation, the sponsor integrated the data from NDAs 21-136 and 21-209 as well as 4 studies done in support of NDAs and the efficacy supplement.

B. Overview of Materials Consulted in Review

This NDA consisted of 15 volumes of printed material comprising 615 pages. There were no electronic submissions with this package.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

All case report forms and supplemental narratives were reviewed in detail for all patients enrolled in the trial. No discrepancy was found between the case report forms and the applicant's data. No DSI audit was conducted of this data.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was performed within accepted ethical standards. It was conducted under the auspices of an Internal Review Board. Each patient signed a detailed informed consent that explained the possible complications of participation.

D. Evaluation of Financial Disclosure

Upon review of the financial disclosure by the investigators, there were no financial improprieties that would cast doubt on the finding of this study. None of the investigators listed by the sponsor are on the FDA debarred list.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Overall, synthetic porcine secretin is efficacious for facilitating cannulation of the minor duct in patients with pancreas divisum during ERCP. The proposed labeling from the sponsor states SecreFlo is indicated for:

"Stimulation of pancreatic secretions to facilitate the identification of the Ampulla of Vater and accessory papilla during endscopic retrograde cholangiopancreatography. (ERCP)."

The applicant's study reveals that in a randomized, placebo controlled crossover study involving 31 patients with pancreas divisum, SecreFlo resulted in 25 of 28 successful cannulations of the minor duct compared to 1 of 16 for placebo.

B. General Approach to Review of the Efficacy of the Drug

The database reviewed to establish efficacy came solely from Study CRC97-2. This study was reviewed in detail and the data analyzed. The study consisted of a randomized, placebo controlled, crossover study with 31 patients.

C. Detailed Review of Trials by Indication

1. Study Hypothesis and Objective

The hypothesis of this trial was that synthetic porcine secretin would prove safe and effective in routine clinical use to facilitate cannulation of minor pancreatic duct during ERCP in patients with pancreas divisum. The study's objective was to obtain pivotal efficacy and safety data in standard clinical use for the indications of facilitation of minor pancreatic duct cannulation in patients with pancreas divisum during ERCP. The primary endpoint of the trial was successful cannulation of the pancreatic duct.

2. Study Design and Methods

The protocol CRC97-2 was a randomized double-blind, placebo controlled multicenter, crossover study of synthetic porcine secretin (sPS) to facilitate minor pancreatic duct cannulation during ERCP in patients with pancreas divisium. Initially, patients were enrolled and prior to randomization they underwent an ERCP in which cannulation was attempted. This was the untreated control phase of the study. A time limit of 1 minute was set to identify the minor papilla and orifice. Once visualized a time limit of 5 minutes was imposed to attempt cannulation. Patients who were not cannulated were randomized to receive placebo or the study drug. Each patient received an initial test dose of 0.2mcg of sPS or placebo intravenously. If no allergic response occurred the patient received either either placebo or 0.2 mcg/kg of the study drug intravenously over 1 minute and cannulation was again attempted. The endoscopist had 3 minutes to identify the minor papilla and orifice and 5 minutes to successfully cannulate the duct. Those patients who were not successfully cannulated went on to receive either placebo or the study drug (based on what they already had received). The primary endpoint of the study was successful cannulation of the pancreatic duct. The secondary endpoint was the measured time for cannulation attempts for sPS and placebo.

Medical Officer Comments: The study design reveals a significant methodological flaw albeit one that does not invalidate the results. The dose of SecreFlo that was given to those randomized to receive it first was effective for longer than the 5 minutes. Since the placebo was given only 5 minutes later, this likely negates the study having a true placebo arm. Although in theory this should have made the placebo arm have results that are more favorable. Another additional flaw is the fact that the SecreFlo would cause a visible spurt of bicarbonate from the pancreatic duct, which would unblind the investigator during the procedure. These shortcomings were noted in the review for synthetic human secretin (NDA 21-256) which was approved for the same indication with an identical study design.

3. Inclusion/Exclusion Criteria

The inclusion criteria for patients to be enrolled in the study were as follows:

- Males or females of non-childbearing potential (if childbearing potential must be using a medically approved contraceptive method).

The exclusion criteria were as listed:

- Active acute pancreatitis

- Use of anticholinergic medications within one week of testing
- Known sensitivity or adverse reaction to secretin
- Pregnant or nursing female

Medical Officer Comment: The inclusion and exclusion criteria were appropriate and would not have contributed to selection bias.

4. Demographics and Other Baseline Characteristics

The following Table displays baseline demographic characteristics of the study population.

TABLE 1 - BASELINE DEMOGRAPHICS

(Reference: Volume 4, pg. 26-27)

Patient #	Site #	Weight (kg)	Age	Gender	Race
1	1	81.8	47	M	W
2	1	40.0	76	F	W
3	1	50.0	66	F	W
4	1	80.0	48	F	W
5	1	90.9	27	M	W
6	1	52.16	76	F	W
7	1	72.73	36	F	W
8	1	95.0	66	M	W
9	1	60.0	21	F	B
10	1	55.45	46	F	W
21	2	68.0	71	F	W
22	2	48.0	26	F	W
23	2	62.0	56	M	W
25	2	74.0	51	F	W
26	2	76.5	31	M	W
27	2	81.0	56	F	B
28	2	63.0	55	F	W
31	3	56.0	38	F	W
41	4	78.02	52	F	W
42	4	106.0	31	F	B
43	4	42.7	72	F	W
44	4	70.0	47	F	W
45	4	93.0	57	M	W
46	4	49.1	63	F	W
47	4	82.1	57	M	W
49	4	70.0	44	F	W
50	4	98.1	58	F	W
51	1	46.82	45	F	W
52	1	81.36	52	F	W
53	1	89.55	30	M	W
54	1	77.27	53	F	W

Si
1
2
3
4

Race: W= White(non-Hispanic)
B= Black

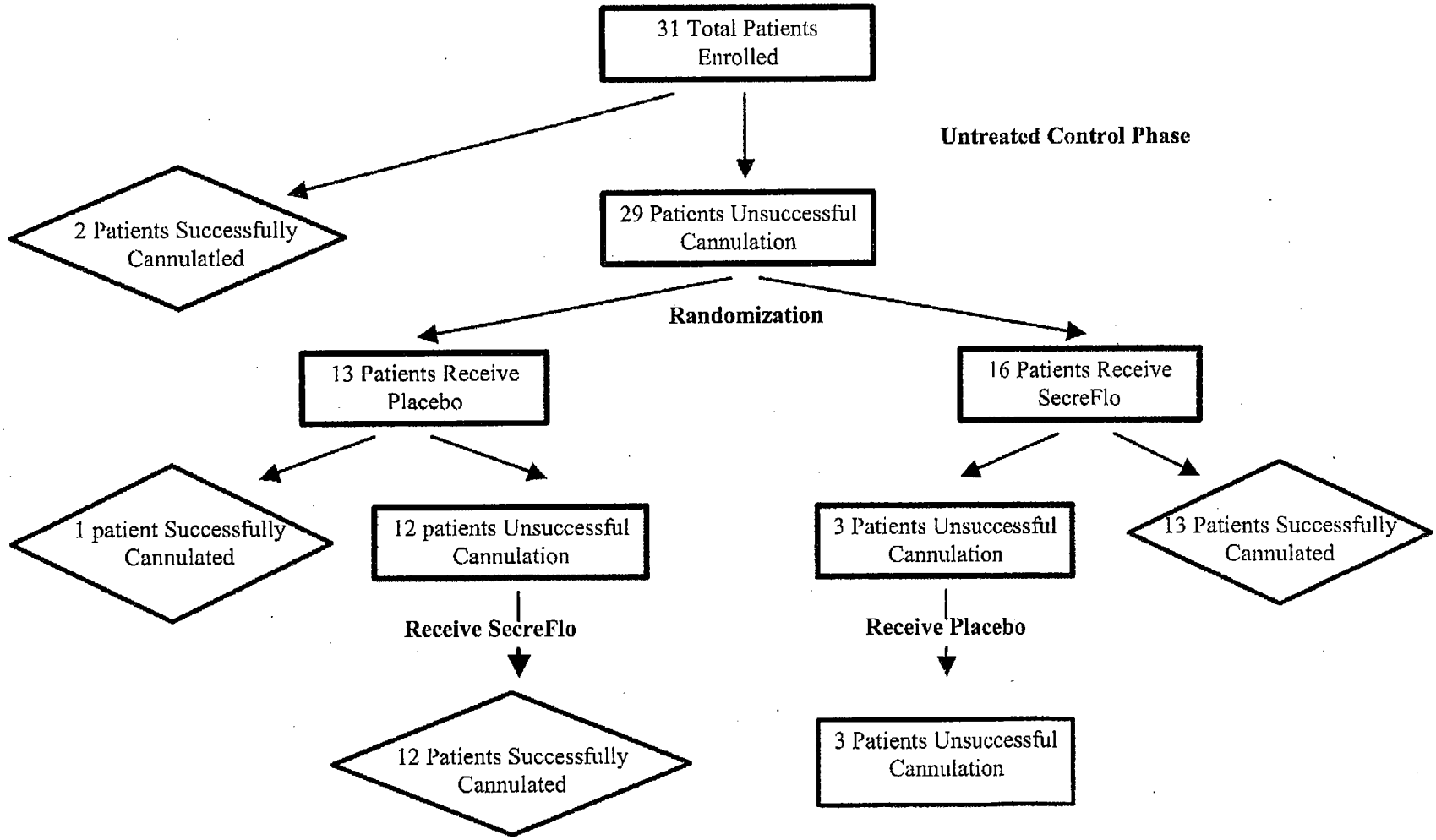
Medical Officer Comments: The trial had a predominance of females as there were 8 males (26%) and 23 females (74%). The age range was 21 to 76 years of age. The weight range was from 40 kg to 106 kg. The case report forms do not reveal concomitant medical conditions or other medications the patients were taking. The patients were not evenly distributed among all study centers. 14 patients were at [redacted] 7 were at [redacted] 1 at [redacted] and 9 patients at [redacted]

5. Efficacy Results

Thirty-one patients enrolled at 4 study centers. The patients underwent the ERCP and the endoscopist attempted cannulation without the patients receiving any therapy. This was the untreated control phase of the trial. Two of the 31 patients were successfully cannulated as untreated controls. As per the protocol of the study, these two were not randomized and did not enter the placebo/treatement phase of the study. Thus, 29 patients were randomized to receive placebo or the SecreFlo. Thirteen received placebo in the initial phase of these only 1 was successfully cannulated. This patient did not go on the second phase to receive the study drug. Sixteen patients received SecreFlo in the initial phase, 13 of which underwent successful cannulation. The 12 patients who received placebo initially and were not cannulated then received SecreFlo. All 12 patients subsequently had successful cannulations. The 3 patients who received SecreFlo initially but were not successful cannulated received placebo. None of these 3 had successful cannulations.

The following diagram displays the study results.

FIGURE 1


31 Total Patients Enrolled
Untreated Control Phase
2 Patients Successfully Cannulatled
29 Patients Unsuccessful Cannulation
Randomization
13 Patients Receive Placebo
16 Patients Receive SecreFlo
1 patient Successfully Cannulated
12 patients Unsuccessful Cannulation
3 Patients Unsuccessful Cannulation
13 Patients Successfully Cannulated
Receive SecreFlo
Receive Placebo
12 Patients Successfully Cannulated
3 Patients Unsuccessful Cannulation

The following table produced by the statistical reviewer Dr. Wen-Jen Chen displays the summary of facilitated cannulation success rates of outcomes for all available, intent to treat , and randomized population.

TABLE 2 - SUMMARY OF FACILITATED CANNULATION SUCCESS RATES OF OUTCOMES

	Untreated Control Group (U)	Placebo (P)	Secretin (S)	P-Value S vs. U	P-Value S vs. P
All Available Population	7% (2/31)	6% (1/16)	89% (25/28)	< 0.0001*	0.0005*
Intent to Treat Population	7% (2/31)	3% (1/31)	81% (25/31)	<0.0001*	<0.0001*
Randomized Population	0% (0/29)	3% (1/29)	86% (25/29)	< 0.0001*	<0.0001*

***: Significance at 0.05 significance level by McNemar's test.**
Note: Missing Data in all patient population and randomized population were replaced with unsuccessful outcome.

Only 16 patients received placebo, this was because of the 16 patients who were randomized to receive SecreFlo in the first phase of the study 13 were successfully cannulated, and thus they did not proceed to the second phase to receive the placebo. The 3 patients who received the SecreFlo first but were not successfully cannulated did go on to receive placebo and were not unsuccessfully cannulated.
Medical Officer Comments: There are are methodologic flaws in two aspects of the trial. There was no true blinding of the operator. The very physiologic effect of the secretin prevented this. Once the patient received the SecreFlo the endoscopist would see the secretion of bicarbonate from the pancreatic duct. Secondly it was not a true crossover study. Only 15 of 31 patients received both placebo and the study drug. This again was due to the physiologic nature of secretin. Those that were randomized to see SecreFlo first had a successul cannulation 81% of the time and thus did not go on to the placebo arm of the trial. Theoritically they could have received the placebo and cannulation could have been re-attempted. However, given the dose of SecreFlo they received the washout period to perform the placebo part of the test would have lengthy. This would have subjected the patients to prolonged sedation and a repeat cannulation both with inherent risks, which would have raised ethical issues.

Dr. Wen-Jen Chen recognized that essentially the study was unblinded and performed a statistical analysis of the first phase of the study, comparing the placebo arm to the study drug.

TABLE 3 - STATISTICAL REVIEWER'S ANALYSIS ON THE DIFFERENCE OF TWO SUCCESSFUL RATES

Placebo	SecreFlo	Exact P-Value#
8% (1/13)	81% (13/16)	0.002

#: Exact p-value for testing the equality of two successful rates from two Binomial samples calculated using StatXact.

A secondary outcome measured was the time used by the endoscopist to cannulate or attempt to cannulate the pancreatic duct. Once the minor papilla was visualized, a time limit of 5 minutes was set for attempting to cannulate. If the operator was not able to visualize the minor papilla and orifice a maximum time of 5 minutes was entered. A summary of mean times for cannulation attempts is displayed in Table 4.

TABLE 4 – SUMMARY OF MEAN TIMES FOR CANNULATION ATTEMPTS

(Reference: Volume 4, pg. 29, Table 5)

Drug (N)	Time in Minutes*	P-Value of SecreFlo vs
SecreFlo	2.63	---
Placebo (16)	4.75	.0001
Untreated Control (31)	5.00	.0001

* - Mean value

Medical Officer Comments: Although not stated explicitly in the protocol, it is assumed that the time was measured beginning when the endoscope entered the duodenum.

E. Efficacy Conclusions

In Summary, this study demonstrates SecreFlo's efficacy in facilitating cannulation of the pancreatic duct during ERCP. Statistically significant differences were seen in rates of successful cannulation in the SecreFlo versus the placebo arm.

However, there were methodological flaws with this trial, notably the lack of blinding and the fact that only half the patients received placebo. These were issues that faced the NDA for synthetic human secretin (NDA 21-256) which was made approvable for the exact same indication with the same study design. At that time the medical reviewer noted the deficiency in study design, however, it was felt that these were inherent due to the action of secretin itself. In her summary Memorandum dated December 14, 2001, Office Director Dr. Florence Houn noted that the issues with the study design resulted from the physiologic action of secretin and at that time. She stated at that time:

> " In reference to the cannulation 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 physiology activity in test subjects."

Using this functional indication approach, the data supplied demonstrates effectiveness of SecreFlo.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Overall, the sponsor has demonstrated that SecreFlo is safe in adults when given as a single intravenous dose. There were no deaths, serious adverse events in the Study 97-2. No patients had to discontinue the medication because of the study drug.

B. Description of Patient Exposure

The applicant includes adverse events from the 31 patients in this study as well patients from studies performed in the approved NDAs 21-136, 21-209 for SecreFlo. The applicant also includes 425 patients from Study 97-3 (Post ERCP pancreatitis study at ✗ / Study 00-2 (Diagnosis of Gastrinoma), and Study 99-1(MRI). The following Table itemizes the number of patients for each study in the approved NDA's.

STUDY NUMBER	# OF PATIENTS
97-1	12
97-2A	31
972	129
97-3	530
98-1	12
98-2	12
99-1	17
99-8	9
99-9	6
99-10	12
00-2	1
00-3	210
TOTAL	981

Each of these patients received the SecreFlo in a single dose based on weight intravenously.

C. Methods and Specific Findings of Safety Review

Among all patients, adverse events were experienced by 7.4%. Table 5 lists the adverse events that occurred.

TABLE 5- ADVERSE EVENTS

ADVERSE EVENTS TABLE

Event	SecreFlo™ N = 981 Incidence (Patients)
Abdominal cramps	2 (2)
Abdominal discomfort	7 (7)
Bleeding - sphincterectomy	6 (6)
Bleeding – upper GI 2° to endoscopic abrasion	2 (2)
Bloating	1 (1)
Bradycardia (mild)	2 (2)
Burning in stomach	3 (2)
Decreased blood pressure	6 (5)
Diaphoresis	6 (4)
Diarrhea	1 (1)
Endoscopic perforation of pancreatic duct	2 (2)
Fatigue	1 (1)
Fever	1 (1)
Flushing	6 (5)
Headache	2 (2)
Hot Sensation	1 (1)
Hunger Pangs	1 (1)
Leukocytoplastic Vasculitis	1 (1)
Lightheaded	3 (2)
Nausea	8 (8)
Numbness/Tingling in extremities	2 (1)
Pallor	1 (1)
Possible seizure	1 (1)
Rash – abdominal	1 (1)
Thready pulse	1 (1)
Transient low O^2 saturation	1 (1)
Transient respiratory distress	2 (2)
Urticaria 2° contrast material (prior to secretin administration)	1 (1)
Vomiting	1 (1)
Total patients with AEs (%)	73 (7.4)

There were 3 serious adverse events but none judged to be related to SecreFlo In Study 97-3, one patient suffered upper GI bleeding secondary to an endoscopic abrasion. In Study 97-3, a patient experienced mild nausea and vomiting which resulted in a brief hospitalization for dehydration. In Study 97-2, a patient had respiratory distress that resolved. No further details are given. One subject in Study 003 had a possible seizure after ERCP. This patient had known epilepsy and had a subtheraputic phenytoin blood level. None of the serious adverse events were judged to be secondary to the study drug.

D. Adequacy of Safety Testing

The applicant recorded all adverse events. Vital signs were recorded as the patients were undergoing conscious sedation for the ERCP. Laboratory evaluations were not performed. Given that SecreFlo has great homology with a naturally occurring hormone, the safety data was adequate.

E. Summary of Critical Safety Findings and Limitations of Data

In summary, SecreFlo is safe to use. No serious adverse events occurred. No patients had to be withdrawn from the study. Secretin has a long history use dating back to 1981 and has been shown to be safe.

VIII. Dosing, Regimen, and Administration Issues

SecreFlo is provided in a vial that contains a pure sterile lyophilized white cake powder acetate salt of secretin. Each vial contains 16 mcg of purified secretin, 15 mg of L-cysteine hydrochloride and 20 mg of mannitol. It is combined with 8 ml of Sodium choride forming a reconstituted solution of 2 mcg of secretin with a pH range of 3-6.5 for intravenous use. The dosage recommended is for 0.2-mcg/kg body weight given over 1 minute. The method of administration is to dissolve the contents of the vial with 8 mL of Sodium Chloride and shake vigorously. No issues exist with administration since the medication will be given by medical personnel. Also there should be no compliance issues. The reconstitution of SecreFlo is a straightforward process that should pose no problems.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

There were too few patients to draw any conclusions in regards to efficacy differences based on gender. There were 8 males and 23 females. The results of the 8 males subjects are as follows:

- 1 patient had successful cannulation as untreated control
- 4 patients received SecreFlo first and all had successful cannulations
- 3 patients received placebo first and 2 had unsuccessful cannulations and 1 had a successful cannulation.
- 3 patients received SecreFlo second after failing placebo and all had successful cannulations

The results of the female patients are as follows:

- 1 patient was successfully cannulated as a untreated control
- 12 patients received SecreFlo first and 9 had successful cannulations, 3 had unsuccessful cannulations
- 10 patients received placebo first all had unsuccessful cannulations
- 3 patients who received SecreFlo first received placebo second and all had unsuccessful cannulations
- 10 patients who received placebo first received SecreFlo second and all had successful cannulations

These small numbers make it impossible to state any differences in efficacy or safety.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Because of the small sample size, no conclusions can be drawn regarding the efficacy and safety differences in different age and ethnic groups. The age range was 21-76 years of age. The majority of patients were Caucasian - 90%(28/31). Three subjects were black, no Asians or other races included. Because of the paucity of data, no firm conclusion can be stated regarding efficacy of SecreFlo in different races.

C. Evaluation of Pediatric Program

This study did not include any pediatric patients. The applicant submitted a request for pediatric waiver reasoning that there would be limited applicability in the pediatric population reasoning that ERCP procedures are performed almost exclusively in adults. This rationale is sound. According to the Pediatric Rule of 1998, if a medication is not used in substantial numbers of pediatric patients it may be granted a waiver. On this basis, SecreFlo should be granted a waiver.

D. Comments on Data Available or Needed in Other Populations

In light of the fact that this sNDA is for an orphan indication with limited applicability, this study is adequate. The small numbers in this study make it impossible to draw any conclusions in reference to differences in safety or efficacy based on gender or race. Secretin is a naturally occurring hormone, and porcine secretin has a great homology with the human secretin. In the long history of research dealing with both man-made and naturally occurring secretin, there has been no evidence of dissimilar effects in different racial groups or sex. These facts make it unlikely that SecreFlo has differences based on ethnicity and gender.

This applicant did not submit any data on patients with hepatic and renal insufficiency. No conclusions can be drawn regarding the use of SecreFlo in these populations

SecreFlo is Pregnancy Category C. It is not known whether secretin causes any fetal harm when given to pregnant patients. It is also unknown if porcine secretin is secreted in breast milk of nursing mothers.

X. Conclusions and Recommendations

A. Conclusions

In summary, from a medical standpoint SecreFlo is approvable for use in adults to facilitate identification of the ampulla of Vater and the accessory papilla during ERCP to assist in cannulation of the pancreatic ducts. This is based on the functional physiologic effect of the drug demonstrated in Study CRC-97-2. The applicant provided sufficient evidence of safety and efficacy. The study demonstrated superior rates of successful cannulation when using SecreFlo versus placebo. The side effects were non-life threatening and self-limiting.

B. Recommendations

From a clinical standpoint, SecreFlo is approvable for this indication. Further study is needed however in patients with liver and renal impairment and pregnant women.

XI. Appendix

A. Other Relevant Materials

LABELING REVIEW:

The applicant ChiRhoClin submitted a proposed label for SecreFlo with this NDA. The proposed label is identical to label that was previously approved with the following exceptions:

CLINICAL STUDIES section

> "Facilitation of identification of the ampulla of Vater and the accessory papilla during ERCP to assist in cannulation of the pancreatic ducts: In a randomized, placebo controlled crossover study in 31 patients with pancreas divisum undergoing ERCP, SecreFlo™ administration at a dose of 0.2 mcg/kg resulted in 25 of 28 successful cannulations of the minor duct compared to 1 of 16 for placebo [redacted]

Medical Officer Comments: This data is correct. However, to improve the continuity of the document a space should be added. In addition, the other studies listed in this section do not list [redacted] *The revised text should appear as follows:*

> "Facilitation of identification of the ampulla of Vater and the accessory papilla during ERCP to assist in cannulation of the pancreatic ducts:
>
> In a randomized, placebo controlled crossover study in 31 patients with pancreas divisum undergoing ERCP, SecreFlo™ administration at a dose of 0.2 mcg/kg resulted in 25 of 28 successful cannulations of the minor duct compared to 1 of 16 for placebo."

INDICATIONS AND USAGE section

" Stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangio-pancreatography (ERCP)."

Medical Officer Comments: These changes are acceptable and consistent with the synthetic human secretin label.

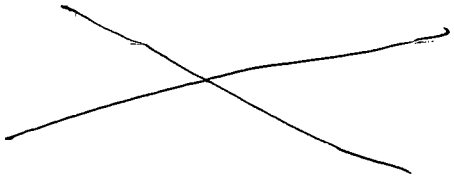
DOSAGE AND ADMINISTRATION section

"FACILITATION OF THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ERCP to aid in cannulation of the pancreatic ducts: 0.2 mcg/kg body weight by intravenous injection over 1 minute."

Medical Officer Comment: These changes are acceptable.

DOSAGE AND ADMINISTRATION section

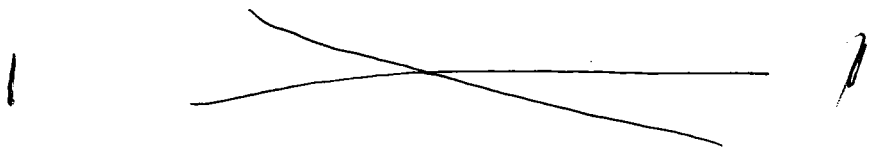
3. "FACILITATION OF THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ERCP



Medical Officer Comments:

The paragraph after being corrected should appear as follows:

"FACILITATION OF THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ERCP



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Narayan Nair
10/25/02 03:03:46 PM
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Joyce Korvick
10/28/02 10:46:12 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136/S001

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS
DIVISION OF BIOMETRICS II

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA:	21136/SE1-001
Name of drug:	SecreFlo™ (synthetic porcine secretin)
Applicant:	ChiRhoClin, Inc.
Indication:	Facilitation of pancreatic and bile duct cannulation during ERCP
Documents reviewed:	NDA volumes 1 to 15 dated 5/3/2002.
Project manager:	Ms. Melissa Furness
Clinical reviewer:	Narayan Nair, MD.
Dates:	Received 5/3/02; PDUFA goal date 11/1/02.
Statistical reviewer:	Wen-Jen Chen, Ph.D.
Statistics team leader:	Thomas Permutt, Ph.D.
Biometrics division director:	Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies.

TABLE OF CONTENTS

1.0 EXECTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

- Based on the sponsor's and this reviewer's analyses through the sponsor's one study data, the successful rate of synthetic porcine secretin, assessed from the statistical perspective, is significantly higher than that of placebo and untreated control.

1.2 Overview of Clinical Program and Studies Reviewed

In this NDA supplement (SNDA) submission, Study CRC97-2 was submitted to support the use of synthetic porcine secretin (sPS) for the clinical indication of stimulation of exocrine pancreas secretions to facilitate the identification of the ampulla of Vater and minor papilla during ERCP procedure in which such identification causes cannulation to be difficult. This study was an ongoing open label study and was submitted in 1999 to support multiple indications, including indication of facilitation of pancreatic and bile duct cannulation during ERCP. However, at that time, because the submitted study report did not contain adequate, meaningful clinical data related to the use of this product to facilitate pancreatic duct cannulation during ERCP, the Agency refused to file this indication.

Study CRC97-2 amended was a Phase III, randomized, crossover multi-center, double blind, and placebo-controlled study with 31 patients enrolled and analyzed. The sponsor indicated at page 19 in Volume 3 that the clinical indication of this study and the study design used to evaluate it are identical to the ones in the synthetic human secretin submitted through NDA 21-256.

1.3 Principal Findings

Based on this reviewer's statistical analyses, the findings for this one study trial is stated below:

- Although this amended double blind study randomized patients to receive either synthetic porcine secretin or placebo as their first treatment in the course of crossover design after untreated control failed, rather than a double blind design, it was, in reality, an open label study since the investigator could identify the treatment (placebo or sPS) for each patient treated by the volume of pancreatic juice produced. Therefore, the assessment on the success of cannulation may be biased toward in favor of the tested drug sPS. However, the bias induced by the implicit open-label scheme for the study may not be serious enough to invalidate the results of the trial.

- In order to avoid the bias induced by missing data replaced with "unsuccessful" as an outcome for the second treatment period in the course of cross over design, this reviewer performs analysis on the difference of two successful rates between sPS and placebo using only first period data. The result shows that the successful rate of sPS is significantly higher than that of placebo at .05 significance level.

2.0 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

In this NDA supplement (SNDA) submission, Study CRC97-2 was submitted to support the use of sPS for the clinical indication of stimulation of exocrine pancreas secretions to facilitate the identification of the ampulla of Vater and minor papilla during ERCP procedure in which such identification causes cannulation to be difficult. This study was an ongoing open label study and was submitted in 1999 to support multiple indications, including indication of facilitation of pancreatic and bile duct cannulation during ERCP. However, at that time, because the submitted study report did not contain adequate, meaningful clinical data related to the use of this product to facilitate pancreatic duct cannulation during ERCP, the Agency refused to file this indication.

The objective of this Phase III study was to obtain efficacy and safety data for sPS to facilitate cannulation of the minor duct in patients with pancreas divisum during ERCP procedure.

This is a randomized, double-blind, crossover multi-center study for the use of sPS (0.2 μg/kg) to facilitate minor pancreatic duct cannulation in patients with pancreas divisum during ERCP procedure. Thirty-one patients were enrolled into this study and evaluated with an untreated control. Of these 31 patients, 2 were successfully cannulated and were not studied further. Each of these 29 patients was then randomized to receive either placebo or secretin as the first treatment in the course of crossover study. However, only when the cannulation was not successful on the first treatment, the opposite treatment was then used for the second period of crossover study. The sponsor indicated at page 28 Volume 4 that of the 29 randomized patients, 13 received placebo first.

The inclusion criteria for study population were 1.) patients suspected diagnosis of pancreas divisum during ERCP and 2.) males or females of non-childbearing potential, 3.) patients without active acute pancreatitis or known sensitivity to secretin.

The primary efficacy variable is the comparative efficacy for minor pancreatic duct localization resulting in successful ERCP cannulation in patients with pancreas divisum. The outcomes for sPS was compared with the outcome for both the untreated control and the placebo treatment using McNemar's test. Statistical significance was declared if the two-sided p-value was ≤ 0.05.

2.2 Statistical Evaluation of Evidence on Efficacy/Safety

2.2.1 Detail Review of Study CRC97-2

Baseline Demographics

Instead of performing statistical analysis on demographic variables and baseline characteristics, the sponsor presented patient's individual data on weight, age, gender, and race. Of the 31 patients, there were 26% (8/31) for males and 90% (28/31) for whites. In addition, the age range

was from 21 to 76 years old while the weight range was from 40 kg to 106 kg.

Efficacy analysis Results and Conclusions

Noted from Data Listing 1 at page 76 of Volume 4, in the course of crossover study, of the 29 patients failed in cannulation evaluated with untreated control, 13 were randomized to receive placebo first versus 16 to sPS. Of the 13 patients who received placebo first, 12 patients with unsuccessful cannulations received sPS as their second treatments and one successful patient was not studied further. As to the 16 patients who received sPS first, 3 patients failed in cannulations received placebo as their second treatments and 13 successful patients were not studied further.

Table 2.2.1, extracted for sponsor's Table 1 at page 6 of Volume 4, presents the results of the comparisons on the successful rates for sPS versus untreated control and sPS versus placebo using all patient population, randomized population, and all available data population. It is noted that all available data population used in McNemar's test consisted of patients with observed data for both treatment periods. However, for the other two populations, the unobserved (missing) data were replaced by "unsuccessful" outcome.

Table 2.2.1 (Sponsor's) Summary of facilitated cannulation success rates of outcomes

	UNTREATED CONTROL GROUP (U)	PLACEBO (P)	SECRETIN (S)	P- VALUE	
				U VS. S	P VS. S
All available population	7% (2/31)	6% (1/16)	89% (25/28)	< 0.0001*	0.0005*
All patient population	7% (2/31)	3% (1/31)	81% (25/31)	<0.0001*	< 0.0001*
Randomized population	0% (0/29)	3% (1/29)	86% (25/29)	< 0.0001*	< 0.0001*

***: Significance at 0.05 significance level by McNemar's test.**
Note: Missing Data in all patient population and randomized population were replaced with unsuccessful outcome.

Table 2.2.1 showed that at .05 significance level, the cannulation successful rate of sPS was significantly greater than that of untreated control and placebo using data from three types of patient populations.

Based on the results of Table 2.2.1, the sponsor concluded that synthetic porcine secretin (sPS) was dramatically effective as an agent to facilitate and make possible the cannulation of the minor pancreatic duct during ERCP for patients with pancreas divisum.

Results of Adverse Events

The sponsor reported that no adverse events were observed and claimed that synthetic porcine secretin was safe and well tolerated in this study.

2.2.2 Statistical Reviewer's Findings

In order to validate the efficacy claim made by the sponsor, this reviewer first comments on issue of the study design and then, performs a statistical analysis using only first period data in the crossover design.

i.) Issue of the study design

- Although this amended double blind study randomized patients to receive either synthetic porcine secretin or placebo as their first treatment in the course of crossover design after untreated control failed, rather than a double blind design, it was, in reality, an open label study since the investigator could identify the treatment (placebo or sPS) for each patient treated by the volume of pancreatic juice produced. Therefore, the assessment on the success of cannulation may be biased toward in favor of the tested drug sPS. However, the bias induced by the implicit open-label scheme for the study may not be serious enough to invalidate the results of the trial.

ii.) Statistical analysis using first period data only

Noted from sponsor's table "CRC97-2 Cannulation" in page 77 of Volume 4, thirteen (13) out of sixteen (16) patients randomized to receive treatment sPS first were successful in cannulation and were not continued to perform ERCP procedure using placebo, based on the assessment rule set up by the study design. Accordingly, data for the 13 patients assessed by placebo as the second treatment in the crossover design were missed because of ERCP procedure not being performed with placebo treatment. In order to avoid the bias induced by missing data replaced with "unsuccessful" as an outcome for placebo, this reviewer performs analysis on the difference of two successful rates between sPS and placebo using only first period data. Table 2.2.2 presents the analysis result.

Table 2.2.2 (Reviewer's) Analysis on the difference of two successful rates

PLACEBO	SPS	EXACT P- VALUE[#]
8% (1/13)	81% (13/16)	0.002

[#]: Exact p-value for testing the equality of two successful rates from two Binomial samples calculated using StatXact.

Table 2.2.2 shows that the successful rate of sPS is significantly higher than that of placebo at .05 significance level.

2.2.3 Conclusions and Recommendations

- Although this amended double blind study randomized patients to receive either synthetic porcine secretin or placebo as their first treatment in the course of crossover design after untreated control failed, rather than a double blind design, it was, in reality, an open label study since the investigator could identify the treatment (placebo or sPS) for each patient treated by the volume of pancreatic juice produced. Therefore, the assessment on the success of cannulation may be biased toward in favor of the tested drug sPS. However, the bias induced by the implicit open-label scheme for the study may not be serious enough to invalidate the results of the trial.
- Based on the sponsor's and this reviewer's analyses through the sponsor's one study data, the successful rate of synthetic porcine secretin, assessed from the statistical perspective, is significantly higher than that of placebo and untreated control.

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

/s/

Wen-Jen Chen
9/6/02 11:08:46 AM
BIOMETRICS

Thomas Permutt
9/9/02 01:44:02 PM
BIOMETRICS
concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136/S001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 21-136
Vol 1

LD 5-1-02
RD 5-3-02

CONFIDENTIAL
April 10, 2002

ChiRhoClin, Inc.
Supplemental Report NDA #21-136, 21-209

PATENT INFORMATION

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

Edward D. Purich, Ph.D.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-136 Supplement Type (e.g. SE5): SE1 Supplement Number: 001

Stamp Date: May 3, 2002 Action Date:

HFD-180 Trade and generic names/dosage form: SecreFlo (secretin) Injection

Applicant: ChiRhoClin,Inc. Therapeutic Class: P

Indication(s) previously approved:

1. For use in secretin stimulation testing for Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction
2. Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma

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

Number of indications for this application(s): 1

Indication #1: Stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangio-pancreatography (ERCP).

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

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

***No pediatric data submitted. No waiver requested. However, is an Orphan Product, so rule is NA.**

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

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

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze

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

/s/

Alice Kacuba
11/6/02 05:04:17 PM

NDA 21-136 LDS-1-02 RAS-3-02

CONFIDENTIAL
April 10, 2002

ChiRhoClin, Inc.
Supplemental Report NDA #21-136, 21-209

1 of 1

DEBARMENT STATEMENT

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

Edward D. Purich

Edward D. Purich, Ph.D.

21-136 LD 5-1-02 RD 5-3-02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See List of Investigators (attached)	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Edward D. Purich, Ph.D.	CEO
FIRM/ORGANIZATION: ChiRhoClin, Inc.	
SIGNATURE: Edward D. Purich	DATE: 5/3/02

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

000001

FORM FDA 3454 (3/99)

ChiRhoClin, Inc.
Certification/Disclosure Form
Financial Disclosure by Clinical Investigators

1. Study Name:
   Synthetic Porcine Secretin Open-Label Clinical Use Protocol

2. Protocol Number:	3. Product Name:
CRC97-2 Amendment	SecreFlo

4. Investigator X Sub-investigator ☐

5. Investigator/Sub-investigator Name:
   Institution Name *(if applicable)*

6. Address:

7. Telephone Number:	8. Fax Number:

9. Indicate by marking Yes or No if any of the financial interests or arrangements of concern to FDA (and described below) apply to you, your spouse, or dependent children:

Yes	No	
☐	X	Financial arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest. *If yes, please describe:*
Yes	No	
☐	X	A proprietary or financial interest in the test product such as patent, trademark, copyright, or licensing agreement. *If yes, please describe:*
Yes	No	
☐	X	A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or an equity interest in a publicly traded company exceeding $50,000. *If yes, please describe:*

Or

X I hereby certify that none of the financial interests or arrangements listed above exist for myself, my spouse, or my dependent children.

In accordance with 21 CFR Parts 54.1 to 54.6, I declare that the information provided on this form is to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the study as specified in the protocol, I will notify ChiRhoClin, Inc.

10. Signature:	11. Date:
	3/20/01

ChiRhoClin, Inc.
Certification/Disclosure Form
Financial Disclosure by Clinical Investigators

1. Study Name:
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2. Protocol Number:	3. Product Name:
CRC97-2 Amendment	SecreFlo

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   Institution Name *(if applicable)*:

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7. Telephone Number	8. Fax Number:

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Yes	No	
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10. Signature:	11. Date: 3.21.01

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Certification/Disclosure Form
Financial Disclosure by Clinical Investigators

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2. Protocol Number:	3. Product Name:
CRC97-2 Amendment	SecreFlo

4. Investigator X Sub-investigator ☐

5. Investigator/Sub-investigator Name:
   Institution Name *(if applicable)*:

6. Address:

7. Telephone Number:	8. Fax Number:

9. Indicate by marking Yes or No if any of the financial interests or arrangements of concern to FDA (and described below) apply to you, your spouse, or dependent children:

Yes	No	
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Or

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10. Signature:	11. Date: 3/22/01

ChiRhoClin, Inc.
Certification/Disclosure Form
Financial Disclosure by Clinical Investigators

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2. Protocol Number:	3. Product Name:
CRC97-2 Amendment	SecreFlo

4. Investigator X Sub-investigator ☐

5. Investigator/Sub-investigator Name:
   Institution Name *(if applicable)*:

6. Address:

7. Telephone Number:	8. Fax Number:

9. Indicate by marking Yes or No if any of the financial interests or arrangements of concern to FDA (and described below) apply to you, your spouse, or dependent children:

Yes	No	
☐	X	Financial arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome, or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest. *If yes, please describe:*
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Or

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In accordance with 21 CFR Parts 54.1 to 54.6, I declare that the information provided on this form is to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last patient has completed the study as specified in the protocol, I will notify ChiRhoClin, Inc.

10. Signature:	11. Date: 3/26/01

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EXCLUSIVITY SUMMARY for NDA # 21-136 SUPPL # SE1-001
Trade Name SecreFlo Generic Name secretin
Applicant Name ChiRhoClin, Inc. HFD- HFD-180
Approval Date November 1, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/__/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1-001

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

      YES /_X__/ NO /___/

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

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

   d) Did the applicant request exclusivity?

      YES /___/ NO /_X__/

      If the answer to (d) is "yes," how many years of

exclusivity did the applicant request?

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

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates

or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

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

NDA # NDA 21-136, original NDA for SecreFlo

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART

III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

For the purposes of this section, studies comparing two

products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /_X_/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /_X_/

If yes, explain:

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

Investigation #1, Study # CRC 97-2

Investigation #2, Study # _____

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency

to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1_, Study # CRC 97-2

Investigation #2_, Study # _____

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 54,196 YES /_X__/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be

used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Division Director Date

cc:

HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Joyce Korvick
11/1/02 03:21:45 PM
for Dr. Robert Justice

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-136/SE1-001

Name of Drug: SecreFlo™ (secretin) Injection

Sponsor: ChiRhoClin, Inc.

Material Reviewed

Type of Submission: Paper

Submission Date: May 1, 2002

Receipt Date: May 2, 2002

Filing Date: July 2, 2002

User-fee Goal Date: November 3, 2002

Proposed Indication: Stimulation of exocrine pancreas secretions to facilitate the identification of the ampulla of Vater and minor papilla during ERCP procedures in which such identification and, therefore, cannulation is difficult.

Other Background Information: NDA 21-136 was originally submitted on May 14, 1999. Two indications (diagnosis of pancreatic exocrine disease; [redacted]) were filed and two indications (diagnosis of gastrinoma and the facilatation of pancreatic duct cannulation during ERCP) were refuse-to-file. The firm was granted a meeting in which they outlined their plans to request that the 2 indications be filed-over-protest. Upon hearing that the indication of the facilitation of pancreatic duct cannulation during ERCP would require the submisison of a user fee, the firm only requested that the indication of diagnosis of gastrinoma (Zollinger-Ellison Syndrome) be filed-over-protest. Being that the indication being over filed-over-protest was granted a 6 month priority review designation, while the original 2 indications were granted a standard review designation, the indication of diagnosis of gastrinoma (Zollinger-Ellison Syndrome) was administratively split into a separate application, NDA 21-209) with a separate review clock.

NDA 21-136 provided for:

1. diagnosis of pancreatic exocrine disease
2. [redacted]

NDA 21-209 provided for:

1. diagnosis of gastrinoma (Zollinger-Ellison Syndrome

NDA 21-209 was issued a Approvable (AE) letter on May 16, 2000 and again on November 28, 2000.

NDA 21-136 was issued a letter on March 24, 2000, which made the first indication (diagnosis of pancreatic exocrine disease) Approvable (AE) and t[redacted]

On November 7, 2000, another AE letter was issued.

Subsequesntly, both applications were approved on April 4, 2002. Please note that the wording of the approved indications are as follows:

NDA 21-136:

1. [redacted] for stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction.

NDA 21-209:

1. [redacted] for stimulation of gastrin secretin to aid in the diagnosis of gastrinoma.

The firm is now submitting this current supplement (SE1-001) to provide for the following indication: Stimulation [redacted]

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	X		Volume 1, page is not numbered
2. Form FDA 356h (original signature)	X		Volume 1, page 1. The 356h form contains the incorrect proposed indication. The firm has been asked to correct this.
a. Establishment information	X		Volume 12, page 1-3

b. Reference to DMF(s) & Other Applications	X		IND ~~~ 56,821; ~~~ NDA21-136; 21-209
3. User Fee FDA Form 3397	X		Volume 14, page 1
4. Patent information & certification	X		Volume 1, page 4; Volume 10, page 1, Volume 11, page 11
5. Debarment certification (Note: Must have a definitive statement)	X		Volume 1, page 3; Volume 13, page 1
6. Field Copy Certification		X	
7. Financial Disclosure	X		Volume 15, page 1-5
8. Comprehensive Index	X		Volume 1, page 5 and ____ Each study has its own index
9. Pagination	X		Each section is paginated beginning with 00001. Page number appears in lower right hand corner. Reviewers will need to include both volume and page numbers in citations
10. Summary Volume	X		Volume 3
11. Review Volumes	X		
12. Labeling (PI, container, & carton labels)	X		Volume 2 (package insert only)
a. unannotated PI	X		Volume 2
b. annotated PI	X		Volume 2
c. immediate container		X	N/A
d. carton		X	N/A
e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	N/A
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Volume 8
14. Case Report Forms (paper or	X		Volume 9

electronic) (for death & dropouts due to adverse events)			

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		
2. Foreign Marketing History	X		
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Volume 3, page 15
b. Nonclinical Pharmacology/Toxicology	X		Volume 3, page 16
c. Human Pharmacokinetic & Bioavailability	X		Volume 3, page 17
d. Microbiology	X		Volume 3, page 18
e. Clinical Data & Results of Statistical Analysis	X		Volume 3, page 19
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Volume 3, page 24
5. Summary of Safety	X		Volume 6, page 1
6. Summary of Efficacy	X		Volume 5, page 597

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)

1. List of Investigators	X		Volume 4, page 1
2. Controlled Clinical Studies			
a. Table of all studies		X	
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Volume 4
c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)	X		Volume 5, page 597
4. Integrated Summary of Safety (ISS)	X		Volume 6,page 1
5. Drug Abuse & Overdosage Information	X		Volume 6, page 3
6. Integrated Summary of Benefits & Risks of the Drug		X	
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		X	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	This is an orphan indication

2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			
a. Proposed unannotated labeling in MS WORD	X		
b. Stability data in SAS data set format (only if paper submission)		X	N/A
c. Efficacy data in SAS data set format (only if paper submission)		X	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement (optional)		X	

Y=Yes (Present), N=No (Absent)

[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).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Additional Comments:
On June 4, 2002 a filing meeting was held. The outcome of that internal meeting was that the application is fileable. There was one statistical information request (IR). This IR was faxed to

the firm on June 7, 2002.

A Time line based on a priority review was distributed to meeting attendees.

Conclusions

This application is fileable from an administrative perspective. The 6 month user fee goal date for this application is November 3, 2002.

Name
Regulatory Health Project Manager

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/s/

Alice Kacuba
7/3/02 02:40:46 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 25, 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

Total no. of pages including cover: 11

Comments: Attached is a copy of the FDA revised labeling for NDA 21-136/SE1-001. Strikeouts denote requested deletions and double underlines denote requested additions. Please let us know in writing if you accept our revisions.

9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓
_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-136
5001

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/s/

Alice Kacuba
10/25/02 12:46:51 PM
CSO

ChiRhoClin, Inc.
15500 Gallaudet Avenue
Silver Spring, MD 20905-4176
301-384-1554
FAX 301-384-1565
epurich@chirhoclin.com
www.chirhoclin.com

facsimile transmittal

To:	Victor Raczkowski, MD	**Fax:**	301-443-9285
From:	E. Purich	**Date:**	10/24/02
Re:	NDA #21-136/SE1-001	**Pages:**	13
CC:			

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

Dear Dr. Raczkowski,

In regards to your fax dated October 23, 2002, please refer to attached letter for our response.

Thank you,

Edward D. Purich

Edward D. Purich, Ph.D
CEO

ChiRhoClin, Inc.
15500 Gallaudet Avenue
Silver Spring, MD 20905
(301) 384-1554 FAX (301) 384-1565

October 24, 2002

Victor F. C. Raczkowski, MD, M.Sc.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
HFD 180
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

Re: NDA #21-136 and #21-209

Dear Dr. Raczkowski,

We have reviewed your proposed changes to the draft package label for the supplemental NDA #21-136 for SecreFlo™ and find them acceptable. We do wish to make one clarification concerning the elimination half-life of secretin (SecreFlo™). You have asked why we changed the value from 27 minutes to 2.7 minutes. The answer is there was a typographical error in the final package label deleting the decimal point, which we corrected in the printed version and submitted to you.

The May 8, 2000 NDA #21-136 amendment contains the pharmacokinetic study. Table 2 (Vol. 6.1, Page 129) provides 2.74 minutes as the half-life for secretin. Attached is the relevant documentation from the PK report of study CRC99-10, which establishes this. We apologize for the typo and any procedural errors we might have made but believed the printed version of the label correcting this obvious typo was satisfactory.

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

Sincerely,

Edward D. Purich

Edward D. Purich, Ph.D.
CEO
FDA/VR102402L

TABLE 2
PORCINE SECRETIN PPHARM INDIVIDUAL PARAMETERS
Gauss-Marquardt Algorithm Estimations

Sub. #	Parameter (Units)														
	Clearance (mL/Min)	Volume (mL)	K12 (1/Min)	K21 (1/Min)	Weight (Kg)	K (1/Min)	AUCobs{0-t} (pgMin/mL)	AUCinf (pgMin/mL)	MRT (Min)	T1/2 (Min)	K+K12+K21 (1/Min)	Alpha (1/Min)	Beta (1/Min)	Cmax (pg/mL)	Cmax {IV bolus only} (pg/mL)
1*															
2															
3															
4															
5															
6															
7*															
8															
9*															
10															
11															
12															
Mean	487.2	1938.2	0.00898	0.02632	78.3	0.25586	36824.1	47086.1	8.13	2.74	0.2912	0.2658	0.0253	8396	9570
SD	136.3	579.2	0.00564	0.00953	11.2	0.03155	13590.3	16102.4	3.14	0.3	0.0365	0.0288	0.0094	5261	4187
CV	28.0	29.9	62.8	36.2	14.4	12.3	36.9	34.2	38.6	11.8	12.5	10.8	37.1	63	44

NOTE: * Subject plasma concentrations profile is inconsistent with IV Bolus Administration

Half life 2.74 minutes

9 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-136
S001

2.0 LABELING

Please find attached two copies of the proposed labeling for SecreFlo™ (synthetic porcine secretin). The first copy has the track changes highlighted; the second is the final copy with changes added.

24 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21436
5001

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 23, 2002

To: Edward D. Purich, Ph.D. CEO	**From:** Alice Kacuba, R.N., MSN, RAC Regulatory Health Project Manager 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

Total no. of pages including cover: 11

Comments: Attached is a copy of the FDA revised labeling for NDA 21-136/SE1-001. Strikeouts denote requested deletions and double underlines denote requested additions. Please let us know if you accept our revisions.

9 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 21-136
S001

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/s/

Alice Kacuba
10/23/02 05:57:05 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 7, 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

Total no. of pages including cover: 3

Comments: Attached is an Information Request regarding SecreFlo, S-001.

In order to review drug synthetic porcine secretin for the indication of cannulation, please have the sponsor provide the following information for Study CRC97-2:

I. Study Design

As noted by this reviewer, the sponsor indicated in the section of Overview of Clinical Studies, printed in Volume 3 submitted through NDA 21-136, that the study design for CRC97-2 is identical to the one submitted through NDA 21-256 for drug synthetic human secretin. However, the detailed procedure for the randomization of patients to the following three treatments is not clear: untreated control, placebo, and synthetic porcine secretin (sPS). Please request the sponsor to provide detailed information of the study design for Study CRC97-2. The information should include the following:

1.) What was the exact procedure for patients randomized to each of the three treatments: untreated control, placebo, and sPS? Was cannulation attempted in all patients without secretin and then failures randomized to either placebo or sPS as their first treatments? Were randomized patients who failed with the first treatment to be cannulated using the second treatment?
2.) Of the 31 enrolled patients, how many patients were assigned to untreated control and how many patients randomized to either placebo or sPS as their first treatment in the course of crossover design?

II. Data set information

As noted by this reviewer, the sponsor provided facilitated cannulation information, page 76 of Volume 4 submitted for Study CRC97-2 through NDA 21-136, for 31 enrolled patients. However, unlike cannulation information provided for Study CRC98-4 at page 789 of Volume 29 submitted through NDA 21-256, the facilitated cannulation information for Study CRC97-2 did not clearly specify the first and the second treatments of the randomized patients. Please let the sponsor use the format of Study CRC98-4 to present the facilitated cannulation information for Study CRC97-2.

The information variables included in the format of Study 98-4 are as follows (please refer to Study CRC98-4):

Subject ID, Site, Subject Initials, Without Treatment Tried Cannulation (untreated control), Without Treatment Cannulation Successful, First Treatment, First Treatment Tried Cannulation, First Treatment Cannulation Successful, Second Treatment, Second Treatment Tried Cannulation, Second Treatment Cannulation Successful.

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/s/

Alice Kacuba
6/7/02 09:16:32 AM
CSO

21-136 CD 5-1-02 RD 5-3-02

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

ChiRhoClin, Inc.
15500 Gallaudet Ave.
Silver Spring, MD 20905

2. TELEPHONE NUMBER *(Include Area Code)*

(301) 384-1554

3. PRODUCT NAME

Secretin-Repligen

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

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

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

21-136

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

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

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

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

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

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

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

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

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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

000001

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Edward D Pugh	CEO	5/3/02

FORM FDA 3397 (5/98)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-136/S-001

PRIOR APPROVAL SUPPLEMENT

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

Dear Dr. Purich:

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

Name of Drug Product: SecreFlo (synthetic porcine secretin)

NDA Number: 21-136

Supplement Number: S-001

Review Priority Classification: Priority (P)

Date of Supplement: May 1, 2002

Date of Receipt: May 3, 2002

This supplement provides for the following change: stimulation of —— pancreas secretions to facilitate the identification of the ampulla of Vater and minor papilla during ERCP

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 2, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 3, 2002.

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

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

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

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-1602.

Sincerely,

{See appended electronic signature page}
Alice Kacuba, R.N., MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
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/

Alice Kacuba
6/18/02 11:12:48 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

March 7, 2000

ChiRhoClin, Inc.
15500 Galludet Ave.
Silver Spring, MD 20905-4176

Attention: Edward D. Purich, PhD
President and CEO

Dear Dr. Purich:

Reference is made to your orphan designation application of October 14, 1999, submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 USC § 360bb) for the designation of synthetic porcine secretin as an orphan drug (application #99-1302). We also refer to your amendment dated February 4, 2000.

We have completed the review of this application and have determined that synthetic porcine secretin qualifies for orphan designation for use in conjunction with diagnostic procedures for pancreatic disorders to increase pancreatic fluid secretion. Please note that it is synthetic porcine secretin and not its formulation that has received orphan designation.

Please be advised that if your synthetic porcine secretin product were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 USC § 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of synthetic porcine secretin as designated. Also an annual progress report must be submitted

2. For the purpose of orphan drug designation, the indication should read as follows: "Secretin is indicated for use in conjunction with diagnostic procedures for pancreatic disorders to increase pancreatic fluid secretion." Please be advised that this indication is not necessarily the same as the indication(s) in the marketing application(s) for secretin.

To facilitate our action on your application, we request that you provide: (1) diagnostic procedures for pancreatic disorders currently performed in clinical setting (besides ERCP and MRCP) that may require the adjunct use of secretin, and (2) the estimated number of patients who will receive secretin during these procedures. These can be submitted as supplemental information to this application for orphan designation, #99-1302.

We note that the same synthetic porcine secretin has previously received separate orphan drug designations for: (1) the evaluation of exocrine pancreas function (Designation # 98-1202), (2) [illegible], and (3) the diagnosis of gastrinoma (Designation # 98-1204). The exclusive approval for these designations, once the marketing applications have been approved, shall be recognized as distinct and separate from the current designation.

Further review of this application is being held in abeyance pending receipt of any new information. A written response to this letter must be received within 90 days from the date of this communication or the file will be considered inactive and withdrawn. Following 90 days, further requests for designation of the same product for the same indication must be made in the form of a new designation application. Information contained in this file may be cross-referenced in support of a new designation request.

Please provide copies of appropriate references used in support of any new submissions. Your cooperation is appreciated.

Sincerely yours,

Marlene E. Haffner

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

within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Tan T. Nguyen, MD, PhD at (301) 827-0983.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner

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