/s/

Brian Strongin
1/19/01 10:22:11 AM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 14, 1999
Time: 1:00PM
Location: Parklawn Building, Conference Room L

Application: NDA 21-136; ——— (synthetic porcine secretin)

Type of Meeting: Informal Conference following a Refusal-to-File

Meeting Chair: Lilia Talarico, M.D.

Meeting Recorder: Brian Strongin

FDA Attendees, Titles, and Office/Division:

The Division of Gastrointestinal and Coagulation Drug Products

Lilia Talarico, M.D.	Director
Steve Aurecchia, M.D.	Deputy Director
Hugo Gallo-Torres, M.D., Ph.D.	Medical Team Leader, GI Drugs
Larry Goldkind, M.D.	Medical Officer
Brian Strongin	Regulatory Health Project Manager

The Division of Biometrics II

Ed Nevius, Ph.D.	Director

External Constituent Attendees and Titles:

ChiRhoClin, Inc.

Seymour Fein, M.D.	Chairman, Medical Director
Ed Purich, Ph.D.	CEO

Background:

NDA 21-136, submitted May 14, 1999, received May 23, 1999, provides for diagnosis of pancreatic exocrine ——— diagnosis of gastrinoma ——— and facilitation of ——— during ERCP. The sponsor is ChiRhoClin, Incorporated.

Secretin-Ferring (BPS), derived from porcine sources, has been approved under NDA 18-290since

May 29, 1981. It is labeled for the first three indications proposed for synthetic porcine secretin (SPS).

Efficacy is supported by the following studies:

1. CRC 98-1, a crossover study of SPS vs. BPS in 12 patients with chronic pancreatitis, compared the diagnostic efficacy of the two products.
2. CRC 98-2, designed similarly to CRC 98-1, compared the diagnostic efficacy of SPS vs. synthetic human secretin (SHS), also a ChiRhoClin product, in 12 patients with chronic pancreatitis.
3. CRC 97-2, an open-label uncontrolled trial of SPS used for the proposed indications. The study had enrolled 16 patients at the time of NDA submission.

Safety is supported by the three efficacy studies as well as study CRC 97-3. This study is an ongoing 1,500 patient, double-blind, placebo-controlled, parallel group study evaluating the use of SPS to prevent post-ERCP pancreatitis. The firm has submitted an interim analysis of 250 patients.

A refusal-to-file letter was sent July 22, 1999 for the diagnosis of gastrinoma and facilitation of [redacted] An "informal conference" to discuss the refusal-to-file letter, per 21 CFR 314.101(a)(3), was requested by the firm August 17, 1999).

Meeting Objectives:

to review the Division's decision to refuse-to-file the diagnosis of gastrinoma and facilitation of [redacted] indications in light of the new data acquired since submission of the application

Discussion Points:

1. The firm briefly reviewed the background of this application and summarized the additional data/information included in the background package for the gastrinoma and facilitation of [redacted] indications. The patients were enrolled in Study CRC 97-2, an open-label, uncontrolled study of synthetic porcine secretin used for the indications proposed for approval.

2. The firm's questions were discussed. The questions are italicized below followed by the
3. division's responses.

A) Zollinger-Ellison Syndrome (ZES)

Are the data from CRC 97-2 now sufficient to support filing of this indication?

Will the results from CRC 99-8 ——————————————————
be required prior to approval of this indication?

The data provided from study CRC 97-2 are not sufficient to support the filing of an application for the diagnosis of gastrinoma. These data are inadequate to characterize your product as a diagnostic tool in patients with ZES. Although this study provided data from 11 patients with suspected gastrinoma, comparative data with biologically derived porcine secretin were either lacking or inadequate. We recommend submitting a complete study report and data from Study CRC 99-8 in support of this indication.

(Note: The firm responded that they will begin Study CRC99-8, a randomized cross-over study of SPS, SHS, and BPS for the diagnosis of ZES in 6-12 patients, as soon as possible. They may submit an interim report for the first 6 patients. We explained that, although we realized that the study would not enroll a sufficient number of ZES patients to perform the type of rigorous statistical analysis usually necessary for a diagnostic agent, data of the type to be gathered in Study CRC 99-8 are necessary to support the ——)

B) Facilitation of ——————

Is the information provided by ——— and the prior extensive use of secretin for this purpose in clinical practice adequate to document this medical use of secretin?

Are the data from CRC97-2 adequate to support the approval of this indication?

The data provided from study CRC97-2 and the information provided by ——— are not sufficient to support the filing of an application for this indication. Replicated data from adequate and well-controlled studies are needed to assess the approvability of SPS for the new indication of "facilitation of——————————
ERCP". You might consider a blinded study in which patients unable to be cannulated within a time limit are randomized to either secretin or placebo and the ability to cannulate within a time limit is compared. A cross-over regimen can be employed for patients with unsatisfactory cannulation within the time limit.

Published literature notes the theoretical potential for injecting contrast against pressure and therefore increasing the pressure within the pancreatic duct when secretin is used in this setting. In addition, repeated attempts at cannulation of the pancreatic duct and the associated trauma to the ampulla may increase the complication rate associated with ERCP. Also, the interim results of study CRC 97-3 may indicate a trend towards a higher rate of complications following the use of secretin in the ERCP setting. In light of these issues, meaningful diagnostic gain (i.e., improved success) and safety must be demonstrated with the use of secretin for approval of this indication. In order to be

adequate for filing, studies of the type described must be submitted for review. We suggest submitting a study protocol to the Division for review and comment.

(Note: The firm responded that they will submit a protocol incorporating these suggestions in 10-20 patients requiring SPS to facilitate cannulation. The Division commented that the protocol must specify the facilitation of cannulation of the accessory (minor) pancreatic duct if applicable. The sponsor's proposed draft labeling must also be changed accordingly. Replication of the data gathered from the planned study, as well as additional safety data in the population to be studied will be necessary. Data from Study CRC 97-2 can be supportive. A statistical plan, including a calculation for confidence intervals, should be submitted. The Division is available for assistance if necessary.)

3. The Division informed the firm that a request to file-over-protest should be submitted in writing and received by the Division by October 17, 1999. The data from Study CRC 99-8 and the planned study for the facilitation of cannulation should be submitted as soon as possible. If a request to file-over-protest is made the data/information regarding the ZES and ——— indications will be administratively split into a separate NDA and probably receive a priority designation. If a major amendment is received within three months of the user fee due date, the due date may be extended by 3 months.)

Minutes Preparer: [/S/] 10/5/99

Chair Concurrence: [ ] 10-5-99

cc: Original
HFD-/Div. Files
HFD-/Meeting Minutes files
HFD-/CSO
HFD-/reviewers & attendees

Drafted by: BKS/October 4, 1999
Initialed by: HGT/October 5, 1999
LT/October 5, 1999
final: BKS/October 5, 1999
filename: c:\wpfiles\minutes\21136910.0

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

MEMORANDUM OF TELECON

DATE: April 2, 2002

APPLICATION NUMBER: NDA 21-136, Synthetic Porcine Secretin for Injection

BETWEEN:

Name: Edward Purich, Ph.D.; CEO ChiRhoClin, Inc.
Phone: (301) 384-1554

AND

Name: Arthur Shaw, Ph.D.; Review Chemist
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: NDA 21-136 Certificate of Analysis for Porcine Secretin Drug Product, MV Package and Post-approval Commitment For Impurity Assay.

In the March 13, 2002 submission to NDA 21-136, ChiRhoClin submitted a revised Final Product Testing Plan (FPTP) and Certificate of Analysis (COA) (Pages 107 and 108). The FPTP contains a test for Identity but the COA does not. I brought this discrepancy to Dr. Purich's attention. He said he would talk to Chesapeake Biological Laboratories, who manufacture and release the drug product, to ask them to amend the COA.

In the March 1, 2002 submission, ChiRhoClin committed to developing an assay for impurities in the drug product. I told Dr. Purich that this would be a post-approval commitment with a time frame of nine months. He agreed to this. He said they were working on an assay — ; he said was suggested by an FDA chemist. I told him I hadn't suggested that. He said this concentration was necessary to gain the sensitivity needed to detect — impurities. I told him I couldn't comment on the necessity for this since I didn't have the data in front of me.

I advised Dr. Purich to submit the Methods Validation Package for the existing assays before the assay for the impurities was finished. He agreed.

The call was then concluded.

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

/s/

Arthur B. Shaw
4/2/02 10:04:03 AM
CHEMIST

MEMORANDUM OF TELECON

DATE: December 15, 2000

APPLICATION NUMBER: NDA 21-136, synthetic porcine secretin

BETWEEN:

Name: Mr. Edward Allera,
Phone: (202) 452-7985
Representing: ChiRhoClin Inc.

AND

Name: Bronwyn Collier, Associate Director for Regulatory Affairs
Office of Drug Evaluation III, HFD-103

SUBJECT: Request for Special Considerations Meeting

Background: NDA 21-136 was submitted May 14, 1999. Approvable letters were issued for this application on March 24, 2000 and November 7, 2000. A meeting was requested (correspondence dated December 4, 2000) to discuss concerns regarding the review of the application. Prior to this call, the review team had had a meeting on December 6, 2000, with the sponsor and a representative from their new contract drug substance manufacturer [redacted] to discuss and clarify the chemistry, manufacturing, and controls deficiencies raised in the November 7, 2000, approvable letter.

Call: The following concerns raised in the meeting request were discussed with Mr. Allera:

1. The drug was inappropriately treated as a new chemical entity.
   Response: The application for synthetic porcine secretin (NDA 21-136) has never been classified as a new chemical entity. It is under review as a 505(b)(1) application.
2. Excessive pre-clinical study requirements have been imposed.
   Response: The standards applied concerning pre-clinical study requirements are consistent with current standards and applications under review.
3. Excessive clinical data requirements [case report forms] were imposed.
   Response: Regulations permit FDA to request any and all case report forms. The overall population studied and submitted to NDA 21-136 was very small, thus, the request did not constitute an undue burden. The case report forms ultimately were helpful in review of the studies submitted to support safety and efficacy.
4. FDA inspections of the manufacturing facilities were inefficient and inexperienced.
   Response: This office cannot address these issues. Mr. Allera was referred to Ms. Pat Alcock, Director of the Drug Manufacturing and Quality Branch of CDER compliance.
5. Review of the chemistry, manufacturing, and controls (CMC) portion of the NDA was inefficient and uncooperative.

Response: The Division of Gastrointestinal and Coagulation Drug Products pursued review of the CMC information in a manner consistent with CDER policy. The division also communicated frequently with the sponsor regarding CMC issues as detailed in our letter dated December 8, 2000.

Mr. Allera maintained that current standards regarding data requirements were being applied inconsistently. In response to my request for examples, Mr. Allera said that mifepristone had been approved for a market formulation different than that used in clinical trials. I informed Mr. Allera that sponsors sometimes do change a drug's formulation from that used in clinical trials but that a bridge supporting bioequivalence between the formulations is required before the drug can be approved. This is one of the standards applied for this application. I suggested that Mr. Allera submit any other examples he has for our consideration.

I informed Mr. Allera that Brian Strongin, project manager for this application, and Dr. Koepke, Deputy Director, Division of New Drug Chemistry II, had reported to me that the December 6, 2000, meeting to discuss CMC deficiencies had been positive and that the representative at the meeting from [redacted] seemed very knowledgeable about the manufacture of peptides and should be very helpful to them. Mr. Allera said that he had not yet talked to Drs. Purich and Fein from ChiRhoClin about the meeting and acknowledged that the concerns raised in his December 4, 2000, letter may have been addressed adequately at that meeting. Mr. Allera agreed that the meeting he requested was not appropriate at this time given our current discussion of the issues above and his need to discuss the outcome of the December 6, 2000, meeting with Drs. Purich and Fein.

_____

Bronwyn Collier
Associate Director for Regulatory Affairs

/s/

Bronwyn Collier
12/29/00 02:59:32 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE October 24, 2000

NDA NUMBER: 21-136 and 21-209
BETWEEN: Edward Purich

Representing ChiRhoClin
Phone Number 301-384-1554
AND
Name: Arthur B. Shaw, Ph.D. [illegible] 10/25/00
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Mr. Purich called to inform me that the procedure and validation for the in-process control of secretin content (requested in my email dated October 23, 2000) could be found in the December 29, 1999 submission on Pages 244-317. He told me that Chesapeake Biological Laboratories (CBL) was performing the in-process control (IPC). He then told me that CBL was not capable of performing the assay on the finished product because, at the low concentration of secretin used in the finial product assay [illegible] CBL did not have the analytical capability of performing the assay. I told him that that was not a good sign, since an assay used for regulatory release should be reproducible and would need to be validated by FDA laboratories. He told me that CBL had [illegible] and that was why they were unable to perform the assay at the low concentration. He then told me that the reason that the concentration of the secretin in the reconstituted finished product was so low was that it could not be reconstituted at the fill volume of one mL. The volume for reconstitution is 8 mL, yielding 2 µg/mL. He told me that if the drug product is reconstituted at [illegible]

Discussion:
I checked the volume of the NDA Mr. Purich told me about. The assay used by CBL uses the same HPLC method as that used for the finished product release assay. However, the bulk drug product solution before filling into the vials is formulated at [illegible] of secretin. The assay as performed by CBL is linear in the range of [illegible] The linearity determination was performed by injecting different volumes of porcine reference standard at [illegible] The actual assay of the in-process samples involves [illegible]

The problem with the finished product assay, as discussed in my reviews, is that the assay is

Conclusion: The applicant should be sent an Information request letter with the following requests:

1. Provide experimental data to demonstrate attempts to reconstitute the finished secretin drug product at the original fill volume of — Include experimental data to determine the minimum volume required for reconstitution.
2. Explain what measures were taken to change the lyophilization process or the formulation in order to achieve a drug product that could be reconstituted at the original fill volume.
3. Explain why the method for the finished product developed by — was not able to be reproduced at Chesapeake Biological Laboratories. A regulatory release method should be rugged enough to be reproducible.

Arthur B. Shaw, Ph.D.

cc: Original NDA 21-136
Original NDA 21-209
HFD-180/Div File NDA 21-136
HFD-180/Div File NDA 21-209
HFD-180/AShaw
HFD-180/LZhou
HFD-180/VRaczkowski
HFD-180/LTalarico
C:\WORD\NG\21-136 SYNTHETIC PORCINE SECRETIN TELECON 24-OCT-2000.DOC

TELECON

MEMORANDUM OF TELECON

DATE: October 23, 2000

APPLICATION NUMBER: NDA 21-136. Synthetic Porcine Secretin for Injection

BETWEEN:

Name: Edward Purich, Ph.D.; CEO ChiRhoClin, Inc.

Phone: (301) 384-1554

AND

Name: Brian Strongin, Regulatory Health Project Manager
Liang Zhou, Ph.D.; Team Leader, Chemistry, Manufacturing and Controls
Art Shaw, Ph.D.; Review Chemist
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: — Assay for Drug Substance Purity and Impurities and Validation of the Assay

Background

NDA 21-136, submitted May 14, 1999 by ChiRhoClin, Inc., provides for the use of Synthetic Porcine Secretin for Injection (SPS) for: (1) diagnosis of pancreatic exocrine —, (3) diagnosis of gastrinoma; and (4) facilitation of pancreatic duct cannulation during ERCP. An approvable letter dated March 24, 2000 cited clinical, CMC, biopharmaceutics, and labeling issues. Today's call concerns the VCU assay for drug substance purity and impurities and validation of the assay.

Today's Call

Dr. Shaw opened by explaining that the Division had questions about the — assay for drug product purity and impurities and its validation. He expressed the Division's concerns about the limit of detection (LOD) and limit of quantitation (LOQ) for the assay and asked the firm if they had submitted data to demonstrate that the assay is capable of detecting impurities in concentrations less than —. Dr. Shaw explained that if the — assay is to be considered stability-indicating, the drug product must be subjected to conditions that degrade it and it then must be analyzed for impurities. A specific, validated procedure must be submitted. It is not sufficient to merely analyze the concentration of drug substance in the drug product. Impurities must be specifically detected and quantified. Dr. Shaw recommended —

Dr. Shaw suggested the firm explore a variety of methods of applying to the drug product the data regarding impurities developed from drug substance testing. In response to the firm's question regarding releasing drug product based on the results of a bioassay only. Dr. Shaw deferred his response until he had completed his review of the October 12, 2000 amendment.

In response to Dr. Shaw's request, the firm agreed to provide a complete description of the exact procedures for the following four assays briefly described in the report entitled, "Method Validation Report for the Determination of Porcine and Human Secretin by [redacted] on page 619 of the October 12, 2000 amendment:

1. Determination of Content Uniformity of Final Parenteral Porcine Secretin Product
2. Determination of Porcine Secretin Amount in Stability Samples of Parenteral Porcine Secretin Product Stored as Per Stability protocol
3. Determination of Porcine Secretin Concentration During In-Process Manufacture of Porcine Secretin Parenteral
4. Determination of Content Purity and Impurities of Porcine Secretin Bulk Drug Substance.

The call was then concluded.

/s/

Brian Strongin
11/14/00 11:03:33 AM
CSO

Brian Strongin
11/14/00 11:11:40 AM
CSO

MEMORANDUM OF TELECON

DATE: October 17, 2000

APPLICATION NUMBER: NDA 21-136, Synthetic Porcine Secretin for Injection

BETWEEN:

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

AND

Name: Brian Strongin, Regulatory Health Project Manager
Liang Zhou, Ph.D.; Team Leader, Chemistry, Manufacturing and Controls
Art Shaw, Ph.D.; Review Chemist
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Chemistry, Manufacturing, and Controls (CMC) Information Request

Background

NDA 21-136, submitted May 14, 1999 by ChiRhoClin, Inc., provides for the use of Synthetic Porcine Secretin for Injection (SPS) for: (1) diagnosis of pancreatic exocrine — (2) — (3) diagnosis of gastrinoma; and (4) facilitation of — during ERCP. An approvable letter dated March 24, 2000 cited clinical, CMC, biopharmaceutics, and labeling issues. A CMC Discipline Review Letter dated September 19, 2000 included several comments regarding deficiencies identified in a review of the CMC section. Today's call concerns the firm's October 12, 2000 response to the Discipline Review Letter.

Today's Call

The following issues were discussed. The Division's questions are italicized below followed by the firm's responses.

1. *Will — the drug substance manufacturing site identified in NDA 21-136.] manufacture any batches of drug substance in the future? Throughout the October 12, 2000 response, there are discussions of procedures to be followed in future batches. However, in the cover letter, — is identified as the second supplier of drug substance.*

   Dr. Purich responded that, although he expects — to eventually become a CGMP compliant manufacturing facility (NOTE: —received withhold recommendations from the Office of Compliance March 23 and October 16, 2000. Lack of compliance with CGMPs was cited.), he thought it wise to develop a second source of drug substance.

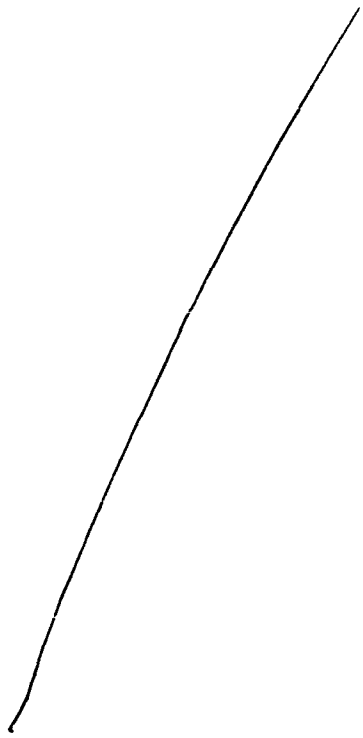
— was contacted as a second drug substance source. Dr. Purich clarified that upon NDA approval, ChiRhoClin plans to —

2.

3

4.

5.



6. *Regarding your response to Question III, please provide a draft package insert as well as mock-up immediate container and carton labeling including your new proposed tradename, SecreFlo.*

Mr. Strongin explained that the Office of Post-Marketing Drug Risk Assessment (OPDRA) must approve all proposed tradenames. He added that OPDRA could review the new proposed tradename when the requested labeling has been submitted.

The call was then concluded.

/S/ 11/14/00

Brian Strongin
Regulatory Health Project Manager

/s/

Brian Strongin
11/14/00 11:00:46 AM
CSO

Brian Strongin
11/14/00 11:09:40 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE August 9,2000

NDA NUMBER: 21-136
BETWEEN: Edward Purich, Ph.D.

Representing ChiRhoClin
Phone Number 301-384-1554
AND
Name: Arthur B. Shaw, Ph.D.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: I called Dr. Purich to request a telecon with him and — tomorrow to clarify a couple of issues related to — manufacturing process (MP) and assay of porcine secretin, the subject of this NDA. In particular I wanted to discuss — proposed changes in the MP and the HPLC assay being performed at — He told me that the first batch of porcine secretin, — , was sufficient to sustain clinical use for — after approval. He told me that any change in the MP, including purification procedure changes, would be filed as a supplement. He also said that — is performing the release of the bulk drug rather than — I told him I would check for that in the NDA. We concluded the telephone conversation with the understanding that a telecon tomorrow with — was not necessary.

/S/ 8/9/00
Arthur B. Shaw, Ph.D.

cc: Original NDA 21-136
Original NDA 21-209
HFD-180/Div File NDA 21-136
HFD-180/Div File NDA 21-209
HFD-180/AShaw
HFD-180/LZhou
HFD-180/SAurecchia /S/
HFD-180/LTalarico
C:\WORD\NG\21-136 SYNTHETIC PORCINE SECRETIN TELECON 09-AUG-2000.DOC

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: July 11, 2000

APPLICATION NUMBER: NDA 21-136; [redacted] (synthetic porcine secretin for injection)

BETWEEN:

Name: Ed Purich, Ph.D.
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical and CMC Information Requests

Background

NDA 21-136, submitted May 14, 1999 by ChiRhoClin, Inc., provides for the use of synthetic porcine secretin for: (1) diagnosis of pancreatic exocrine [redacted], (3) diagnosis of gastrinoma; and (4) facilitation of [redacted] during ERCP. An approvable letter dated March 24, 2000 cited clinical, CMC, biopharmaceutics, and labeling issues. Today's call concerns the firm's May 8, 2000 response to the approvable letter.

Today's Call

The following questions were faxed to the firm.

1. Clinical

Please provide the following to assist the development of marked-up draft labeling for NDAs 21-136 and 21-209:

The small number of subjects and the wide range of results in the pooled analysis of Studies CRC 99-8 and CRC 97-2 submitted May 26, 2000 suggests that an analysis showing no statistical differences in change from baseline between SPS and BPS is not a meaningful method of assessing the proposed SPS. Table 8, pages 221 and 222 of the May 26 submission, shows that there is at least a twofold difference in the change from baseline between the two secretin products at 1 and 2 minutes from secretin bolus infusion (BPS>SPS). Minute 5 shows a dramatic reversal of effect with a more than 80% greater change from baseline for SPS over BPS. This type of variability is not well

analyzed by simple comparisons of means and medians. The wide variances guarantee no statistical differences despite apparent differences between the two assays.

Please provide analyses that address the impact of the potential differences in pharmacodynamic effects in gastrinoma patients that has been identified in your analysis. Address the issue of diagnostic accuracy in the intended population of patients with elevated serum gastrin less than 1000pg/ml and the clinical setting suggesting gastrinoma.

2. Chemistry, Manufacturing, and Controls

Regarding your May 8, 2000 responses to the following questions in our March 24, 2000 approvable letter for NDA 21-136

The call was then concluded.

/S/

7/11/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/L.Goldkind
HFD-180/A.Shaw

TELECON

MEMORANDUM OF TELECON

DATE: April 11, 2000

APPLICATION NUMBER: NDA 21-136 ——— (synthetic porcine secretin)

BETWEEN:

Name: Seymour Fein, M.D.; Medical Director
Edward Purich, Ph.D.; CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND:

Names:	Steven Aurecchia, M.D.	Deputy Director
	Hugo Gallo-Torres, M.D., Ph.D.	Team Leader, GI Drugs
	Larry Goldkind, M.D.	Medical Officer
	Brian Strongin	Regulatory Health Project Manager

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

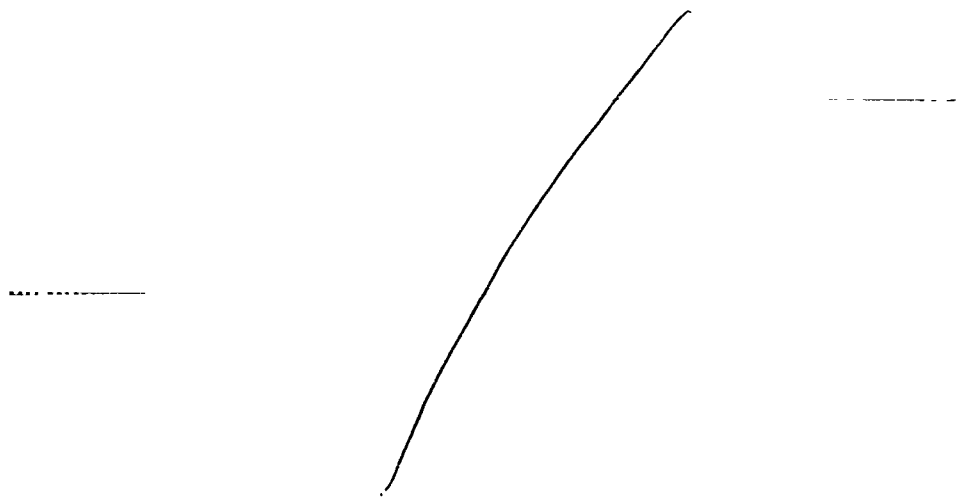
SUBJECT: Questions Regarding the Division's March 24, 2000 Approvable Letter for NDA 21-136

Background

NDA 21-136, submitted May 14, 1999 by ChiRhoClin, Inc., provides for the use of synthetic porcine secretin for: (1) diagnosis of pancreatic exocrine ———; (3) diagnosis of gastrinoma; and, (4) facilitation of ——— during ERCP. The Agency's approvable letter dated March 24, 2000 cited clinical, CMC, biopharmaceutics, and labeling issues. The firm requested today's telecon to assist in preparation of their response. The firm's questions are italicized below, followed by our responses.

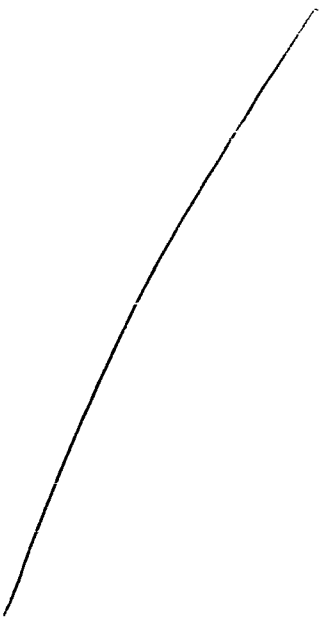
Today's Call

1. *In the package insert, the second paragraph under Clinical Pharmacology is a statement from the* ———



The Division recommended that the firm submit their proposed labeling revisions with their complete response to the approvable letter.

2.



3.

Only data driven, clearly supported statements may be included in the labeling.

4. *The issue of collecting baseline samples of pancreatic juice prior to secretin administration was rendered moot by Toskes' development of a categorical diagnostic paradigm for chronic pancreatitis in terms of exocrine pancreas response bicarbonate concentration to secretin stimulation independent of baseline values. We collected them in study CRC 98-1, in one sample from –15 to 0 minutes for analytical purposes, but they are not necessary for diagnostic evaluation.*

   We recommend drawing at least one baseline sample to insure proper placement of the Dreiling tube.

5. *A package insert should provide guidance concerning the interpretation of the diagnostic test results. Therefore, we propose adding a sentence at the end of the current dosage section as follows:*

   > *"Chronic pancreatitis is indicated if the peak bicarbonate concentration for all samples is <80mEq/L."*

   We suggest the following statement:

6. *We have previously submitted on March 8, 2000 an amendment to NDA #21-136 with proposed final labeling (vial, box, and insert). These materials indicate a new name for sPS, [redacted] This change from [redacted] was mandated after ChiRhoClin signed a licensing agreement with Repligen to market sPS. We understand that such "proprietary" names must be extensively checked for clarity and overall acceptability and that this process can be time consuming. Even though this is a straightforward trademark, we would hope to avoid any additional delay in approval merely on the basis of checking the new proposed trademark. Is there any way for this checking to occur now while we are preparing the full set of responses to the approvable letter?*

   A sixty-day period is normally required for an OPDRA tradename review. This is not normally a rate-limiting step in the review process and requesting a tradename review at this time is probably not necessary. In the event that all other issues

have been resolved before the tradename has been approved, we will make every effort to facilitate the tradename review.

7. *NDA #21-209 for gastrinoma is scheduled for action around May 25, 2000. We will submit a full report on the required 6 crossover patients shortly, probably during the first week in April. We realize this "administrative" NDA is subject to the same issues and conditions listed in the approvable letter for NDA #21-136. Given the critical need by the medical community for secretin for this diagnostic indication, we propose to address the report requirements for NDA #21-209 and responses to NDA #21-136 in parallel in hope that both matters can be concluded simultaneously or at least in close proximity. Therefore, we request you allow us to include wording in the proposed package insert for the gastrinoma indication for your reviewer with the other responses to the approvable letter. If NDA #21-136 receives approval first, we can easily and quickly delete those few paragraphs concerning gastrinoma.*

   While it is acceptable to include wording for the gastrinoma indication in your response to our approvable letter, your proposal must be reviewed and approved.

8. *When may we submit the requested introductory promotional materials to your division and DDMAC? Does this have to wait and be part of the full set of responses to the approvable letter or can it be submitted separately as soon as it is available?*

   Your proposed promotional materials should be submitted separately to the Division and DDMAC. At this time, it is premature to submit these materials. DDMAC reviews them in the context of finalized labeling. We suggest waiting until labeling is closer to finalization.

The call was then concluded.

[/S/] 4/28/00

Brian Strongin
Regulatory Health Project Manager

cc:
Original NDA 21-136
HFD-180/Div.File
HFD-180/B.Strongin
HFD-180/L.Goldkind

TELECON

MEMORANDUM OF TELECON

DATE: June 22, 2000

APPLICATION NUMBER: NDA 21-209; — (synthetic porcine secretin for injection)

BETWEEN:

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

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Request

Background

NDA 21-209 for — ynthetic porcine secretin for injection) provides for the diagnosis of gastrinoma — . An approvable action pending clinical, CMC, biopharmaceutics, and labeling issues was taken May 16, 2000. A complete response to the approvable letter was received May 26, 2000 and is under review. These information requests concern the complete response.

Today's Call

The following information requests were faxed to the firm:

Regarding NDA 21-209, Study CRC 99-8:

1. The case report form for patient #5 was included in your May 26, 2000 submission to NDA 21-209 beginning on page 00107. Clarify why the data from this patient was not used in your analysis of this study.

2. Provide all primary source documents for patient #6. Explain why this patient was not noted in your submissions and not included in your analysis of this study.

The firm called to promise to respond quickly in writing.

/S/ 6-22-00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-209
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/L.Goldkind

TELECON

MEMORANDUM OF TELECON

DATE: February 15, 2000

APPLICATION NUMBER: NDA 21-209; — (synthetic porcine secretin)

BETWEEN:

Name: Edward Purich, Ph.D.
Phone: (301) 384-1554
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: CMC Information Request

Background:

NDA 21-209 for — (synthetic porcine secretin) provides for the diagnosis of gastrinoma —. It was created by administratively splitting off this indication from NDA 21-136. NDA 21-136 also for — submitted May 14, 1999, provides for the following indications: (1) the diagnosis of pancreatic exocrine —, (2) — (3) diagnosis of gastrinoma; and, (4) facilitation of — during ERCP. A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4. The firm requested an "informal conference:" per 21 CFR 314.101(a)(3) to discuss the refusal-to-file. At the September 14, 1999 meeting the Division recommended performing additional studies for both indications, including Study CRC 99-8 in gastrinoma patients. The protocol entitled, "A Randomized, Controlled Crossover Study Evaluating Synthetic Porcine Secretin, Synthetic Human Secretin, and Biologically Derived Porcine Secretin for the Diagnosis of Gastrinoma", was submitted August 31, 1999. The firm agreed and, on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 was created because the diagnosis of gastrinoma is a priority indication and the submission, receipt, and filing dates for NDA 21-209 differ from NDA 21-136.

Today's Call

The following was discussed in today's call:

Please provide the lot numbers and manufacturing dates of all lots of finished drug product used in clinical trials for both NDA 21-136 and NDA 21-209. The list should

include the study numbers associated with each lot. If the information is available, provide the assay data (including impurity levels) at the time of release of the lots, any relevant stability data and the dates the lots were used.

The call was then concluded.

/S/ 2/15/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-209
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/A.Shaw

TELECON

MEMORANDUM OF TELECON

DATE: February 14, 2000

APPLICATION NUMBER: NDA 21-209 — (synthetic porcine secretin)

BETWEEN:

Name: Edward Purich, Ph.D.
Phone: (301) 384-1554
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clarification of the status of Study CRC 99-8, Notice of Extension Due to a Major Amendment and Advice

Background:

NDA 21-209 for — (synthetic porcine secretin) provides for the diagnosis of gastrinoma — It was created by administratively splitting off this indication from NDA 21-136. NDA 21-136 also for Porsec, submitted May 14, 1999, provides for the following indications: (1) the diagnosis of pancreatic exocrine — (2) — , (3) diagnosis of gastrinoma; and, (4) facilitation of — during ERCP. A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4. The firm requested an "informal conference:" per 21 CFR 314.101(a)(3) to discuss the refusal-to-file. At the September 14, 1999 meeting the Division recommended performing additional studies for both indications, including Study CRC 99-8 in gastrinoma patients. The protocol entitled, "A Randomized, Controlled Crossover Study Evaluating Synthetic Porcine Secretin, Synthetic Human Secretin, and Biologically Derived Porcine Secretin for the Diagnosis of Gastrinoma", was submitted August 31, 1999. The firm agreed and, on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 was created because the diagnosis of gastrinoma is a priority indication and the submission, receipt, and filing dates for NDA 21-209 differ from NDA 21-136.

Today's Call

The following was discussed in today's call:

1. Dr. Purich was advised that the washout period actually used for Study 99-8 should be justified based on scientific data.
2. The Division has classified the submission dated February 4, 2000 as a major amendment

and, therefore the new user fee due date for this application is May 17, 2000.

3. In response to my question regarding the status of Study 99-8, Dr. Purich stated that one patient had been given the first treatment. He added that Dr — will continue to enroll patients in the open-label study and data from these patients will be submitted as they become available.

The call was then concluded.

/S/ 2/14/00

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-209
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/L.Goldkind

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: January 7, 2000

APPLICATION NUMBER: NDA 21-209; — (synthetic porcine secretin)

BETWEEN:

Name: Seymour Fein, M.D.
Phone: (800) 616-7180
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clarification of the status of Study CRC 99-8 and Information Request

Background:

NDA 21-209 for — synthetic porcine secretin) provides for the diagnosis of gastrinoma — . It was created by administratively splitting off this indication from NDA 21-136. NDA 21-136 also for — , submitted May 14, 1999, provides for the following indications: (1) the diagnosis of pancreatic exocrine — (2) — 3) diagnosis of gastrinoma; and, (4) facilitation of — during ERCP. A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4. The firm requested an "informal conference:" per 21 CFR 314.101(a)(3) to discuss the refusal-to-file. At the September 14, 1999 meeting the Division recommended performing additional studies for both indications, including Study CRC 99-8 in gastrinoma patients. The protocol entitled, "A Randomized, Controlled Crossover Study Evaluating Synthetic Porcine Secretin, Synthetic Human Secretin, and Biologically Derived Porcine Secretin for the Diagnosis of Gastrinoma", was submitted August 31, 1999. The firm agreed and, on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 was created because the diagnosis of gastrinoma is a priority indication and the submission, receipt, and filing dates for NDA 21-209 differ from NDA 21-136.

Today's Call

In response to my questions, Dr. Fein clarified that it is the firm's goal to submit a complete report with data and analysis for Study 99-8 by the end of January, 2000. I also requested that he submit the data previously submitted to NDA 21-136 from all ZE patients enrolled in any open-

label studies to NDA 21-209. He agreed and the call was completed.

BS 1/7/00

Brian Strongin
Regulatory Health Project Manager

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

TELECON

MEMORANDUM OF TELECON

DATE: December 10, 1999

APPLICATION NUMBER: NDA 21-136 — (synthetic porcine secretin)
NDA 21-209 — (synthetic porcine secretin)

BETWEEN:

Name: Edward Purich Ph.D.; CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Request

Background:

NDA 21-209 for — (synthetic porcine secretin) provides for the diagnosis of gastrinoma —). It was created by administratively splitting off this indication from NDA 21-136. NDA 21-136, submitted May 14, 1999, provides for the following indications: (1) the diagnosis of pancreatic exocrine — (2) — — , (3) diagnosis of gastrinoma; and, (4) facilitation of — during ERCP. A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4. The firm requested an "informal conference" per 21 CFR 314.101(a)(3) to discuss the refusal-to-file. At the September 14, 1999 meeting the Division recommended performing additional studies for both indications. The firm agreed and, on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 was created because the diagnosis of gastrinoma is a priority indication and the submission, receipt, and filing dates for NDA 21-209 differ from NDA 21-136.

Today's Call

The following information was requested from the firm:

1. Please submit investigator notes and hospitalization records (at least discharge summaries) for the following groups of patients:

   A. any patient listed in the Integrated Summary of Safety for NDA 21-136, page 4766 of the original submission, that had a hospitalization within a week of the study;

   B. any patient in ongoing studies that had a hospitalization within a week of the study;

C. and any patient hospitalized for pancreatitis in study CRC 97-3.

Include the duration for all hospitalizations.

2. Please submit a table similar to the table in the Integrated Summary of Safety for NDA 21-136 for all placebo controlled completed and ongoing autism studies. Submit case report forms and hospitalization records for any hospitalizations associated with the use of secretin in these studies.

/S/

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-209
Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: December 7, 1999

APPLICATION NUMBER: NDA 21-136; — (synthetic porcine secretin)
NDA 21-209; — (synthetic porcine secretin)

BETWEEN:

Name: Seymour Fein, M.D.; Chairman, Medical Director
Phone: (301) 384-1554
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Request

Background:

NDA 21-209 for — (synthetic porcine secretin) provides for the diagnosis of gastrinoma — It was created by administratively splitting off this indication from NDA 21-136. NDA 21-136, submitted May 14, 1999, provides for the following indications: (1) the diagnosis of pancreatic exocrine — (2) — (3) diagnosis of gastrinoma; and, (4) facilitation of — uring ERCP. A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4. The firm requested an "informal conference" per 21 CFR 314.101(a)(3) to discuss the refusal-to-file. At the September 14, 1999 meeting the Division recommended performing additional studies for both indications. The firm agreed and, on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 was created because the diagnosis of gastrinoma is a priority indication and the submission, receipt, and filing dates for NDA 21-209 differ from NDA 21-136.

Today's Call

The following information was requested from the firm:

1. Regarding Study CRC 97-1 entitled, "A Double Blind, Randomized, Four Treatment Latin Square Crossover, Pharmacodynamic, Dose Response Study of Intravenously Administered Synthetic and Extracted Porcine Secretin for Use as a Diagnostic Agent to Evaluate Exocrine Pancreatic Function in Normal Healthy Subjects":

   A. The washout period for patients 4A, 6, 7, 8, 9, 10, and 12 was not one week. Justify with documentation how this may effect results of the study.

B. Patients 8-12 have CRFs without the study drug identified. Provide evidence for what order the study drug was used.

C. Clarify the discrepancy between the randomization tables in the original protocol and those in the final report.

2. Provide the results of the non-secretin diagnostic testing that provide external validation of the diagnosis of chronic pancreatitis in all patients from all studies. The prior secretin test results using the approved Ferring product is important but not adequate to assess the diagnostic value for chronic pancreatitis. Simply listing the type of diagnostic studies performed is also not adequate.

   Similar clinical data will be needed as well for the ZE patients included in NDA 21-209.

3. Clarify the units of measurement used in Data Listing 7 on page 79 of the submission dated August 31, 1999 to NDA 21-136.

4. Clarify how the ABABAB randomization scheme in studies CRC 98-1 and 98-2 was random.

5. Clarify the purpose of study CRC 99-9.

6. Protocol CRC 97-2, including the changes provided for in the November 29, 1999 amendment to IND 54,196, is not adequate to study the value of secretin in cannulating the accessory papilla. It only tests the value in identifying the papilla. Without a specified time limit for successful cannulation, the endoscopist may put more time and effort into the secretin portion of the cannulation period.

7. Given the 2 ductal perforations observed in study CRC 97-3 and the published concerns over high-pressure injections into the main pancreatic duct, adequate safety data will be needed before —

The firm stated that they would submit responses as soon as possible. The call was then concluded.

LST

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-209
Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin

TELECON

STRONGIN

MEMORANDUM OF TELECON

NOV 4 1999

DATE: November 4, 1999

APPLICATION NUMBER: NDA 21-209 — (synthetic porcine secretin)
NDA 21-136 — synthetic porcine secretin)

BETWEEN:

Name: Edward Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Request

Background:

NDA 21-209 for — (synthetic porcine secretin) provides for the diagnosis of gastrinoma — . It was created by administratively splitting off this indication from NDA 21-136. NDA 21-136 also for —, submitted May 14, 1999, provides for the following indications: (1) the diagnosis of pancreatic exocrine — 2) —; (3) diagnosis of gastrinoma; and, (4) facilitation of — during ERCP. A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4. The firm requested an "informal conference" per 21 CFR 314.101(a)(3) to discuss the refusal-to-file. At the September 14, 1999 meeting the Division recommended performing additional studies for both indications. The firm agreed and, on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 was created because the diagnosis of gastrinoma is a priority indication and the submission. receipt, and filing dates for NDA 21-209 differ from NDA 21-136.

Today's Call

Regarding NDAs 21-136 and 21-209 for — synthetic porcine secretin), to adequately assess issues related to accuracy of your product for the proposed indications, please provide a literature search/meta-analysis, by an independent academic consultant, on the diagnostic accuracy of Kabi/Ferring biologic secretin for the diagnosis of pancreatic insufficiency, pancreatic malignancy and gastrinoma. The attributes of the literature search/meta-analysis should include:

1. Trial characteristics and search terms to be used for literature search should be prespecified.
2. The results of the search and copies of the articles chosen should be provided. A summary of the process employed and the reason to omit any potentially relevant study

should be provided as well.

3. For each indication accuracy should be assessed using the following parameters:

1.sensitivity
2.specificity
3.positive predictive value
4. negative predictive value
5. negative likelihood ratio
6. positive likelihood ratio

4. Attributes of the studies reviewed:

1. Appear in referred journals
2. GIH/Kabi/Ferring product used in the study
3. Consistent dose of secretin used in the study (1CU/kg for pancreatic function test and 2 CU/kg for gastrinoma diagnostic test as bolus injection.
4. The study population should be "undiagnosed" or "newly diagnosed" patients that reflect the clinical setting in which the diagnostic test is used.
5. The "gold standard" diagnostic test for each indication sought should be:

A. Pancreatic insufficiency: defined by the expert consultant with the rationale for choice of gold standard definition clearly stated. At a minimum chronic pancreatitis based on a rational, well defined and consistent set of criteria should be used as the gold standard for comparison since this is the most common clinical setting for the use of the secretin stimulation test. The criteria for defining a positive case should exclude the secretin stimulation test to avoid verification or incorporation bias. The diagnostic threshold value and parameter of pancreatic secretory function should be consistent among studies or the review should note the diagnostic accuracy at various thresholds.

B. Gastrinoma: ultimate tissue diagnosis. The accuracy parameters noted above should be considered in patients with normal and abnormal resting gastrin levels and clinical suspicion of gastrinoma.

LS 11/4/99

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-209
Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin

TELECON

MEMORANDUM OF TELECON

DATE: October 29, 1999

APPLICATION NUMBER: NDA 21-136; ——(synthetic porcine secretin)

BETWEEN:

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

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clinical Information Requests

Background

NDA 21-136, submitted May 14, 1999, received May 23, 1999, provides for diagnosis of pancreatic exocrine [redacted] diagnosis of gastrinoma [redacted], and facilitation of [redacted] during ERCP. The sponsor is ChiRhoClin, Incorporated.

A clinical information request letter was sent September 2, 1999. The firm's response dated October 6, 1999 was received October 7, 1999. In today's call, medical officer Larry Goldkind. M.D., conveyed these additional questions to the firm.

Today's Call

The following questions were faxed to Dr. Purich:

1. For Studies CRC 97-1 and CRC 98-1, clarify if the submitted case report forms are copies of the primary source documents recorded at the study sites or are any of them transcriptions from primary source documents.
2. For Study CRC 97-1:

   A. Clarify why the randomization scheme was changed between the proposed scheme on page 3270 and the actual scheme on page 3227 of the NDA.
   B. Provide the location in the NDA of the description of the protocol revisions listed on page 3245.

3. Clarify when you will be able to respond to question II.D. in our September 2, 1999 information request letter.

A response in writing was requested to help ensure proper documentation.

[/S/] 10/29/99

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/L.Goldkind

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 26, 1999

APPLICATION NUMBER: NDA 21-209 — (synthetic porcine secretin)

BETWEEN:

Name: Edward Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Letter of Reference

Background:

NDA 21-209 for — (synthetic porcine secretin) provides for the diagnosis of gastrinoma — . It was created by administratively splitting off this indication from NDA 21-136. NDA 21-136 also for — , submitted May 14, 1999, provides for the following indications: (1) the diagnosis of pancreatic exocrine — , (2) — 3) diagnosis of gastrinoma; and, (4) facilitation of — during ERCP. A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4. The firm requested an "informal conference:" per 21 CFR 314.101(a)(3) to discuss the refusal-to-file. At the September 14, 1999 meeting the Division recommended performing additional studies for both indications. The firm agreed and, on October 15, 1999 requested that indication #3 be filed "over protest". NDA 21-209 was created because the diagnosis of gastrinoma is a priority indication and the submission, receipt, and filing dates for NDA 21-209 differ from NDA 21-136.

Today's Call

1. I requested that the firm submit a letter to NDA 21-209 referencing the CMC, pharm/tox, microbiology, and biopharmaceutics information in NDA 21-136 to NDA 21-209.
2. I directed the firm to submit all future information regarding the — indication to NDA 21-209.
3. I told the firm that an acknowledgment letter would be forthcoming.

The firm agreed to both items. The call was completed —

/S/ 10/26/99

Brian Strongin
Regulatory Health Project Manager

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

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 14, 1999

APPLICATION NUMBER: NDA 21-136 (synthetic porcine secretin)

BETWEEN:

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

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: CMC Information Requests

Background

NDA submitted May 14, 1999, received May 23, 1999, provides for diagnosis of pancreatic exocrine diagnosis of gastrinoma ( ), and facilitation of during ERCP. The sponsor is ChiRhoClin, Incorporated.

An information request letter for the clinical, statistical. pharmacology/toxicology, and chemistry/manufacturing/control disciplines was sent July 22, 1999. The firm's response dated October 6, 1999 was received October 7, 1999. In today's call, review chemist Art Shaw Ph.D., conveyed the questions listed below to the firm.

Today's Call

Regarding our July 22, 1999 IR letter:

1. Respond to Question II.B.1. Submit hardcopies of all DMF letters of authorization to the NDA.
2. Provide the addresses for and the testing lab at as requested in Question II.B.3.d.
3. Respond to question II.B.3.e. NDAs should include separate sections for drug substance and drug product regulatory specifications and methods.
4. Respond to question II.B.3.f.

The firm stated that they would provide the addresses requested in item #2 tomorrow and

respond to the other requests as soon as possible.

[/S/] 10/18/99

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/A.Shaw
HFD-180/L.Zhou

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 1, 1999

APPLICATION NUMBER: NDA 21-136; [redacted] (synthetic porcine secretin)

BETWEEN:

Name: Edward Purich, Ph.D., CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Incorporated

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Status of Outstanding Information Requests and the Firm's Intention to Request Filing "Over Protest"

Background:

NDA 21-136, submitted May 14, 1999, received May 23, 1999, provides for diagnosis of pancreatic exocrine [redacted] diagnosis of gastrinoma [redacted] facilitation of [redacted] during ERCP. The sponsor is ChiRhoClin, Incorporated.

Secretin-Ferring (BPS), derived from porcine sources, has been approved under NDA 18-290 since May 29, 1981. It is labeled for the first three indications proposed for synthetic porcine secretin (SPS).

Efficacy is supported by the following studies:

1. CRC 98-1, a crossover study of SPS vs. BPS in 12 patients with chronic pancreatitis, compared the diagnostic efficacy of the two products.
2. CRC 98-2, designed similarly to CRC 98-1, compared the diagnostic efficacy of SPS vs. synthetic human secretin (SHS), also a ChiRhoClin product, in 12 patients with chronic pancreatitis.
3. CRC 97-2, an open-label uncontrolled trial of SPS used for the proposed indications. The study had enrolled 16 patients at the time of NDA submission.

Safety is supported by the three efficacy studies as well as study CRC 97-3. This study is an ongoing 1,500 patient, double-blind, placebo-controlled, parallel group study evaluating the use of SPS to prevent post-ERCP pancreatitis. The firm has submitted an interim analysis of 250 patients.

A refusal-to-file letter was sent July 22, 1999 for the diagnosis of gastrinoma and facilitation of indications. An "informal conference" to discuss the refusal-to-file letter, per 21 CFR 314.101(a)(3), was held with the firm September 14, 1999. The firm promised to provide additional data for both indications and may request the Division to file them "over protest" per 21 CFR 314.101(a).

Today's Call

1. The firm was asked for the status of their response to the following information requests (IRs) and telecon:

   Clinical: July 22, August 6 (telecon) and September 2, 1999
   Statistical: July 22, and August 6 (telecon), 1999
   Pharmacology: July 22, 1999
   CMC: July 22, 1999
   Biopharm: July 27, 1999

   The firm responded that they will submit a response to all outstanding IR letters and telecons the week of October 4, 1999. They added that they also intend to submit protocols for Study CRC 99-8 in Zollinger-Ellison patients and a protocol for the facilitation of pancreatic duct cannulation this week. Finally, they said that they will submit a protocol for a biopharm study in response to our IR letter dated July 27, 1999.

2. The firm was asked if they have made a final decision regarding a request to file the Zollinger-Ellison and cannulation indications "over protest".

   They responded that they have not yet made a final decision. I reminded them that the request to file "over protest", preferably in writing, must be received by the Division by October 15, 1999. I added that if these indications are filed "over protest", the information from the NDA concerning them will be administratively split into a separate NDA and will probably receive a priority designation.

/S/ 10-5-99
Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/Reviewers and Team Leaders

TELECON

MEMORANDUM OF TELECON

DATE: September 17, 1999

APPLICATION NUMBER: NDA 21-136; [redacted] (synthetic porcine secretin)

BETWEEN:

Name: Ed Purich, Ph.D.; CEO
Phone: (301) 384-1554
Representing: ChiRhoClin, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Follow-Up Information Requests after Informal Conference

Background

NDA [redacted], submitted May 14, 1999, provides for:

1. diagnosis of pancreatic exocrine [redacted]

3. diagnosis of gastrinoma [redacted]
4. and, facilitation of [redacted] during ERCP.

Efficacy and safety are supported by Study CRC 97-1 entitled, "A Double Blind, Randomized Four Treatment Latin Square Crossover, Pharmacodynamic Dose Response Study of Intravenously Administered Synthetic and Extracted Porcine Secretin for Use as a Diagnostic Agent to Evaluate Exocrine Pancreatic Function in Normal Healthy Subjects" and Study CRC 98-1 entitled, "A Randomized, Crossover Study Evaluating Synthetic Porcine Secretin And Biologically Derived Porcine Secretin for the Assessment of Exocrine Pancreas Function in Patients with a Diagnosis of Chronic Pancreatitis". A refusal-to-file letter was sent July 22, 1999 for indications #3 and #4.

An "Informal Conference" was held September 14, 1999 with ChiRhoClin, Inc. to discuss the July 22, 1999 refusal-to-file letter. The firm promised to provide additional data for both indications and will request the Division to file them "over protest" per 21 CFR 314.101(a).

Today's Call

The following information request was conveyed to Dr. Purich.

Please address the following issues to follow-up from our September 14, 1999 Informal Conference:

1. When you request filing the ZE Syndrome and [redacted] indications over protest and submit your new data:

   A. If your intent is to gain approval for [redacted] then the study will need to show benefit in this setting compared to no secretin.

   B. If your intent is to gain approval for: [redacted] then change the draft labeling submitted to reflect this and plan your study accordingly.

2. We will be glad to review and comment on the protocol you are developing for [redacted] incorporating the suggestions made during the September 14, 1999 meeting.

He promised to promptly address these issues. The call was then concluded.

/S/ 9/17/99

Brian Strongin
Regulatory Health Project Manager

cc: Original NDA 21-136
HFD-180/Div. File
HFD-180/Brian Strongin
HFD-180/L.Goldkind

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 14, 1999
Time: 1:00PM
Location: Parklawn Building, Conference Room L

Application: NDA 21-136: — (synthetic porcine secretin)

Type of Meeting: Informal Conference following a Refusal-to-File

Meeting Chair: Lilia Talarico, M.D.

Meeting Recorder: Brian Strongin

FDA Attendees, Titles, and Office/Division:

The Division of Gastrointestinal and Coagulation Drug Products

Lilia Talarico, M.D.	Director
Steve Aurecchia, M.D.	Deputy Director
Hugo Gallo-Torres, M.D., Ph.D.	Medical Team Leader, GI Drugs
Larry Goldkind, M.D.	Medical Officer
Brian Strongin	Regulatory Health Project Manager

The Division of Biometrics II

Ed Nevius, Ph.D.	Director

External Constituent Attendees and Titles:

ChiRhoClin, Inc.

Seymour Fein, M.D.	Chairman, Medical Director
Ed Purich, Ph.D.	CEO

Background:

NDA 21-136, submitted May 14, 1999, received May 23, 1999, provides for diagnosis of pancreatic exocrine —, diagnosis of gastrinoma —, and facilitation of — during ERCP. The sponsor is ChiRhoClin, Incorporated.

Secretin-Ferring (BPS), derived from porcine sources, has been approved under NDA 18-290since

May 29, 1981. It is labeled for the first three indications proposed for synthetic porcine secretin (SPS).

Efficacy is supported by the following studies:

1. CRC 98-1, a crossover study of SPS vs. BPS in 12 patients with chronic pancreatitis, compared the diagnostic efficacy of the two products.
2. CRC 98-2, designed similarly to CRC 98-1, compared the diagnostic efficacy of SPS vs. synthetic human secretin (SHS), also a ChiRhoClin product, in 12 patients with chronic pancreatitis.
3. CRC 97-2, an open-label uncontrolled trial of SPS used for the proposed indications. The study had enrolled 16 patients at the time of NDA submission.

Safety is supported by the three efficacy studies as well as study CRC 97-3. This study is an ongoing 1,500 patient, double-blind, placebo-controlled, parallel group study evaluating the use of SPS to prevent post-ERCP pancreatitis. The firm has submitted an interim analysis of 250 patients.

A refusal-to-file letter was sent July 22, 1999 for the diagnosis of gastrinoma and facilitation of — indications. An "informal conference" to discuss the refusal-to-file letter, per 21 CFR 314.101(a)(3), was requested by the firm August 17, 1999).

Meeting Objectives:

to review the Division's decision to refuse-to-file the diagnosis of gastrinoma and facilitation of — indications in light of the new data acquired since submission of the application

Discussion Points:

1. The firm briefly reviewed the background of this application and summarized the additional data/information included in the background package for the gastrinoma and facilitation of — indications. The patients were enrolled in Study CRC 97-2, an open-label, uncontrolled study of synthetic porcine secretin used for the indications proposed for approval.

2. The firm's questions were discussed. The questions are italicized below followed by the
3. division's responses.

A) —

Are the data from CRC 97-2 now sufficient to support filing of this indication?

Will the results from CRC 99-8 (— be required prior to approval of this indication?

The data provided from study CRC 97-2 are not sufficient to support the filing of an application for the diagnosis of gastrinoma. These data are inadequate to characterize your product as a diagnostic tool in patients with ZES. Although this study provided data from 11 patients with suspected gastrinoma, comparative data with biologically derived porcine secretin were either lacking or inadequate. We recommend submitting a complete study report and data from Study CRC 99-8 in support of this indication.

(Note: The firm responded that they will begin Study CRC99-8, a randomized cross-over study of SPS, SHS, and BPS for the diagnosis of ZES in 6-12 patients, as soon as possible. They may submit an interim report for the first 6 patients. We explained that, although we realized that the study would not enroll a sufficient number of ZES patients to perform the type of rigorous statistical analysis usually necessary for a diagnostic agent, data of the type to be gathered in Study CRC 99-8 are necessary to support the — indication.)

B) Facilitation of ERCP Cannulation

Is the information provided by Dr. — and the prior extensive use of secretin for this purpose in clinical practice adequate to document this medical use of secretin?

Are the data from CRC97-2 adequate to support the approval of this indication?

The data provided from study CRC97-2 and the information provided by Dr. — are not sufficient to support the filing of an application for this indication. Replicated data from adequate and well-controlled studies are needed to assess the approvability of SPS for the new indication of "facilitation of — for ERCP". You might consider a blinded study in which patients unable to be cannulated within a time limit are randomized to either secretin or placebo and the ability to cannulate within a time limit is compared. A cross-over regimen can be employed for patients with unsatisfactory cannulation within the time limit.

Published literature notes the theoretical potential for injecting contrast against pressure and therefore increasing the pressure within the pancreatic duct when secretin is used in this setting. In addition, repeated attempts at cannulation of the pancreatic duct and the associated trauma to the ampulla may increase the complication rate associated with ERCP. Also, the interim results of study CRC 97-3 may indicate a trend towards a higher rate of complications following the use of secretin in the ERCP setting. In light of these issues, meaningful diagnostic gain (i.e., improved success) and safety must be demonstrated with the use of secretin for approval of this indication. In order to be

adequate for filing, studies of the type described must be submitted for review. We suggest submitting a study protocol to the Division for review and comment.

(Note: The firm responded that they will submit a protocol incorporating these suggestions in 10-20 patients requiring SPS to facilitate cannulation. The Division commented that the protocol must specify the facilitation of cannulation of the accessory (minor) pancreatic duct if applicable. The sponsor's proposed draft labeling must also be changed accordingly. Replication of the data gathered from the planned study, as well as additional safety data in the population to be studied will be necessary. Data from Study CRC 97-2 can be supportive. A statistical plan, including a calculation for confidence intervals, should be submitted. The Division is available for assistance if necessary.)

3. The Division informed the firm that a request to file-over-protest should be submitted in writing and received by the Division by October 17, 1999. The data from Study CRC 99-8 and the planned study for the facilitation of cannulation should be submitted as soon as possible. If a request to file-over-protest is made the data/information regarding the — — . indications will be administratively split into a separate NDA and probably receive a priority designation. If a major amendment is received within three months of the user fee due date, the due date may be extended by 3 months.)

Minutes Preparer: LT 10/5/99

Chair Concurrence: LT 10-5-99

cc: Original
HFD-/Div. Files
HFD-/Meeting Minutes files
HFD-/CSO
HFD-/reviewers & attendees

Drafted by: BKS/October 4, 1999
Initialed by: HGT/October 5, 1999
LT/October 5, 1999
final: BKS/October 5, 1999
filename: c:\wpfiles\minutes\21136910.0

MEETING MINUTES

JUN 16 2000

Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER REVIEW

Application Numbers: NDA 21-136 and NDA 21-209

Name of Drug: [redacted] (synthetic porcine secretin for injection)

Sponsor: ChiRhoClin, Incorporated

Material Reviewed

Submission Date: May 8, 2000

Receipt Date: May 9, 2000

Background and Summary Description:

NDA 21-136 for [redacted] (synthetic porcine secretin), submitted May 14, 1999, provides for the following indications:

1. Diagnosis of pancreatic exocrine disease;

[redacted]

3. Diagnosis of gastrinoma [redacted] and,
4. The facilitation of [redacted] during ERCP.

On July 22, 1999 a refusal-to-file letter was sent for indications #3 and #4. An informal conference was held September 14, 1999 to discuss the refusal-to-file decision. At the meeting, the Division recommended performing small studies to provide additional support for the diagnosis of gastrinoma and the facilitation of [redacted] during ERCP indications. The firm agreed and asked that these indications be filed "over protest" per 21 CFR 314.101(a)(2). On October 15, 1999 the firm submitted a letter to the Division requesting that indication #3 be filed "over protest". They intended to pursue indication #4 at a later time. NDA 21-209 was created for indication #3 since it is a priority indication. Approvable actions were taken on NDA 21-136 and NDA 21-209 on March 24 and May 16, 2000 respectively. In their May 8, 2000 complete response to the approvable letter for NDA 21-136 the firm submitted revised draft labeling including a new trade name, and completely revised immediate container, carton, and package insert labeling. The revised draft labeling submitted May 8 (April 2000) will be compared with the marked-up draft labeling attached to the approvable letter for NDA 21-136 and the draft labeling submitted July 9, 1999 (April 1999) and the differences noted below.

Review

I. Immediate Container

A. The following statement appears on the lower right corner of the April 2000 labeling:

"Manufactured for [redacted] by ChiRhoClin, Inc. Silver Spring, MD 02494."

Per 21 CFR 201.1(h), no person other than the manufacturer, packer, distributor, person to be contacted for product information, and the holder of a trademark appearing on the label may be identified on the label. In a June 7, 2000 telephone call with Ed Purich, Ph.D. of ChiRhoClin, the following companies were identified to perform these functions:

Manufacturer	**Chesapeake Biological Laboratories, Inc.**
Packer	**Chesapeake Biological Laboratories, Inc.**
Distributor	[redacted]
Marketer	[redacted]
Holder of Trademark	
Product information	**ChiRhoClin, Inc.**

To improve accuracy and consistency with the regulations, I recommend the following change in the aformentioned statement:

"Manufactured by Chesapeake Biological Laboratories, Inc., Baltimore, MD, 21215. Marketed by [redacted]

B. The phrase, [redacted], appearing on the July, 1999 draft immediate container label is deleted from the April, 2000 labeling. In its place, the phrase "for injection" is added to the established name and a reference to the package insert for dosage and administration instructions is added.

This change is acceptable.

C. The statement, "Caution: Federal law prohibits dispensing without a prescription." appears on the lower left corner.

Per Section 126 of the Modernization Act, this sentence should be changed to "Caution: Rx only".

D. Except as noted above, the April 2000 labeling is acceptable.

II. Carton

A. The statement, [redacted] appears on the rear panel.

This statement should be changed as recommended in item I.A.

B. The statement, "Caution: Federal law prohibits dispensing without a prescription." appears on the front panel.

This statement should be changed as recommended in item I.C.

C. With the exception of the items noted above, the April 2000 labeling is acceptable.

III. Package Insert (PI)

The draft package insert submitted May 8, 2000 (April 2000) is substantially different from the package insert submitted July 9, 1999 (April 1999) with changes included in every section.

The clinical, clinical pharmacology and biopharmaceutics, pharmacology/toxicology, and chemistry, manufacturing, and controls reviewers were informed of substantial changes in the draft PI submitted May 8, 2000 and asked to develop comments and recommendations by the end of July, 2000. In developing these comments, it was suggested that they consider previous reviews, previous labeling comments, and the May 8 and May 26, 2000 submissions to NDAs 21-136 and 21-209 respectively.

Conclusions

A clinical labeling meeting has been scheduled for July 20, 2000. Reviewers from the other disciplines were requested to have comments and recommendations ready by the end of July, 2000. Marked-up draft labeling will be developed at that time and conveyed to the firm, with

comments regarding the immediate container and carton labeling, when appropriate.

[/S/] 6/15/00
Regulatory Health Project Manager

cc:
Original NDA 21-136
Original NDA 21-209
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Lilia Talarico, M.D. [/S/] 6/16/00
HFD-180/[/S/]
draft: BKS/June 15, 2000/c:\my documents\reviews\21136006.0
r/d Initials: LT/June 15, 2000
final: BKS/June 15, 2000

PM REVIEW

**APPEARS THIS WAY
ON ORIGINAL**

PROJECT MANAGER REVIEW

Application Numbers: 21-136 and 21-209

Name of Drug: ——— (synthetic porcine secretin)

Sponsor: ChiRhoClin, Inc.

Material Reviewed

Submission Date: July 9, 1999

Receipt Date: July 13, 1999

Background and Summary Description: NDA 21-136 for ——— (synthetic porcine secretin) was submitted May 14, 1999, received May 25, 1999. It provided for the following indications:

1. diagnosis of pancreatic exocrine ⟶
2. [ ]
3. diagnosis of gastrinoma ; and
4. the facilitation of during ERCP.

On July 22, 1999 a refusal-to-file letter was sent for indications #3 and #4. An informal conference was held September 14, 1999 to discuss the refusal-to-file decision. At the meeting, the Division recommended performing small studies to provide additional support for the diagnosis of gastrinoma ———— The firm agreed and asked that these indications be filed "over protest" per 21 CFR 314.101(a)(2). On October 15, 1999 the firm submitted a letter to the Division requesting that indication #3 be filed "over protest". They intended to pursue indication #4 at a later time.

NDA 21-209 was created for indication #3 since it is a priority indication. The submission date was August 17, 1999 (the date the informal conference was requested), and the user fee due date was February 17, 2000. A three month extension in the user fee due date was granted February 17, 2000 due to a major clinical amendment dated February 3, 2000. The new user fee due date for NDA 21-209 is May 17, 2000.

The submission dated July 9, 1999 includes a draft package insert, immediate container, and carton labeling. This labeling was reviewed by the Review Chemist in CMC Review #1 and by The Office of Post-Marketing Drug Risk Assessment (OPDRA) in their review dated January 19, 2000. In addition, the labeling was compared to the applicable regulations by the Project Manager. Comments and recommendations regarding the immediate container and carton labels,

in addition to those previously stated in CMC Review #1 and the OPDRA review will be stated below. A marked-up draft package insert will be prepared separately.

Review

Immediate Container and Carton Label

Per 21 CFR 201.100(b)(2) the "recommended or usual dosage" is required on the label, but does not appear. Per 21 CFR 201.10(i)(2) this information may be omitted from the immediate container label if it is contained in the package insert.

It is recommended that the labeling refer to the package insert for information regarding dosage and administration.

Conclusions

Labeling comments from CMC Review #1, OPDRAs review dated January 19, 2000, and this review should be added to the action letter.

[/S/] 3/7/00

Regulatory Health Project Manager

/S/ 3-7-00

cc:
Original NDA 21-136
Original NDA 21-209
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Lilia Talarico, M.D.

APPEARS THIS WAY
ON ORIGINAL

draft: BKS/March 7, 2000/c:\wpfiles\reviews\21136003.0
r/d Initials:LT/March 7, 2000
final: BKS/March 7, 2000

CSO REVIEW

MEMORANDUM OF 45-DAY PLANNING/FILING MEETING

Date: July 20, 1999

Application Number: NDA 21-136

Drug: — (synthetic porcine secretin) Injection

Attendees:

Dr. Lilia Talarico	Director	HFD-180
Dr. Hugo Gallo-Torres	Medical Team Leader/GI Drugs	HFD-180
Dr. Lawrence Goldkind	Medical Officer	HFD-180
Dr. Eric Duffy	Team Leader, CMC	HFD-180
Dr. Art Shaw	Review Chemist	HFD-180
Dr. Jasti Choudary	Team Leader, Pharm/Tox	HFD-180
Dr. Tamal Chakraborti	Review Pharmacologist	HFD-180
Dr. Paul Flyer	Team Leader, Biometrics	HFD-715
Dr. Wen-Jen Chen	Mathematical Statistician	HFD-715
Dr. David Lee	Team Leader, Biopharmaceutics	HFD-870
Dr. Alfredo Sancho	Biopharmaceutics Reviewer	HFD-870
Dr. Khairy Malek	Medical Officer	HFD-45

Background:

NDA 21-136, submitted May 14, 1999, received May 23, 1999, provides for diagnosis of pancreatic exocrine —, diagnosis of gastrinoma — and facilitation of — during ERCP. The sponsor is ChiRhoClin, Incorporated.

Secretin-Ferring, derived from porcine sources, has been approved under NDA 18-290 since May 29, 1981. It is labeled for the first three indications proposed for Synthetic Porcine Secretin.

Efficacy is supported by the following studies:

1. CRC 98-1, a crossover study of synthetic porcine secretin (SPS) vs. biologically derived porcine secretin (BPS) in 12 patients with chronic pancreatitis, compared the diagnostic efficacy of the two products.
2. CRC 98-2, designed similarly to CRC 98-1, compared the diagnostic efficacy of synthetic porcine secretin vs. synthetic human secretin, also a ChiRhoClin product in 12 patients with chronic pancreatitis.
3. CRC 97-2, an open-label uncontrolled trial of synthetic porcine secretin used for the proposed indications. The study had enrolled 16 patients at the time of NDA submission.

Safety is supported by the three efficacy studies as well as study CRC 97-3. This study is an ongoing — patient, double-blind, placebo-controlled, parallel group study evaluating the use of synthetic porcine secretin to prevent post-ERCP pancreatitis. The firm has submitted an interim analysis of 250 patients.

Meeting:

I. Filing Issues

A. Administrative: None

B. Clinical:

1. Diagnosis of Gastrinoma: Dr. Goldkind explained that the application does not contain adequate clinical data related to the use of SPS for the diagnosis of gastrinoma. He added that data from the literature related to the use of BPS is not adequate to evaluate SPS for this indication. BPS contains approximately — impurities that may have activity in the diagnosis of gastrinoma. Without adequate clinical data from SPS used for the diagnosis of gastrinoma, no statement regarding the appropriate dose or the sensitivity and specificity can be made.

2. Facilitatior during ERCP: Dr. Goldkind explained that the application does not contain adequate, meaningful clinical data in support of this indication. He added that the bioassay for pancreatic function couldn't be accepted as a surrogate for this proposed indication. In addition, there is inadequate medical literature on the safety and efficacy of either SPS or BPS for this indication

C. Pharmacology: None

D. Chemistry/Manufacturing/Controls: None

E. Statistics: None

F. Microbiology: None

G. Biopharmaceutics: None

II. Requests for Information

A. Administrative: The following items were requested in a June 17, 1999 telephone conversation between Dr. Edward Purich of ChiRhoClin,

Incorporated and Brian Strongin of The Division of GI and Coagulation Drug Products:

1. a completed financial disclosure form;
2. microbiology review copies of CMC Volumes 2,3, and 4;
3. a clinical review copy of Volume 15 which included Case Report Tabulations;
4. mock immediate container and carton labeling;
5. and, an unannotated package insert in text and on diskette in WORD 97.

All items were submitted before the filing meeting.

B. Clinical: Information requests were included in e-mails from Dr. Goldkind to the Project Manager dated July 21, 1999.

C. Pharmacology: At the Filing Meeting the Project Manager was asked to convey one information request to the firm.

D. Chemistry/Manufacturing/Controls: Information requests were included in e-mails to the Project Manager dated July 13 and 21, 1999.

E. Statistics: Information requests were included in e-mails to the Project Manager dated July 20 and 21, 1999.

F. Microbiology: The microbiology reviewer conveyed her information requests directly to the firm.

G. Biopharmaceutics: Information requests were included in a memo dated July 23, 1999

III. Conclusions

It was decided that the application would be filed for the — — — — ndications only. (Note: A refusal to file letter, for the diagnosis of gastrinoma — —, and facilitation of — — during ERCP indications, dated July 22, 1999 was faxed to Seymour Fein, M.D. of the firm July 23, 1999. The letter included information requests for the clinical, CMC, pharm/tox, and statistics reviewers. An information request including biopharmaceutics issues will be sent under a separate cover.)

Minutes Preparer: LS 7/27/99

Concurrence: LS 7-22-99