CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

CORRESPONDENCE

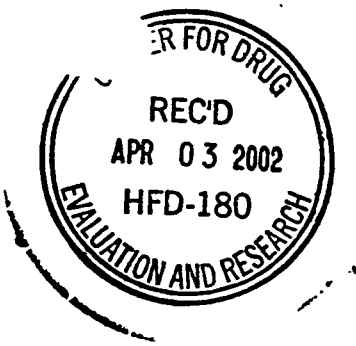
ChiRhoClin, Inc.
15500 Gallaudet Avenue
Silver Spring, MD 20905
(301) 384-1554 FAX (301) 384-1565

April 3, 2002

Victor Raczkowski, M.D.
Division Director
Division of Gastrointestinal & Coagulation Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attn: Document Control Room

DUPLICATE



Re: NDA #21-136 ✓
NDA #21-209

Dear Dr. Raczkowski:

BC BZ

Please find the revised labeling for the package insert, the vial label and the carton label as requested from teleconference call on April 3, 2002. The requested data for Table 1 with NDA citations and copies are provided with Excel spreadsheet for normal and chronic pancreatitis patients. The spreadsheet is also provided on a floppy disk containing a file titled "Table 1 from package insert NDA 21-136". In addition, a second copy of the file is provided on the floppy disk titled "Second copy".

Sincerely yours,

Edward D. Purich

Edward D. Purich, Ph.D.
CEO

Dporcine/Letters/VR040302L

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

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314)

NAME OF APPLICANT
ChiRhoClin, Inc.

DATE OF SUBMISSION:
April 3, 2002

ADDRESS (Number, Street, City, State, and Zip Code)
15500 Gallaudet Avenue
Silver Spring, MD 20905-4176

TELEPHONE NO. (Include Area Code)
(301) 384-1554

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
21-136

DRUG PRODUCT

ESTABLISHED NAME (e.g. USP/USAN)
Secretin

PROPRIETARY NAME (if any)
SecreFlo™

CODE NAME (if any)

CHEMICAL NAME
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

DOSAGE FORM
Lyophilized Sterile Powder

ROUTE OF ADMINISTRATION
Intravenous

STRENGTH(S)
16 µg

PROPOSED INDICATIONS FOR USE

1. Diagnosis of pancreatic exocrine [redacted]
2. [redacted]
3. Diagnosis of gastrinoma [redacted]
4. Facilitation of [redacted] during ERCP

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 *CFR* PART 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 *CFR* PART 314), AND DRUG MASTER FILES (21 *CFR* 314.20) REFERRED TO IN THIS APPLICATION:

IND 54-196 Synthetic Porcine Secretin for Diagnostic Use
IND 56-821 Synthetic Human Secretin for Diagnostic Use

NDA #21-136 Synthetic Porcine Secretin
NDA #21-209 Synthetic Porcine Secretin
NDA #21-256 Synthetic Human Secretin

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

X THIS SUBMISSION IS A FULL APPLICATION (21CFR 314.50

THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21CFR 314.55

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

PRESUBMISSION
ORIGINAL APPLICATION
X AN AMENDMENT TO A PENDING APPLICATION
RESUBMISSION
SUPPLEMENTAL APPLICATION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS (Check one)

X APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)

APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION	
This application contains the following items: (Check all that apply)	
✓	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d)(1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
✓	i. draft labeling (4 copies)
	ii. Final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
✓	15. OTHER (Specify) Response to FDA Conference Call (Concerning Clinical Data)

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, Warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after The initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I Agree to comply with all laws and regulation that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Edward D. Purich, Ph.D.	Edward D. Purich	April 3, 2002

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
15500 Gallaudet Avenue Silver Spring, MD 20905-4176	(301) 384-1554

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

000002

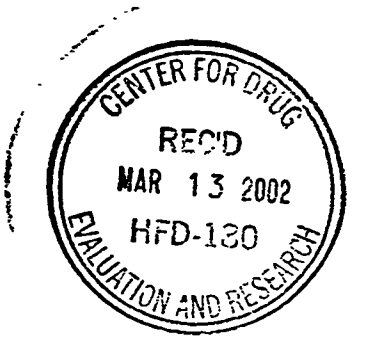
64 Draft Labeling Page(s) Withheld

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

ORIGINAL

March 13, 2002

Victor Raczkowski, M.D.
Division Director
Division of Gastrointestinal & Coagulation Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Attn: Document Control Room

Re: NDA #21-136

Dear Dr. Raczkowski:

BC

Please find enclosed a complete response to your Discipline Review letter (Chemistry) dated March 8, 2002. ChiRhoClin has provided a response to all deficiencies identified in the letter. In addition, ChiRhoClin has provided post-marketing commitments in writing with time frames relative to NDA #21-136 approval date.

We look forward to our teleconference call at 11:40am on Friday, March 22, 2002.

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

Sincerely yours,

Edward D. Purich

APPEARS THIS WAY
ON ORIGINAL

Edward D. Purich, Ph.D.
CEO

Dporcine/Letters/VR031302L

17 Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-136
NDA 21-209

DISCIPLINE REVIEW LETTER

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

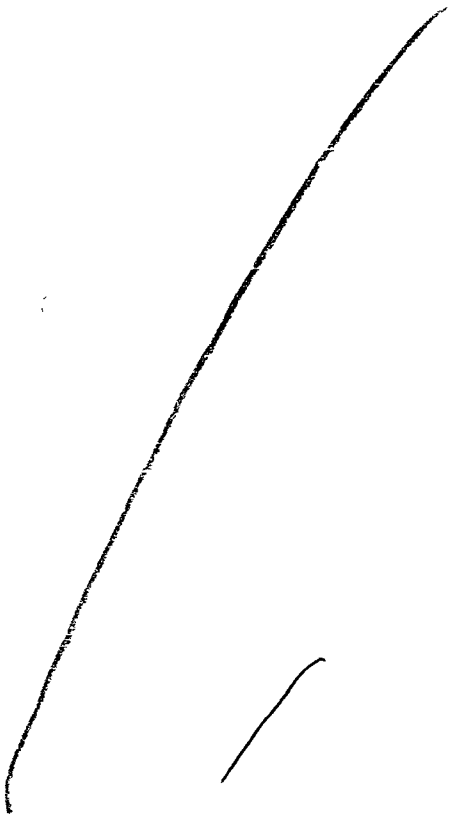
Dear Dr. Purich:

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

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

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

2 Page(s) Withheld



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

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

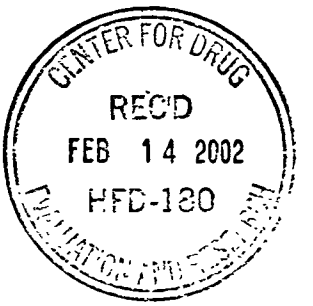
Sincerely,

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

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

February 13, 2002

Victor Raczkowski, M.D.
Division Director
Division of Blood and Gastroenterology
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Attn: Document Control Room

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

Dear Dr. Raczkowski:

Please find the draft labeling response for synthetic porcine secretin for injection as requested in the January 28, 2002 letter.

If you have any questions, please feel free to call.

Sincerely yours,

Edward D. Purich, Ph.D.
CEO

APPEARS THIS WAY
ON ORIGINAL

Dporcine/Letters/VR021302

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

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314)

NAME OF APPLICANT	DATE OF SUBMISSION:
ChiRhoClin, Inc.	February 13, 2002
ADDRESS (Number, Street, City, State, and Zip Code) 15500 Gallaudet Avenue Silver Spring, MD 20905-4176	TELEPHONE NO. (Include Area Code) (301) 384-1554 NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 21-209

DRUG PRODUCT

ESTABLISHED NAME (e.g. USP/USAN)	PROPRIETARY NAME (if any)
Synthetic Porcine Secretin	SecreFlo™

CODE NAME (if any)	CHEMICAL NAME
	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

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Lyophilized Sterile Powder	Intravenous	16 µg

PROPOSED INDICATIONS FOR USE

1. Diagnosis of pancreatic exocrine —
2. —
3. Diagnosis of gastrinoma —
4. Facilitation of — during ERCP

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 *CFR* PART 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 *CFR* PART 314), AND DRUG MASTER FILES (21 *CFR* 314.20) REFERRED TO IN THIS APPLICATION:

IND 54-196 Synthetic Porcine Secretin for Diagnostic Use
IND 56-821 Synthetic Human Secretin for Diagnostic Use

NDA #21-136 Synthetic Porcine Secretin
NDA #21-209 Synthetic Porcine Secretin —
NDA #21-256 Synthetic Human Secretin

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

X THIS SUBMISSION IS A FULL APPLICATION (21CFR 314.50

THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21CFR 314.55

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

RESUBMISSION — X AN AMENDMENT TO A PENDING APPLICATION — SUPPLEMENTAL APPLICATION

ORIGINAL APPLICATION — RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS (Check one)

X APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)

APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION	
This application contains the following items: (Check all that apply)	
✓	1. Index
	2. Summary (21 CFR 314.50 (c))
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✓	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
✓	i. draft labeling (4 copies)
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	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
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	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER (Specify)

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, Warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after The initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I Agree to comply with all laws and regulation that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Edward D. Purich, Ph.D.	Edward D. Purich	February 13, 2002

ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
15500 Gallaudet Avenue Silver Spring, MD 20905-4176	(301) 384-1554

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

36 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

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

Dear Dr. Purich:

Please refer to the meeting between representatives of your firm and FDA on February 12, 2002. The purpose of the meeting was to discuss deficiencies that have been identified to date in the NDAs for synthetic porcine and human secretin for injection.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

Enclosed document appears in administrative section of approval package

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/s/

Melodi McNeil
3/8/02 02:47:22 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-136
NDA 21-209

INFORMATION REQUEST LETTER

1/28/02

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

Dear Dr. Purich:

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

We also refer to your submissions dated September 17, 2001.

We are reviewing your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide draft labeling for synthetic porcine secretin for injection. The submitted draft labeling (package insert, immediate container, and carton labeling) should include each of the revisions requested in the March 24, 2000 approvable letter.

Please provide five copies of your response (one archival and four technical copies). In addition, please provide an electronic copy (MS Word 97) of the unnanotated package insert text.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Julieann DuBeau
1/28/02 05:41:37 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

11/14/01

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

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

Dear Dr. Purich:

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

We have the following comments and recommendations:

[
]

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

1. We are currently reviewing the second resubmission of these NDAs, received September 17 and October 9, 2001, following two previous approvable actions.

2. By December 2001 we anticipate being able to complete a preliminary review of the resubmissions and convey any resulting information requests to you. We advise that you wait until that time to request a meeting to discuss these NDAs.

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

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY
ON ORIGINAL

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

/s/

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-136

10/19/01

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

Dear Dr. Purich:

We acknowledge receipt on September 17, 2001 of your September 17, 2001 submission to your new drug application (NDA) for SecreFlo (synthetic porcine secretin) for Injection.

This submission contains additional chemistry, manufacturing, and controls and safety update information submitted as a partial response to our November 7, 2000 action letter.

We also acknowledge receipt on October 9, 2001 of [redacted] October 5, 2001 submission. This submission is a new DMF [redacted] that provides supportive information for the NDA.

We consider the September 17, 2001 and October 5, 2001 submissions to be a complete class 2 response to our action letter. Therefore, the user fee goal date is April 9, 2002.

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

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Melodi McNeil
10/19/01 12:11:04 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-136

Mr. Edward John Allera
Buchanan Ingersoll
1776 K Street, N.W.
Suite 800
Washington, D.C. 20006-2365

Dear Mr. Allera,

This is in response to the concerns you raised in your November 3, 2000, letter to Dr. Woodcock regarding the review of the ChiRhoClin's new drug application for synthetic porcine secretin (NDA 21-136). Dr. Woodcock has asked that I respond to you since this matter is still under active consideration in the Division of Gastrointestinal and Coagulation Drug Products (the division). The requests stated in your letter are listed below followed by my response.

(1) Request to grant a 30-day extension to the user fee action date.

The user fee time frames for NDA review and action are among the performance goals and procedures negotiated as part of the reauthorization of the Prescription Drug User Fee Act. The performance goals are stated in the November 12, 1997, letters from the Secretary of Health and Human Services, Donna Shalala, to Senator Jeffords, Chair of the Senate Committee on Labor and Human Resources, and Congressman Bliley, Chair of the House Committee on Commerce (refer to www.fda.gov/cder/news/pdufadesletter.htm). The user fee time frames do not provide for a discretionary 30-day extension. Additionally, your request is no longer relevant since the approvable action was taken on November 8, 2000. This action stopped the user fee review clock for the most recent review cycle and was the appropriate regulatory procedure to communicate the definitive deficiencies that must be addressed before the application can be approved.

(2) Request to ensure swift resolution of the chemistry issues related to manufacture of the bulk drug substance.

Concerns and deficiencies related to chemistry, manufacturing, and controls have been conveyed to you from the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) throughout the review process. The deficiencies relate to manufacture of the bulk drug substance and the bulk drug manufacturer named in the NDA, [redacted], as well as deficiencies in the testing of the finished drug product. Please refer to the following communications regarding these deficiencies:

- letters dated July 22, 1999; March 24, September 19, and November 8, 2000,

- telephone discussions with you on October 14, 1999; July 11, August 9, October 17, 23, and 24, 2000, and

- compliance inspections of manufacturing facilities conducted in March, June, and September 2000.

You note in your letter that a treatment protocol has been permitted to go forward using one batch of drug product produced from drug substance manufactured at [redacted] To gain approval to market a drug, it is necessary to demonstrate that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug can maintain the identity, strength, quality, purity, and potency of the drug as related to its safety and effectiveness [Federal Food, Drug, and Cosmetic Act section 505(d)]. The treatment protocol is an appropriate means of facilitating patient access to the investigational drug until the NDA deficiencies can be resolved to assure that the drug can and will be manufactured in a manner and by a facility that meets regulatory standards and good manufacturing practices.

To facilitate resolution of the deficiencies, DGCDP is prepared to meet with you to clarify any questions you have regarding the deficiencies. Please contact Mr. Brian Strongin, Regulatory Project Manager, at 301-827-7473 to make the appropriate arrangements.

I hope this information provides clarification to the issues raised in your letter.

Sincerely,

Florence Houn, M.D., MPH, FACP
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

Florence Houn
12/8/00 08:28:02 AM

APPEARS THIS WAY
ON ORIGINAL

NDA 21-136

Food and Drug Administration
Rockville MD 20857

DISCIPLINE REVIEW LETTER

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

SEP 19 2000

Dear Dr. Purich:

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

We also refer to your submissions dated March 20, May 8, July 13, August 3 and August 31, 2000.

Our review of the chemistry, manufacturing, and controls section of your submissions is complete, and we have identified the following deficiencies. Unless stated otherwise, all page numbers refer to the May 8, 2000 submission.

I. Drug Substance

A. Characterization

7 Page(s) Withheld

III. Regarding the proposed proprietary name

The proposed tradename, [redacted], is of concern for the following reasons:

1. In the event of subsequent NDA approval of other secretin products, confusion could arise between either the proposed tradename and the non-proprietary names for the other secretin products.
2. Since the proposed name is a [redacted], the product could mistakenly be referred to as either [redacted] The name "Repligen Corporation" may appear on the package of other Repligen products possibly causing confusion.
3. [redacted] could be misinterpreted as Neupogen, Epogen, or Respigam.

We recommend choosing a different tradename.

IV. Establishment Inspections

During a recent inspection of the drug substance manufacturing facility for your NDA, a number of deficiencies were noted and conveyed to [redacted] by the inspector. Satisfactory inspections of all establishments are required before this application may be approved.

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

If you have any questions, call Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the

Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-136
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/A.Shaw
HFD-180/L.Zhou
HFD-820/DNDC Division Director - only for CMC related issues
DISTRICT OFFICE

Drafted by: BKS/September 15, 2000
Initialed by: AS/September 18, 2000
LZ/September 18, 2000
final: BKS/September 19, 2000
filename: 21136009.0

DISCIPLINE REVIEW LETTER (DR)

N-21136
Doc. Rm. 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Phillip Toskes, M.D.
1600 SW Archer Road
Gainesville, Florida 32610

SEP 15 2000

Dear Dr. Toskes:

Between August 15 and August 17, 2000, Ms. Barbara T. Carmichael representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # CRC908-1) of the investigational drug, Synthetic Porcine Secretin performed for ChiRhoClin Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your letter of August 24, 2000, addressed to Investigator Carmichael, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note at the conclusion of the inspection, Ms. Carmichael presented and discussed with you the items listed on Form FDA 483, inspectional observations. We wish to emphasize the following:

1. Your records were inadequate in that source data was recorded in pencil and corrections in test results were found to have no identification of who made the changes.

2. The record of disposition of the study drugs was inaccurate.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Carmichael during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN: 3003070860
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:
Deficiencies noted:
____inadequate informed consent
_X _inadequate drug accountability
____failure to adhere to protocol
_X _inadequate records
____failure to report ADRS
____other

cc:
HFA-224
HFD-180 Doc.Rm. NDA# 21-136
HFD-180 Review Div.Dir. Talarico
HFD-180 MO Gallo Torres
HFD-180 PM Strongin
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP/CIB File # 10179
HFD-46 GCP/CIB Reviewer Malek
HFD-46 CSO Huff
HFR-SE250 DIB Chappell
HFR-SE2585 Bimo Monitor Torres
HFR-SE2585 Field Investigator Carmichael
r/d: KM 8/28/00
reviewed:JRM:9-12-00
f/t:mb:9-13-00
o:\km\toskes.doc

Note to Rev. Div. M.O.
The field investigator reviewed the records of 7 subjects out of 12 enrolled. There were few CRFs with inaccurate recordings but these will not affect the validity of the data. The data appear acceptable for use in support of the NDA.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Strong

David C. Metz, M.D.
University of Pennsylvania Medical Center
3400 Spruce Street, 3rd Floor Ravdin
Philadelphia, PA 19104

Food and Drug Administration
Rockville MD 20857

SEP 13 2000

Dear Dr. Metz:

Between August 14 and August 17, 2000, Mr. Mike Rashti representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # CRC99-8) of the investigational drugs, Synthetic Porcine Secretin and Synthetic Human Secretin, performed for ChiRhoClin, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note at the conclusion of the inspection, Mr. Rashti presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. The consent form used in the study stated that the subject would receive the three study drugs at different times on the same day. Five out of six subjects in the study received the 3 injections on different days.
2. There is no documentation that the final report at the closure of the study was sent to the IRB.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Rashti during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

LS1

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN: 3000215368
Field Classification: VAI
Headquarters Classification:
_____1)NAI
__X _2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:
Deficiencies noted:
_ X_inadequate informed consent
____inadequate drug accountability
____failure to adhere to protocol
____inadequate records
____failure to report ADRS
_X _other:failure to report to the IRB

cc:
HFA-224
HFD-180 Doc.Rm. NDA# 21-209
HFD-180 Review Div.Dir. Talarico
HFD-180 MO Gallo Torres
HFD-180 PM Strongin
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File # 9183
HFD-46 GCP Reviewer Malek
HFD-46 CSO Huff
HFR-CE150 DIB Eagan
HFR-CE150 Bimo Monitor Rashti
HFR-CE150 Field Investigator Rashti
r/d: KM- 8/28/00
reviewed:JRM:9-11-00
f/t:mb:9-12-00
o:**km/metz.doc**

Note to Rev. Div. M.O.

The field investigator reviewed the records of all 6 subjects in the study. There were few violations that will not affect the integrity of the data.
The data appear acceptable to use in support of the NDA.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 13 2000

William Y. Chey, M.D.
222 Alexander Street, Suite 3100
Rochester, New York 14607

Dear Dr. Chey:

Between August 18 and August 23, 2000 Mr. Joseph A. Famiglietti representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # CRC97-2) of the investigational drug synthetic porcine secretin, performed for ChiRhoClin Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Famiglietti presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. For the 3 subjects in the study, each received a lower than the protocol required dose at least once. Subjects 1 and 3 received a lower dose of synthetic porcine secretin, while subjects 2 and 3 received a lower dose of biological porcine secretin.

2. Two of the 3 subjects enrolled missed blood sample collection at the protocol specified times, subject 1 missed sample collection at the 1 and 15 minutes, while samples for subject 3 were not taken at 15, 20, and 30 minutes.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

Please inform this office, in writing, of the actions you have taken or plan to take to bring your procedures into compliance with FDA regulations.

We appreciate the cooperation shown Investigator Famiglietti during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

CFN: 3003097900
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_ __2)VAI- no response required
_X __3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:
Deficiencies noted:
____inadequate informed consent
____inadequate drug accountability
_X _failure to adhere to protocol
____inadequate records
____failure to report ADRS
____other

cc:
HFA-224
HFD-180 Doc.Rm. NDA# 21-209
HFD-180 Review Div.Dir. Talarico
HFD-180 MO Gallo Torres
HFD-180 PM Strongin
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP/CIB File # 2192
HFD-46 GCP/CIB Reviewer Malek
HFD-46 CSO Huff
HFR-NE150 DIB Woyshner
HFR-NE1500 Bimo Monitor Hansen
HFR-NE1500 Field Investigator Famiglietti

r/d: KM-8/30/00
reviewed:JRM:9-11-00
f/t:mb:9-12-00
o:**km\chey**

Note to Rev. Div. M.O.
The field investigator reviewed the records of the 3 subjects involved. For patient # 1, the blood samples after sPS dose were not taken 2 out of 7 times at 1 minute and 15 minutes, while for patient # 3, blood samples were not collected 3 times out of 7 after the sPS, dose, and once at 30 minutes after the bPS dose. With this small number of subjects, it is difficult to determine the effect of the missing samples on the efficacy comparison between the 2 test drugs.

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-209

Food and Drug Administration
Rockville MD 20857

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

JUN - 1 2000

Dear Dr. Purich:

We acknowledge receipt on May 30, 2000 of your May 26, 2000 resubmission to your new drug application (NDA) for _ — (synthetic porcine secretin) Injection.

This resubmission contains additional clinical; chemistry, manufacturing, and controls; microbiology; and clinical pharmacology and biopharmaceutics information submitted in response to our May 16, 2000 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is November 30,2000.

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

Sincerely,

BS

Brian Strongin
Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-209
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Reviewers and Team Leaders

DISTRICT OFFICE

Drafted by: BKS/June 1, 2000
final: BKS/June 1, 2000
filename: 21209006.0

151 /6-1-00

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

APPEARS THIS WAY
ON ORIGINAL

NDA 21-136

Food and Drug Administration
Rockville MD 20857

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

MAY 18 2000

Dear Dr. Purich:

We acknowledge receipt on May 9, 2000 of your May 8, 2000 resubmission to your new drug application (NDA) for ———synthetic porcine secretin) .

This resubmission contains additional clinical; microbiology; clinical pharmacology and biopharmaceutics; chemistry, manufacturing, and controls; and labeling information submitted in response to our March 24, 2000 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is November 9, 2000.

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

Sincerely,

[/S/]

Brian Strongin
Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

cc:
Archival NDA 21-136
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Reviewers and Team Leaders

DISTRICT OFFICE

/S/ 5-18-00

Drafted by: BKS/May 18, 2000
final: BKS/May 18, 2000
filename: 21136005.0

CLASS 2 RESUBMISSION ACKNOWLEDGMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-209

Food and Drug Administration
Rockville MD 20857

ChiRhoClin, Incorporated
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

FEB 17 2000

Dear Dr. Purich:

We acknowledge receipt on February 3, 2000, of your February 3, 2000, amendment to your new drug application for — (synthetic porcine secretin) Injection.

This amendment includes efficacy information for three new gastrinoma patients enrolled in Study CRC 97-2 entitled, "Synthetic Porcine Secretin Open Label Clinical Use Protocol", a copy of the meta-analysis requested by the Division in November, 1999, as well as a synopsis of Study CRC 99-10 entitled, "A Single Center Study Evaluating the Pharmacokinetic Profile of a Single Intravenous Dose of Synthetic Porcine and Synthetic Human Secretin in Normal Subjects". Under 21 CFR 314.60, this is a major amendment received by the Agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is May 17, 2000.

If you have any questions, please contact Brian Strongin, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely yours,

/s/

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 21-209
HFD-180/Div.File
HFD-180/B.Strongin
HFD-180/Reviewers and Team Leaders

DISTRICT OFFICE

Drafted by: BKS/February 17, 2000
R/d init: LT/February 17, 2000
Final: BKS/February 17, 2000
Filename: 20219002.0

2-17-00

REVIEW EXTENSION

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

12/17/9

NDA 21-136
NDA 21-209

INFORMATION REQUEST LETTER

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

Dear Dr. Purich:

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

We also refer to your submissions dated September 17, 2001.

We are reviewing the chemistry, manufacturing, and controls section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the following information regarding the response to our Question E.1 in the November 7, 2000 approvable letter.

   a. Provide the "purity assay — referred to on Page 106 of the September 14, 2001 amendment.

   b. If the — method discussed in the validation report beginning on Page 107 is to be used as a regulatory test method for the drug substance provide the following information:

      i. A complete description of the method.
      ii. A new specification for the drug substance (a list of tests, references to analytical procedures and acceptance criteria) including a reference to the specific method. (See ICH Q6A: Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.)

   c. Data to establish that the peak with the Relative Retention Time of — (Page 114) is —. The data should be submitted to the NDA rather than referencing a

supporting DMF.

2. Provide the following information regarding the response to our Question D.2 from the November 7, 2000 approvable letter:

   Provide the following stability data:

   a. Primary data (three months under accelerated storage conditions and six months at labeled storage conditions) from drug product manufactured using drug substance manufactured at
   b. Supporting data (accelerated storage conditions and labeled storage condition) from drug product manufactured using drug substance manufactured at

      The report should include the following:

      i. A linear regression analysis of the stability data at the labeled storage condition, using the original values with no correction for zero-time values. (See "Guideline for Submitting Documentation for the Stability of human Drugs and Biologics, 1987). Specifically Section C.2.a.:

         "Also, percent label claim, not percent of initial value, is the variable of interest." (emphasis in original)

      ii. Calculation of the expiration date based on the intersection of the 95% confidence limits around the regression lines with the acceptance limits (See the above Guideline):

         "It is not acceptable to determine the allowable expiration dating period by determining where the fitted least-squares line intersects the appropriate specification limit."

      iii. The data in SAS format, in both print and electronic formats.

      iv. An analysis and evaluation of the data to assess whether pooling is appropriate to set the expiration data. (See above Guideline, Section C.2.b.) If pooling is not appropriate, then the expiration date should be calculated using the lot that gives the shortest expiration date.

   c. Provide stability data using a suitable stability-indicating assay capable of detecting impurities. If such an assay could not be developed, provide experimental data to demonstrate what attempts have been made.

3. Obtain a United States Adopted Name (USAN) for the drug substance.

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

Sincerely,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Liang Zhou
12/17/01 03:46:06 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-136
NDA 21-209

Food and Drug Administration
Rockville MD 20857

ChiRhoClin, Incorporated
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

OCT 28 1999

Dear Dr. Purich:

Please refer to your May 14, 1999 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for — (synthetic porcine secretin) Injection.

We also refer to our July 22, 1999 letter stating that the indications for the diagnosis of gastrinoma , and the facilitation of — during ERCP were not sufficiently complete to merit a critical medical and technical review and were therefore refused to file.

We further refer to the September 14, 1999 informal conference with this Division, requested per 21 CFR 314.101(a)(3) to discuss the refusal to file.

We finally refer to your October 15, 1999 letter requesting that the indication for the diagnosis of gastrinoma — e filed over protest per 21 CFR 314.101(a)(3).

It is necessary for us to administratively create another NDA for the indication for the diagnosis of gastrinoma — The following information applies to that application:

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

Therapeutic Classification: Priority (P)

Date of Application: August 17, 1999

Date of Receipt: August 17, 1999

Our Reference Number: NDA 21-209

Under 21 CFR 314.102© 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 NDA number 21-209 at the top of the first page of any communications concerning

this application. All communications concerning the indication for the diagnosis of gastrinoma (should be submitted to NDA 21-209 and 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

Information that pertains to both NDA 21-136 and NDA 21-209 need only be submitted to one NDA and a copy of the cover letter with a reference to the location of the information to the second NDA.

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

Sincerely,

/S/

Brian Strongin
Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-209
Archival NDA 21-136
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: BKS/October 26, 1999
Initialed by: BC/October 28, 1999
final: BKS/October 28, 1999
filename: 21209910.0

151 10-28-99

GENERAL CORRESPONDENCE (GC)

APPEARS THIS WAY
ON ORIGINAL

OCT - 7 1999

NDA 21-136

ChiRhoClin, Incorporated
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

Dear Dr. Purich:

Please refer to the meeting between representatives of your firm and FDA on Tuesday, September 14, 1999. The purpose of the meeting was to review the Division's decision to refuse-to-file the diagnosis of gastrinoma and facilitation [redacted] indications in light of the new data acquired since submission of the application.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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

Sincerely yours,

Brian Strongin
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

[/S/]/10-7-99

Archival NDA 21-136
HFD-180/Division File
HFD-180/B. Strongin
HFD-180/M. Kidwell

Drafted by: mk 10/5/99
Initialed by: B. Strongin 10/5/99
Final: M. Kidwell 10/6/99
Filename: N211361001.bs
GENERAL CORRESPONDENCE (Minutes Sent)

APPEARS THIS WAY
ON ORIGINAL

Enclosed document appears in administrative section of approval package

NDA 21-136 -

ChiRhoClin, Incorporated
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

SEP 2 1999

Dear Dr. Purich:

Please refer to your pending May 14, 1999 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (synthetic porcine secretin) Injection.

We are reviewing the Clinical data section of your submission and have the following information requests:

I. Provide the basis for the statements on pages 000024 and 000058 in Volume 1 that Secretin-Ferring is — pure. Include any available information about the nature of the ——— impurities.

II. The Integrated Summary of Safety Information, page 004766, Volume 13, notes 274 patients evaluated from four studies. The total number of patients in the five studies included in the application (Studies CRC 97-1, CRC 97-2, CRC 97-3, CRC 98-1, and CRC 98-2) is 302.

A. Clarify whether there is overlap in patients between studies.
B. Clarify why only four studies are included in the Integrated Summary of Safety Information database.
C. Clarify whether the patients in Studies 98-1 and 98-2 are the same patients.
D. Submit clinical data/medical records for the chronic pancreatitis patients in Study 98-1. Compare their clinical status at the time of the study (i.e., concurrent labs, radiographic tests, and symptoms) to their status at the time of prior initial diagnostic secretin administration. In addition, provide the results of the secretin test for patients in Study 98-1.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject

BEST POSSIBLE COPY

to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

[/S/] 9/2/99

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-136
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/L.Goldkind
DISTRICT OFFICE

Drafted by: BKS/August 31, 1999
Initialed by: LG/August 31, 1999
HGT/September 1, 1999
KJ/September 1, 1999
final: BKS/September 2, 1999
filename: 21136908.0 -

9-2-99

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

NDA 21-136

Food and Drug Administration
Rockville MD 20857

ChiRhoClin, Incorporated
Attention: Edward Purich, Ph.D.
Chief Executive Officer
15500 Gallaudet Avenue
Silver Spring, MD 20905

JUL 27 1999

Dear Dr. Purich:

Please refer to your pending May 14, 1999 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (synthetic porcine secretin) Injection.

We are reviewing the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following information requests:

1. Provide a rationale for submitting articles discussing biologically derived porcine secretin, approximately — and —, to characterize the pharmacokinetics of your product, which is said to be —

2. Fully characterize the pharmacokinetics of your product, including its distribution, metabolism, elimination, protein binding, and the pharmacokinetics of special populations. In addition, compare the structural information for your product and the biologically derived secretin. Regarding the compendium of literature articles submitted in support of the requirement for pharmacokinetic information for your product, identify the articles that are relevant to both the biologically derived and the synthetic product. In addition, categorize the articles in terms of the following information areas:

    a. structural and stability information for synthetic porcine secretin, including possible "impurities";
    b. pharmacokinetic parameters of synthetic porcine secretin, i.e., clearance;
    c. distribution of synthetic porcine secretin, including the volume of distribution;
    d. metabolism of synthetic porcine secretin, including protein binding;
    e. and, pharmacokinetics of synthetic porcine secretin in special population groups, including pediatrics.

3. Submit, as requested at the November 18, 1998 Pre-NDA meeting, either a complete study report from an appropriate pharmacokinetic study or a request for a waiver of this requirement. (See the attached Memorandum of Meeting Minutes.)

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee

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reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

[/S/]

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-136
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-870/A.Sancho
HFD-870/D.Lee
DISTRICT OFFICE

ISN 7-27-99

Drafted by: BKS/July 26, 1999
Initialed by: AS/July 27, 1999
DL/July 27, 1999
KO/July 27, 1999
final: BKS/July 27, 1999
filename: 21136907.2

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

NDA 21-136

Food and Drug Administration
Rockville MD 20857

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

JUL 22 1999

Dear Dr. Purich:

Please refer to your May 14, 1999 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for ——— synthetic porcine secretin) Injection.

We have given your NDA a preliminary review, and we find that the following indications are not sufficiently complete to merit a critical medical and technical review: (1) diagnosis of gastrinoma); and (2) facilitation of during ERCP. Thus, these indications will not be filed within the meaning of section 505(b)(1) of the Act.

We are refusing to file these indications under 21 CFR 314.101(d) for the following reasons:

1. Diagnosis of gastrinoma The application does not contain adequate clinical data related to the use of your product for the diagnosis of gastrinoma. Data from the literature related to the use of the biologically derived product for this indication is not adequate to evaluate your product. The approved biologically derived product contains approximately peptides that, although not bioactive in the pancreatic secretion assay, are biologically derived from tissue that are also the source of other gut hormones. As such, these peptides may have activity in other physiologic situations such as the gastrinoma diagnostic model. Without adequate clinical data from your product used for the diagnosis of gastrinoma, no statements can be made regarding the appropriate dose or sensitivity and specificity of synthetic porcine secretin. Extrapolation from the biological product cannot serve as the basis of approval for this indication.

2. Facilitation of during ERCP: The application does not contain adequate, meaningful clinical data related to the use of your product to facilitate during ERCP. The bioassa cannot be accepted as a surrogate for this purposed indication. In addition, there is inadequate medical literature on the safety and efficacy of biologically derived or synthetic porcine secretin for use in this proposed indication.

While not filing issues, please address the following scientific issues/requests:

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I. Clinical

A. Clarify whether glass or plastic syringes were used for the administration of secretin in the conduct of the studies. If both types were used, specify the type used for each injection.

B. Define the terms "adjusted" and "unadjusted" bicarbonate (used in the baseline and 1-60 minute measurements) and explain the A, B and AB labels wherever they appear, i.e., Table 5 of the Study Report for CRC 97-1, page 32 and 33, Volume 10.

C. Please supply a graphic display of all tables from each study with error bars included.

D. Please supply graphic data comparisons of healthy volunteers and chronic pancreatitis patients for the parameters studied in CRC 97-1 and CRC 98-1.

E. Please supply a scatter plot graphic display of the results from the 24 patients in Studies CRC 97-1 and CRC 98-1 for the parameters studied.

F. Please supply the original source documents for the adverse events from the entire submission.

G. Please provide data from your investigations or the literature regarding the pediatric use of your product.

II. Chemistry, Manufacturing, and Controls

A. Please note that the "Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances" (November 1994) deals only with those issues that are unique to synthetic peptide substances. Please refer to the "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances" and "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products", both published in February, 1987.

B. Please provide the following information immediately:

1. a complete list of Drug Master Files (DMFs) referenced in the NDA on the Form FDA 356h;

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2. regarding the drug substance:

   a. the description and characterization, including proof of structure;
   b. the qualifications and suppliers of the solvents and reagents used in the manufacture of the drug substance;
   c. the batch record (There is a tab marked "batch record" but the only information provided is a list of specifications for the finished drug substance);
   d. the names, addresses, and responsibilities of all testing facilities;
   e. the process controls employed in the synthesis of the drug substance;
   f. the preparation and specifications for the reference standard;
   g. a description of the methods used for analysis of the drug substance, including sample preparation and system suitability tests;
   h. a complete detailed description of the container/closure system, including letters of authorization for all component manufacturers and information on how the container/closure protects the drug substance from air and moisture;
   i. and, stability data using the "new" assay performed at [redacted]

3. regarding the drug product:

   a. the specifications for the inactive ingredients;
   b. a description of the acceptance specification for the active drug substance by Chesapeake Biological Laboratories (CBL);
   c. the address of CBL;
   d. the names, addresses, and responsibilities of all testing facilities;
   e. a description of the assay procedures used by CBL and other testing facilities;
   f. a complete description of the container/closure system, including letters of authorization for all component manufacturers;
   g. and, stability data from three batches for at least six months using the new [redacted]" assay.

4. A request for a waiver for an environmental assessment is required. The statement on Page 353 is not acceptable. Please refer to the Federal Register notice, Volume 62, Number 145, Tuesday, July 29, 1997.

III. Pharmacology/Toxicology

For the acute toxicity studies in mice and rabbits, please explain if they were conducted in

accord with Good Laboratory Procedures (GLPs) as described in 21 CFR, Part 58. If they are not, please explain the deviations from GLPs with an evaluation of the significance of these deviations.

IV. Statistics

A. Please provide the following information from Studies CRC 97-1 and CRC 98-1 for the statistical analyses:

1. the definition and rationale of the margins (delta) used for the bio-equivalence analysis;
2. the analyses used to investigate the carry-over effect;
3. a description (including "delta" used to define equivalence) of how the resulting models were used to establish equivalence (Clarify whether the lack of a significant difference was used to test equivalence.) as well as references to journal article(s) used to develop the approach;
4. the formula used to determine the sample size using the parameters specified on page 28 of Volume 10 for Study CRC97-1 as well as references to journal article(s) used to develop the approach. (Clarify how a contrast of 23.0 maps to a change of 20%, and whether the same formula was used to determine the sample size for Study CRC98-1.);
5. clarification of which statistical result was used to reach the conclusions for sections 11.4.1 and 11.4.3 on page 31 and 34, respectively, of volume 10 for Study CRC97-1 including the citation of the specific pages of Appendix 15.4 used to suggest these conclusions;
6. and clarification of which statistical result was used to reach the conclusions for sections 11.4.1 and 11.4.4 on page 29 and 33, respectively, of volume 11 for Study CRC98-1 including citation of the specific pages of Appendix 15.4 used to suggest these conclusions.

B. Please provide the SAS data sets used for the efficacy and safety analyses on diskettes. These data sets should include data variables described in Appendix 15.4 in Volume 10 and 11 for Studies CRC97-1 and 98-1, respectively. Provide a text description for each variable on the data diskettes.

C. Please provide the SAS programs used to perform the statistical efficacy (described in the section 9.7.1 of the sponsor's statistical and analytical plan) and safety analyses, for the data sets described in item #2. The SAS programs provided should be able to read data from item # 2 and recreate the analyses contained in the NDA.

Clinical Pharmacology and Biopharmaceutics

Comments and requests for information regarding the Clinical Pharmacology and Biopharmaceutics section will be sent under a separate cover.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file these indications. To file these indications over FDA's protest, you must avail yourself of this informal conference. If you have any questions please call Brian Strongin, Regulatory Health Project Manager, (301) 827-7310.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the indications over protest, as authorized by 21 CFR 314.101©. If you do so, the indications shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference.

Sincerely yours,

[/S/]

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

Drafted by: BKS/July 22, 1999
R/d init: PF/July 23, 1999
JC/July 23, 1999
EPD/July 23, 1999
LT/July 23, 1999
Final: BKS/July 23, 1999
Filename: 21136907.0

/S/ 7-23-99

INFORMATION REQUEST

APPEARS THIS WAY
ON ORIGINAL

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NDA 21-136

Food and Drug Administration
Rockville MD 20857

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

JUL 22 1999

Dear Dr. Purich:

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

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

Therapeutic Classification: Standard (S)

Date of Application: May 14, 1999

Date of Receipt: May 25, 1999

Our Reference Number: NDA 21-136

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 24, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 23, 2000 and the secondary user fee goal date will be May 23, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA 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

APPEARS THIS WAY
ON ORIGINAL

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

Sincerely,

[/S]

Brian Strongin
Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-136

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

Dear Dr. Purich:

Please refer to the meeting between representatives of your firm and FDA on December 6, 2000. The purpose of the meeting was to receive the Division's responses to questions concerning the November 8, 2000 approvable letter.

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

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

Sincerely,

Brian Strongin
Project Manager
Division of Gastrointestinal &
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

APPEARS THIS WAY
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Enclosed document appears in administrative section of approval package

12 Page(s) Withheld