CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

ADMINISTRATIVE DOCUMENTS

1.4 Patent Information

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

Edward D. Purich, Ph.D.
Chief Executive Officer

EXCLUSIVITY SUMMARY for NDA # 21-209 SUPPL # N/A
Trade Name SecreFlo Generic Name secretin
Applicant Name ChiRhoClin, Inc. HFD- HFD-180
Approval Date April , 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/_X__/ NO /___/

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

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

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

      YES /_X__/ NO /___/

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

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

   d) Did the applicant request exclusivity?

      YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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

YES /___/ NO /_X__/

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

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

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_X__/

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

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

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

   YES /_X_/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /_X_/ NO /___/

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

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

YES /___/ NO /_X_/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /_X_/

If yes, explain:

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

Investigation #1, Study # CRC 97-2

Investigation #2, Study # CRC 99-8

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

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

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

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation # 1, Study # CRC-97-2

Investigation # 2, Study # CRC-99-8

Investigation #__, Study #

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

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

Investigation #1

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

Investigation #2

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

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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/s/

Alice Kacuba
4/4/02 03:25:16 PM
CSO

Joyce Korvick
4/4/02 03:42:03 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-136 SUPPL # N/A
Trade Name SecreFlo Generic Name secretin
Applicant Name ChiRhoClin, Inc. HFD- HFD-180
Approval Date April , 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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   a) Is it an original NDA? YES/_X__/ NO /___/

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

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

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

      YES /_X__/ NO /___/

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

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

   d) Did the applicant request exclusivity?

      YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

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

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

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_X__/

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

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(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

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

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

   YES /_X__/ NO /___/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /_X__/ NO /___/

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

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

YES /___/ NO /_X_/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /_X_/

If yes, explain:

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

Investigation #1, Study # CRC 97-1

Investigation #2, Study # CRC 98-1

Investigation #3, Study #

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

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

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

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #1_, Study # CRC 97-1

Investigation #2_, Study # CRC 98-1

Investigation #__, Study #

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

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

Investigation #1

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

Investigation #2

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

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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/s/

Alice Kacuba
4/4/02 09:11:42 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

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/s/

Alice Kacuba
4/4/02 03:23:19 PM
CSO

Joyce Korvick
4/4/02 03:36:31 PM
MEDICAL OFFICER
for Victor Raczkowski

APPEARS THIS WAY
ON ORIGINAL

1.3 Debarment Statement

Debarment Certification

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

Edward D. Purich

Edward D. Purich, Ph.D.
Chief Executive Officer

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-209 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: August 17, 1999 **Action Date:** April 4, 2002

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

Applicant: ChiRhoClin **Therapeutic Class:** GI diagnositic

Indication(s) previously approved: None, this is the NDA

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

Number of indications for this application(s): 1

Indication #1: Indication #1: SecreFlo is indicated for use in secretin stimulation testing for Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma.

*****No pediatric studies, no waiver request.**

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

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

ction A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

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

/s/

Alice Kacuba
4/4/02 09:15:17 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

cycle 1

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21209	**Trade Name:**	(SYNTHETIC PORCINE SECRETIN) INJ
Supplement Number:		**Generic Name:**	SYNTHETIC PORCINE SECRETIN
Supplement Type:		**Dosage Form:**	
Regulatory Action:	AE	**Proposed Indication:**	Diagnosis of Gastrinoma

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

March 8, 2000: The diagnosis of gastrinoma is not a pediatric indication. NDA 21-136 was submitted by the same company, for the same drug product, but for the indication of the diagnosis of pancreatic exocrine . Pediatric labeling will be evaluated in conjunction with the action for NDA 21-136. Both NDAs have Orphan Drug designation.

A pediatric plan will be discussed in the action letter for the companion NDA 21-136 for the diagnosis of pancreatic exocrine

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, BRIAN STRONGIN

[S] 5/1/00

Signature Date

[S] 5/1/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

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

Stamp Date: May 14, 1999 Action Date: April 4, 2002

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

Applicant: ChiRhoClin Therapeutic Class: GI diagnositic

Indication(s) previously approved: None, this is the NDA

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

Number of indications for this application(s): 1

Indication #1: Indication #1: SecreFlo is indicated for use in secretin stimulation testing for Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction

***No pediatric studies, no waiver request.

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

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

ction A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

Revised 1-18-02

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21136	**Trade Name:**	SYNTHETIC PORCINE SECRETIN LYOPHILIZED S
Supplement Number:		**Generic Name:**	SYNTHETIC PORCINE SECRETIN LYOPHILIZED S
Supplement Type:		**Dosage Form:**	FIJ
Regulatory Action:	AE	**Proposed Indication:**	1. Diagnostic use in pancreatic dysfunction. 2.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
March 14, 2000: Application is to be approvable only for indication #1 pending facilities inspections. The sponsor will be requested to develop a pediatric plan when the application is approved.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, BRIAN STRONGIN

[/S/] _____ 3/14/00

Signature Date

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: 4/3/02

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: **Director (Deputy)** Summary **Approval Comments**
NDA 21-136 and 21-209

APPLICANT: ChiRhoClin Inc.

DRUG: SecreFlo™ (secretin)

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

Regulatory History:

In 1999 Ferring Pharmaceuticals, the sole manufacturer of biologically derived porcine secretin, stopped marketing it in the US. Recently, Ferring Pharmaceuticals has formally withdrawn the NDA. Thus, there are no approved pharmaceutical secretin products currently on the market. This product has been used in diagnostic testing for pancreatic dysfunction and gastrinoma. There are other clinical signs and symptoms; as well as radiological tests which support these diagnoses. However, the community of gastrointestinal physicians insisted on the availability of this product as a aid to diagnosis.

Orphan Drug designation has been granted for SecreFlo™ for these indications.

ChiRhoClin Inc. submitted the original NDA 21-136 for this product on May 14, 1999. Four indications were proposed:

- For diagnosis of pancreatic exocrine function
-
- Diagnosis of gastrinoma
- Facilitation of during ERCP.

There were no controlled data on the last two indications and no subjects with Zollinger-Ellison Syndrome had received secretin in the entire database. Thus, these two indications were not filed in view of the lack of clinical data to review. This decision was communicated to the applicant on September 14, 1999. The applicant chose to file over

protest and a separate NDA (NDA 21-209) was filed. NDA 21-209 was given a priority review due to the life threatening nature of the disease of gastrinoma. Gastrinoma was the only indication filed to this application.

NDA 21-136, for the diagnosis of pancreatic exocrine dysfunction, was found to be approvable at the end of the first review cycle (March 24, 2000). However, the indication for the use as ' — was not approvable. Additional chemistry and manufacturing deficiencies were outlined in this action letter. In May of 2000, ChiRhoClin submitted a complete response to the FDA. An action letter dated November 7, 2000 stated that this NDA was still approvable, however, there was substantial chemistry, manufacturing and clinical control (CMC) issues to address. The current complete response was submitted October 5, 2001. CMC issues were addressed and a clinical safety update was provided. This current submission adequately addressed the CMC issues and SecreFlo™ will issued an approval letter (indications described below).

NDA 21,209, for the diagnosis of gastrinoma, was filed over protest October 16, 1999. On May 16, 2000 an approvable letter was issued to the applicant. Requests for additional clinical efficacy and safety data, as well as CMC data (see NDA 21-136) were made. On May 26, 2000 the applicant provided additional information which was considered a complete response to the May 16, 2000 action letter. An action letter was issued November 28, 2000 which again found the application approvable for the diagnosis of gastrinoma, however, CMC issues were still unresolved (NDA21-136). On October 5, 2001 the current complete response was submitted. This current submission adequately addressed the CMC issues and SecreFlo™ will issued an approval letter.

Clinical Indications:
The studies upon which approval is based are listed in the medical review and label. These studies demonstrated the similarity between biologically derived porcine secretin and SecreFlo™. In the validated cat bioassay, SecreFlo™ demonstrated a potency of approximately 5000 clinical units (CU) per milligram of peptide as opposed to 3000 CU for biologically derived porcine secretin.

Secretin stimulation testing:

1) to stimulate pancreatic secretions, including bicarbonate, to aid in the diagnosis of exocrine pancreas dysfunction. There is inter-investigator variability in secretin testing for pancreas secretory response. Also, the studies were not designed to rigorously define the positive and negative predictive values or false positive and false negative rates. Therefore this testing will be referred to as an "aid in the diagnosis" and is to be used in addition to clinical signs and symptoms and other diagnostic methodologies. Thus, it was felt that wording in the label of the Ferring product instructing the clinician to use the "cutoffs" as guideline was appropriate to this label and is incorporated therein.
2) stimulation of gastrin to aid in the diagnosis of gastrinoma. The studies were not designed to rigorously define the positive and negative predictive values or false

positive and false negative rates. Therefore this testing will be referred to as an "aid in the diagnosis" and is to be used in addition to clinical signs and symptoms and other diagnostic methodologies.

Phase 4 commitments:
There is only one phase 4 commitment that refers to chemistry, manufacturing and controls (CMC) issues. This commitment is for the applicant to develop an impurity assay. This assay would be more sensitive for assessing degradation impurities than the current one. Please refer to the chemistry review for complete details.

Regulatory Recommendation:
The division recommends approval of SecreFlo™ (secretin) for the following indications:

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

Joyce A. Korvick, MD, MPH
Deputy Division Director
Division of Gastrointestinal and Coagulation Drug Products
ODE III/CDER
FDA

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

/s/

Joyce Korvick
4/4/02 03:51:28 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: November 28, 2000

TO: NDA 21-209; SecreFlo (synthetic porcine secretin) injection

FROM: Brian Strongin, Regulatory Health Project Manager, HFD-180

SUBJECT: Chemistry, Manufacturing and Controls; Microbiology; and Clinical Pharmacology and Biopharmaceutics Reviews

NDA 21-209, submitted August 17, 2000, provides for SecreFlo (synthetic porcine secretin) injection for the diagnosis of gastrinoma [redacted]. NDA 21-209 references the companion NDA 21-136, from the same sponsor and for the same drug product, for all disciplines except clinical and statistical. An approvable action for NDA 21-209 taken May 16, 2000 cited as a condition for approval the need for adequate responses to the chemistry, manufacturing, and controls (CMC), microbiology, and clinical pharmacology and biopharmaceutics issues listed in our March 24, 2000 approvable letter for NDA 21-136. Please refer to the following reviews of the firm's May 8, 2000 response to our March 24, 2000 approvable letter for NDA 21-136:

DISCIPLINE	REVIEW TITLE	REVIEW DATE
CMC	NDA 21-136, Review #4	August 11, 2000
CMC	NDA 21-136, Review #5	November 2, 2000
Clinical Pharmacology and Biopharmaceutics	NDA 21-136	July 27, 2000
Microbiology	NDA 21-136, Review #2	October 16, 2000

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

Drafted by: BKS/November 28, 2000
Final: BKS/November 28, 2000
Filename: c:\my documents\nda\21209011.0

MEMORANDUM

/s/

Brian Strongin
11/28/00 03:36:23 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

B. Strongin
(HFD 180)

MEMORANDUM

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

DATE: March 6, 2000

FROM: Brian Strongin, Project Manager, HFD-180 /S/ 3/5/00

SUBJECT: Form FDA 483, —

TO: Ayesha Dhru, Document Control Room 6B-24, HFD-180

Please submit the attached Form FDA 483 to NDAs 21-136 and 21-209. Thanks.

cc:
HFD-180/B.Strongin
HFD-180/A.Shaw

APPEARS THIS WAY
ON ORIGINAL

1 Page(s) Withheld

IND 54,196

DEC 15 1998

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

Dear Dr. Purich:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Synthetic Porcine Secretin.

We also refer to the Pre-NDA meeting held on November 18, 1998, between representatives of your firm and this Agency. The following represents our summary of the meeting.

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 18, 1998

Time: 3PM – 5PM

Location: Parklawn Building, Conference Room "O"

Application: IND 54,196 for Synthetic Porcine Secretin

Type of Meeting: Pre-NDA

Meeting Chair: Lilia Talarico, M.D.

Meeting Recorder: Brian Strongin

FDA Attendees, Titles, and Office/Division:

The Division of Gastrointestinal and Coagulation Drug Products

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

Tim Robison, Ph.D. — Review Pharmacologist

Division of Biometrics II

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

Division of Pharmaceutical Evaluation II

David Lee, Ph.D. — Team Leader, Biopharmaceutics

Office of Orphan Products Development

Michael Dreis — Senior Reviewing Pharmacist

Office of the Commissioner, Office of Health Affairs

Freddie Ann Hoffman, M.D. — Deputy Director

External Constituent Attendees and Titles:

Seymour Fein, M.D.	Chairman, ChiRhoClin, Inc.
Edward Purich	CEO, ChiRhoClin, Inc.
Phillip Toskes, M.D.	Chairman, Dept. of Medicine College of Medicine, University of Florida President, QualTech Laboratories VP, Quality and Regulatory Affairs, CBL, Inc.

Background:

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

Secretin extracted from porcine intestine has been approved since 1981 for the diagnosis of pancreatic exocrine

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

Meeting Objectives:

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

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

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

Discussion Points:

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

2. Dr. Toskas briefly discussed the currently used methods for diagnosing chronic pancreatitis including tests of pancreatic structure and function.

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

Decisions Reached:

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

Chemistry, Manufacturing, and Controls

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

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

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

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

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

You must provide a demonstration that the drug substance synthesis is [redacted]

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

See the response to question #1.

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

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

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

See the response to question #1.

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

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

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

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

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

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

Non-clinical Pharmacology and Toxicology Section

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

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

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

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

Preclinical toxicology studies required to support the proposed NDA should include a

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

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

   ChiRhoClin believes these studies fully satisfy the requirements for NDA approval. Since synthetic porcine secretin is a pure peptide product, ChiRhoClin believes that the cat bioassay will not be a required test for the commercial product. Does the FDA agree that the HPLC assay should be used as the release assay?

   See the response to CMC question #8.

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

   See the response to Pharm/Tox question #1.

Clinical Section

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

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

   Any decision regarding the approvability of an application is based on the data for your product submitted in the NDA. It is premature at this time to make any conclusions

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

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

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

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

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

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

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

Human Pharmacokinetics and Bioavailability Section

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

ChiRhoClin believes these published data fully satisfy the pharmacokinetic requirements

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

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

If you have any questions concerning this IND, please contact:

Brian Strongin
Regulatory Health Project Manager
(301) 872-7310

Sincerely yours,

[/S/] 12-15-98

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:
Orig IND
HFD-180
HFD-180/CSO

{S}/12-15-98

Drafted: BKS/December 15, 1998
Final: BKS/December 15, 1998

Advice

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

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

TYPE OF MEETING: Discussion of NDA Deficiencies

MEETING CHAIR: Dr. Liang Zhou, Chemistry Team Leader

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

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Joyce Korvick, Deputy Division Director
Dr. Marcelo Barreiro, Medical Officer
Dr. Liang Zhou, Chemistry Team Leader
Dr. Art Shaw, Chemistry Reviewer
Ms Alice Kacuba, Regulatory Health Project Manager
Ms. Melodi McNeil, Regulatory Health Project Manager

Division of New Drug Chemistry II (HFD-820)
Dr. Eric Duffy, Division Director

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:
ChiRhoClin, Inc.
Dr. Edward Purich, Chief Executive Officer

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

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

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

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

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

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

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

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

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

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

Regarding Synthetic Porcine Secretin:

1. Are the data to support [redacted] porcine secretin assignment in the chromatogram from [redacted] assay VAL00-04 sufficient?

   FDA Response: Available data appear sufficient. Now that the impurity has been positively identified, data to assess biological activity should be provided or referenced. (According to the firm, the requested data are already in the NDA. FDA asked the firm to either resubmit the data or provide a specific reference [volume, page number, and submission date] where the data can be found.)

2. Can the continuing development of a purity assay for the drug product become a Phase IV commitment?

FDA Response: See discussion below in Appendix: Drug Product, Stability

3. Is the information pertaining to the manufacture of porcine secretin drug substance by [redacted] acceptable for the approval of NDA #21-136?

FDA Response: Review of DMF [redacted] is proceeding. At this point no major deficiencies have been identified.

4. Are the data in the NDA #21-136 and [redacted] DMF sufficient to demonstrate the equivalence between [redacted] 's batch used in the clinical and toxicological studies and the [redacted] s batch?

FDA Response: At this point the drug substances have not been shown to have any major differences in terms of chemical characterization.

5. Are the stability data in the NDA sufficient to support the [redacted] month expiration date?

FDA Response: There are insufficient data available to support a [redacted]-month expiration date for synthetic porcine or human secretins.

6. Are there any other outstanding chemistry issues that need to be addressed before NDA #21-136 can be approved?

See Comments in Appendix 1. (FDA representatives noted that review of the porcine secretin NDAs is ongoing. Accordingly, the list of deficiencies outlined in the appendix may not be complete.)

[redacted]

[redacted]

Regarding Synthetic Porcine Secretin:

1. Drug substance:
   a. Provide the full specification sheet for the drug substance.
   b. The acceptance criteria for the drug substance purity (Page 40 of January 21, 2002 amendment) should be significantly narrowed ([redacted]

2. Drug product:
   a. Regarding the manufacturing procedure:
      i. Amend the manufacturing process to include acceptance criteria for secretin content at [redacted]

      Applicant's Response: The applicant will address this issue.

      ii. Explain the [redacted] (see QC 11-QC14 on Page 754-757 of the September 14, 2001 amendment).

      Applicant's Response: The applicant stated that the assay used during the in-process testing was not validated and therefore not reliable.

      Reviewer's Comment: The assay was reported to be validated in the NDA (Page 244 of the 29-Dec-1999 submission). The applicant still needs to address the [redacted] during

iii. Set acceptance criteria for the secretin content in the
Applicant's Response: The applicant will address this issue.

b. Regarding the drug product specifications:
   i. The "specifications" for the drug product should include a specific method. The description of the method should be a "stand-alone" description of all procedures necessary to perform the particular assay, including and system suitability requirements. Other information (e.g. validation procedures) should not be included in the method description.
   Applicant's Response: The applicant will address this issue.

   ii. Provide a test for "Identity" as part of the drug product specifications.
   Applicant's Response: The applicant will address this issue.

   iii. Include the bio-assay as a release specification.
   Applicant's Response: The applicant will address this issue.

   iv. The acceptance criterion for "Assay" should be since there are no data to justify wider acceptance criteria.
   Applicant's Response: The applicant stated that this would be difficult to do because of the variability in the assay procedure.
   Reviewer's Comment: This assay was validated and shown to be precise (Page 1723 of the original submission.) The applicant should provide data demonstrating the variability in the assay.

c. Regarding the drug product stability:
   i. Provide accelerated stability data for the drug product manufactured using drug substance and drug substance, as requested.
   Applicant's Response: The applicant will address this issue.

   ii. Continue with efforts to develop an assay for impurities in order to permit the assignment of an appropriate expiration date.
   Applicant's Response: The applicant will address this issue.

3. Provide the USAN as soon as it is approved.
Applicant's Response: The applicant will address this issue.

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

Minutes Preparer: _____

Chair Concurrence: _____

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

MEETING MINUTES

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
2/28/02 10:33:11 AM

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

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 6, 2000

Time: 3:00PM

Location: Parklawn Building, 6B-45 Conference Room

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

Type of Meeting: End of Review Conference

Meeting Chair: Steve Koepke, Ph.D.

Meeting Recorder: Brian Strongin

FDA Attendees, Titles, and Office/Division:

The Division of Gastrointestinal and Coagulation Drug Products

Liang Zhou, Ph.D.	Team Leader; Chemistry, Manufacturing, and Controls
Art Shaw, Ph.D.	Review Chemist
Ali Al-Hakim, Ph.D.	Review Chemist
Maria Ysern	Review Chemist
Brian Strongin	Regulatory Health Project Manager

The Division of New Drug Chemistry II

Steve Koepke, Ph.D.	Deputy Director

External Constituent Attendees and Titles:

ChiRhoClin, Inc.

Seymour Fein, M.D.	Chairman
Edward Purich, Ph.D.	Chief Executive Officer

Consultants

Background:

NDA 21-136 was submitted May 14, 1999 for the following indications: (1) diagnosis of pancreatic exocrine [redacted] (3) diagnosis of gastrinoma; (4) facilitation [redacted] during ERCP. An approvable letter dated March 24, 2000 cited chemistry, manufacturing and controls (CMC); clinical pharmacology and biopharmaceutics; microbiology; and labeling deficiencies. The sponsor, ChiRhoClin, Inc., submitted a complete response May 8, 2000. A second approvable letter dated November 8, 2000 cited CMC deficiencies and deferred comment on the proposed labeling until the CMC issues were resolved.

Meeting Objective:

To receive the Division's responses to ChiRhoClin's questions concerning the November 8, 2000 approvable letter

Discussion Points:

ChiRhoClin's questions regarding the November 8, 2000 approvable letter to NDA 21-136 were discussed. The relevant sections of the November 8 letter are bolded below followed by the firm's italicized questions and the Division's response.

I. Drug Substance

A. Provide data to demonstrate the equivalence of the next batch of drug substance to the current batch of drug substance.

- *Does ChiRhoClin need to provide data on a new batch of drug substance prior to approval of NDA 21-136?*

  Yes. You must demonstrate the capability of manufacturing the drug substance in a reproducible manner. [NOTE: The firm explained that a batch of drug substance produced at [redacted] is nearing completion. This batch was made using the same synthetic method and purification scheme as the batch previously manufactured at [redacted] An [redacted] was added. In addition, the firm explained that [redacted] is validating a new method for assaying impurities. In response to the firm's questions, the Division explained that normally a minimum of three lots of drug substance must be produced prior to NDA approval. Fewer lots may be acceptable if the data provided supports the capability of reproducibly manufacturing drug substance. The Division emphasized the importance of consistent application of regulatory standards.]

- *Can we use the batch of porcine secretin begin manufactured at* [redacted]

  This will depend upon the results of your characterization and analysis of the product and, to the best of your ability, a demonstration of equivalence.

- *What do you mean by equivalence to the current [redacted] batch?*

  Assessment will be based on, at a minimum, complete physical/chemical characterization as reported in the amendments in the NDA, impurity profile, bioassay, and manufacture of at least [redacted] lot of finished drug product that meets finished drug product specifications. [NOTE: In response to the firm's question, the Division explained that it may be acceptable to validate the [redacted] manufacturing process concurrent with the manufacture of the drug substance. The Division also explained that if there is a marked reduction in impurities in the [redacted] product, additional pharmacology/toxicology data concerning impurities may not be necessary.]

B. Provide a determination of the precision of the assay for peptide sequence by mass spectrometry by testing a sample at least five time.

- *What is meant by the determination of the precision for peptide sequence of sPS by mass spectrometry?*

  If peptide sequence is to be a specification, precision must be demonstrated. [NOTE: The firm stated that they would use the lot of drug substance manufactured at [redacted] as a reference standard. They clarified that the test for peptide sequence was not a specification.]

C. Provide complete validation for the following assays using the current batch of synthetic porcine secretin:

1. [redacted],

2. [redacted] assay;

3. [redacted] assay.

- *Can the validation and qualification of these assays utilize sPS batches other than the current batch of sPS?*

  Yes. These assays must be validated using one or both batches of drug substance. Both batches of drug substance must be tested using the validated methods. [NOTE: The firm stated that they would fully validate all analytical methods for release tests prior to their use. In addition, they will perform the validated methods on both the [redacted] and [redacted] lots of drug substance.]

D. Provide data to identify and characterize the impurities reported on Page 388 of the May 8, 2000 amendment, using the [redacted] from [redacted] In addition, provide data to show how these impurities behave on the current release assay developed by [redacted]

- *Does this need to be completed as a condition for approval of the NDA?*

  Yes. [NOTE: The Division reminded the firm of the need for a purity profile from the ——— batch of drug substance. Pharmacology/toxicology data concerning the impurities may be necessary depending on their concentrations. If the firm believes that the impurities do not present a safety concern, the Division suggested that they submit data to support this contention.]

E. Provide data from multiple batches of synthetic porcine secretin to support the acceptance criterion of ——, for the single largest impurity. The data provided on Page 114 of the October 12, 2000 amendment are insufficient, since there is data for only one lot.

- *Does the Division intend to require multiple batches of bulk sPS to be made to establish this specification prior to approval of the NDA?*

  Yes. The number of batches of bulk drug substance required to establish this specification will be determined by analysis of the reproducibility of the data.

F. Provide information to identify and characterize the major impurity peaks seen in the —— Assay. In particular, identify and characterize the following impurity peaks seen in the chromatogram on the following pages of the October 12, 2000 submission:

Page	Retention Time (minutes)	Relative Retention Time	Area %
217		—	
296		—	

These peaks cannot be accounted for by matching relative retention times in the chromatogram for the — on Page 183 of the October 12, 2000 submission.

- *Will the Division holdup approval until all of these peaks are identified and characterized?*

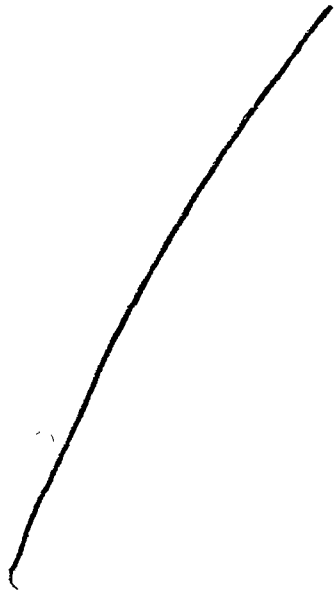
  We normally would expect all of these peaks to be identified and characterized. It is likely that identification and characterization will be required, but more data from the impurity profile from at least one lot of drug substance is required for a definitive determination. [NOTE: The firm said that they were considering processing the ——— lot of drug substance through the ——— manufacturing process to reduce the impurity levels of the original lot of drug substance.]

G. Provide data to demonstrate that the ——Assay is capable of detecting likely process-related impurities, including peptides arising from failure of incorporation of an amino acid, duplicate incorporation of amino acids, and racemization of amino acids.

- *Why do you expect that the ——Assay (——assay) be capable of detecting*

We expect the ——Assay to be capable of detecting —

NOTE: The firm stated that their assay is not capable of detecting



H. Provide data from stability studies of the drug substance using the ——Assay, including evaluation of impurities, to determine the retest date.

- *If ChiRhoClin agrees to always — the bulk drug substance using the ——assay prior to manufacture of parenteral product — can these studies be conducted after NDA approval?*

It is premature to comment at this time. [NOTE: The Division emphasized that the — must be based on data from a validated, stability-indicating assay of the drug substance.]

II. Drug Product

A. Provide a specific test method for reconstitution of synthetic porcine secretin with instructions to examine the reconstituted vial after 60 seconds, since that is the acceptance criterion. The response provided in the October 12, 2000 submission is not adequate.

- *Why was the [redacted] nadequate?*

The standard procedure must reflect actual practice and the proposed specification. [NOTE: ChiRhoClin agreed that the actual practice and the proposed specification should be consistent.]

B. Provide an assay for impurities in the finished drug product that is sensitive enough to detect impurities known to be present in the drug substance. The assay should also be shown to be able to detect impurities present at a level of greater than [redacted] in forced stability studies.

- *Since this assay requires detection sensitivity beyond the limits of current methodology, can the development of such a assay be a post approval commitment?*

No. You must develop a method sensitive enough to detect impurities in the drug product. The Division indicated that the methodologies used for impurities and for assay did not have to be identical. [NOTE: The Division recommended [redacted]

C. The following information must be provided before an expiration date can be assigned:

1. **An analysis of the stability data as Percent of Label Claim for Lots 1100-1, 92704C, and 927-5. The data for Lot 78104 should not be used for this analysis since some of the data was collected using the [redacted] method. It is inappropriate to normalize the data to the zero-time point.**

- *Since this question is clearly the result of an incorrect observation will the Division remove this question?*

This question is no longer relevant. [NOTE: The Division explained that stability data must be based on an acceptable regulatory test method to assay impurities. The Division explained that a specification for impurities is required and that it is not acceptable to merely measure the concentration of drug substance.]

III. Establishment Inspections

During recent inspections of the manufacturing facilities for your NDA ——— ——————— a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections of all manufacturing facilities will be required before this application may be approved.

- *Has the — laboratory sufficiently corrected all deficiencies and not require any re-inspection?*

The decision to require a re-inspection of — is a joint decision between the Division, the Office of Compliance, and the Field. It will depend upon the status of the application when a complete response to the approvable letter has been received.

IV. Miscellaneous

[NOTE: Several times during the meeting ChiRhoClin complained that the Division was requiring excessively difficult standards that are inappropriate to their application. They also complained that the Division included deficiencies in the November 8 approvable letter that were not previously stated in the March 24 letter. The Division responded that it had utilized a great deal of thoroughness and care in reviewing ChiRhoClin's application and had applied regulatory standards in an appropriate and fair way. The firm was invited to provide details of situations in which other firms were, in their opinion, treated differently. The Division would explore these situations and respond appropriately. In addition, the Division explained that although they may have been stated differently, no new deficiencies were included in the November 8 approvable letter.]