

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-256

Chemistry Review(s)



NDA 21-256

(Human Secretin for Injection)

ChiRhoClin, Inc.

Chien-Hua Niu, Ph.D., HFD-510

For

**Division of Gastrointestinal &
Coagulation Drug Products, HFD-180**

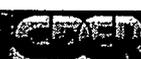


Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment.....	10
I. DRUG SUBSTANCE	
II. DRUG PRODUCT	
III. LABELING & PACKAGE INSERT	
IV. Claim Of Categorical Exclusion	
V. List Of Deficiencies To Be Communicated	



Chemistry Review Data Sheet

1. NDA 21-256
2. REVIEW #: 3 (review of response to discipline review letter on February 23, 2004)
3. REVIEW DATE: March 18, 2004
4. REVIEWER: Chien-Hua Niu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

RESUBMISSION
AMENDMENT
IR LETTER
AMENDMENT
TELECON
AMENDMENT
AMENDMENT
AMENDMENT
Resubmission
IR LETTER
AMENDMENT
AMENDMENT

14-May-2001
16-July-2001
08-Aug-2001
10-Aug-2001
20-Aug-2001
26-Sep-2001
30-Nov-2001
03-Dec-2001
10-Oct-2003
11-Feb-2004
02-Mar-2004
15-Mar-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
See above Section (# 5)

Document Date
See above section (# 5)



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: ChiRhoClin, Inc.
Address: 4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129
Representative: Edward D. Purich, Ph.D.
Telephone: (301)476-8388

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: —
- b) Non-Proprietary Name (USAN): Synthetic human secretin
- c) Code Name/# (ONDC only): None
- d) Type/Submission Priority (ONDC only):
 - Chem. Type: —
 - Submission Priority: 1 P

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Hormone

11. DOSAGE FORM: Lyophilized Sterile Powder

12. STRENGTH/POTENCY: 16 µg

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product



Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Human Secretin

Structural Formula:

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH₂

Molecular Formula:

C₁₃₀H₂₂₀N₄₄O₄₀ (CH₃COOH)_x (H₂O)_y

Molecular Weight (Free Base): —

17. RELATED/SUPPORTING DOCUMENTS:**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	III	/	/	3	Adequate	27-December-99	Review by Arthur Shaw
/	II	/	Synthetic Human Secretin	1	Adequate	4-February-04	Reviewed by Arthur Shaw and Chien-Hua Niu for NDA #21-256

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-136	Synthetic Porcine Secretin for diagnosis of exocrine pancreatic dysfunction
NDS	21-209	Synthetic Porcine Secretin

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	27-Feb-2004	Office of Compliance
Pharm/Tox	Acceptable	19-Jan-2004	Dr. Jasti Choudary
Biopharm	Acceptable	05-Mar-2004	Dr. Suliman Al-Fayoumi
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		Dr. Chien-Hua Niu
DMETS	Revision of the labels and labeling		
EA	Categorical exclusion	15-Mar-2004	Dr. Chien-Hua Niu
Microbiology	Pending		Dr. Stephen E. Langille

REVIEW NOTE

The Chemistry Review for NDA 21-256

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application can be APPROVED from chemistry viewpoint since (1) all outstanding CMC issues have been resolved; and (2) cGMP inspection of facilities utilized to manufacture the drug substance and the drug product as well as used for analytical testing has been completed and acceptable by the Office of Compliance. However, a satisfactory response to a number of issues raised during the microbiology review is pending.

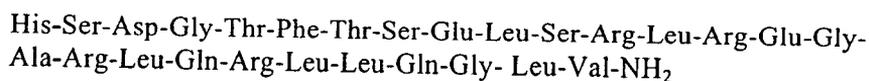
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(human secretin) for injection is utilized for diagnosis of pancreatic exocrine and gastrinoma (), and for the facilitation () during ERCP.

DRUG SUBSTANCE: Synthetic human secretin is a gastrointestinal peptide hormone. The primary action of secretin is to increase the volume and bicarbonate content of secreted pancreatic juices. Human secretin is an acetate salt of a synthetic 27 amino acid polypeptide. The structural formula for human secretin is presented below:



The structure of human secretin was elucidated by a variety of analytical and spectrophotometric techniques,

Human secretin has a and is
The product is,

Conformation of secretin has been investigated by a variety of techniques, including CD, NMR, and molecular dynamic. The results have appeared in the literature. These studies indicate that the molecule is highly structured in the solvents known to support secondary structure. The data show that secretin adopts a conformation consisting of an N-terminal irregular strand (residue 1-6) followed by two helices (residue 7-13 and 17-25) connected by a "half-turn" (residue 14-16); the last two residues (26-27) are again irregular.

The major impurities in human secretin are. These impurities are in fact with secretin. This is affected by several factors, including pH and temperature.

REVIEW NOTE

The proposed release specifications include appearance, _____)

The proposed regulatory methods have been validated. The impurity and degradation profiles have been investigated. Reference standards for API have been developed and characterized.

Based on stability data from Lot # _____ HSEC0001, human secretin is stable for at least 6 months at -20°C when stored in _____ vial, _____ cap with tape seal.

During drug development, human secretin manufactured by _____ was used for clinical and non-clinical studies. Since the drug substance, manufactured by _____ was not manufactured with adequate controls, the material manufactured by _____ is used for the commercial product.

The human secretin and porcine secretin comprise the same amino acid sequence except at positions 15 and 16 [Glu-Gly for human secretin and Asp-Ser for porcine secretin]. Because of the difference in amino acid residuals between these two peptides, the molecule of human secretin is assigned an NME designation by the ONDC management (see the e-mail attachment). However, the final decision whether the orphan drug status should be granted to human secretin will be made by the clinical division (see the attached 1/21/04 Memo to File for NDA 21-256).

DRUG PRODUCT: The proposed commercial formulation for _____ is a white to off-white lyophilized powder. Each vial contains 16 µg of human secretin combined with mannitol, cysteine, and sodium chloride. Excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail. There is no provision for reprocessing.

Because of the loss of secretin content, the formulation and manufacturing procedures were revised in the 10/10/03 NDA resubmission. _____ in the initial formulation was replaced with 0.9% sodium chloride solution and the _____ tube inserted for _____ secretin human is added. Since changes in _____ in the new formulation can affect rate and extent of drug absorption, the bridging study between the old formulation and the new formulation may need to be considered by medical reviewer and biopharmacologist.

The drug product is currently manufactured by Bell-More Laboratories (Hampstead, MD) instead of _____ which was utilized to manufacture the clinical and non-clinical batches _____

The proposed release specifications included appearance, _____

The proposed regulatory methods have been validated.

REVIEW NOTE

The drug product is packaged in a _____ vial _____ closed with a stopper _____ and sealed with a seal _____.

Based on data from the three primary stability batches (0134589, 0134590, and 0134591), the batches fail to meet the acceptance criterion _____ during storage at -15 to -30°C, 2 to 8°C and 25°C for a period of _____. In order to prevent these high assay values _____ the Agency recommends to control manufacturing procedure to permit filling at target of _____ of label claim instead of _____. Moreover, variations in the volume filled should be controlled to permit consistent fill of the target. In the mean time, the agency recommends to widen interim specification for assay of from _____ to _____ given consideration of orphan drug indication and usage of the product. To resolve this issue, the sponsor has committed to narrow the assay specification to _____ of label claim when new batches are manufactured with a filling target of _____ % label claim instead of _____ (see the 3/15/04 amendment).

B. Description of How the Drug Product is Intended to be Used

The recommended dose of: _____ is 0.2 µg/kg for pancreatic function testing. For diagnosis of gastrinoma (_____ the usual dose is 0.4 µg/kg. _____ is administered by intravenous injection over 1 minute.

C. Basis for Approvability or Not-Approval Recommendation

This application can be **approved** from a CMC viewpoint pending satisfactory microbiology consult. This recommendation is based upon several issues identified during the review. (1) General procedures for the synthesis of human secretin are outlined in DMF # _____. All chemistry deficiencies have been addressed the DMF holder, _____ and found satisfactory. (2) Chemical structures of major impurities and degradation products are illustrated. (3) The recommended interim acceptance criterion for assay of _____ is accepted by the firm. The firm commits to change manufacturing procedure to permit filling target of _____ of label claim instead of _____. (4) The manufacturing sites for the drug substance and the drug product as well as the testing facilities have been inspected and found to be acceptable by the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./HFD-510/March 18, 2004
 Chemistry Team Leader Name/Date: Liang Zhou, Ph.D., HFD-180
 Project Manager Name/Date: Ryan, Baraco, HFD-180

C. CC Block

HFD-820: Dr. Eric Duffy/ Dr. Duu-Gong Wu

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pages of trade

secret and/or

confidential

commercial

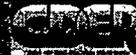
information

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

/s/

Chien-Hua Niu
3/18/04 04:10:54 PM
CHEMIST

Liang Zhou
3/18/04 04:52:02 PM
CHEMIST
Approval is recommended pending Micro consult



NDA 21-256

(Human Secretin for Injection)

ChiRhoClin, Inc.

Chien-Hua Niu, Ph.D., HFD-510

For

**Division of Gastrointestinal &
Coagulation Drug Products, HFD-180**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
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III. Administrative.....	10
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B. Endorsement Block.....	10
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Chemistry Assessment	11
I. DRUG SUBSTANCE	
II. DRUG PRODUCT	
III. LABELING & PACKAGE INSERT	
IV. Claim Of Categorical Exclusion	
V. List Of Deficiencies To Be Communicated	



Chemistry Review Data Sheet

1. NDA 21-256
2. REVIEW #: 2
3. REVIEW DATE: February 12 , 2004
4. REVIEWER: Chien-Hua Niu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

RESUBMISSION
AMENDMENT
IR LETTER
AMENDMENT
TELECON
AMENDMENT
AMENDMENT
AMENDMENT

Document Date

14-May-2001
16-July-2001
08-Aug-2001
10-Aug-2001
20-Aug-2001
26-Sep-2001
30-Nov-2001
03-Dec-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

See above Section (# 5)

Document Date

See above section (# 5)

7. NAME & ADDRESS OF APPLICANT:

Name: ChiRhoClin, Inc.
Address: 4000 Blackburn Lane, Suite 270
Burtonsville, MD 20866-6129
Representative: Edward D. Purich, Ph.D.
Telephone: (301)476-8388



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: —
- b) Non-Proprietary Name (USAN): Synthetic human secretin
- c) Code Name/# (ONDC only): None
- d) Type/Submission Priority (ONDC only):
 - Chem. Type: —
 - Submission Priority: 1 P

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Hormone

11. DOSAGE FORM: Lyophilized Sterile Powder

12. STRENGTH/POTENCY: 16 µg

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Human Secretin

Structural Formula:

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH₂

Molecular Formula:

C₁₃₀H₂₂₀N₄₄O₄₀ (CH₃COOH)_x (H₂O)_y

Molecular Weight (Free Base): —

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	III	—	—	3	Adequate	27-December-99	Review by Arthur Shaw
—	II	—	Synthetic Human Secretin	1	Adequate	4-February-04	Reviewed by Arthur Shaw and Chien-Hua Niu for NDA #21-256

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-136	Synthetic Porcine Secretin for diagnosis of exocrine pancreatic dysfunction and ;
NDS	21-209	Synthetic Porcine Secretin ;

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		Dr. Sue Jane Wang
EES	Pending		Office of Compliance
Pharm/Tox	Acceptable	19-Jan-2004	Dr. Jasti Choudary
Biopharm	Pending		Dr. Suliman Al-Fayoumi
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		Dr. Chien-Hua Niu
DMETS	Revision of the labels and labeling		
EA	Categorical exclusion		Dr. Chien-Hua Niu
Microbiology	Pending		Dr. Neal Sweeney

REVIEW NOTE

The Chemistry Review for NDA 21-256

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending (1) submission of additional CMC information described in List of Deficiencies; and (2) Satisfactory cGMP inspection of facilities used to manufacture the drug product.

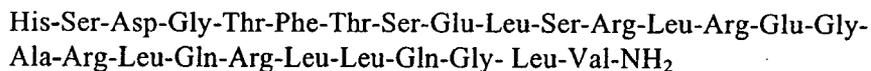
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(human secretin) for injection is utilized for diagnosis of pancreatic exocrine and gastrinoma

DRUG SUBSTANCE: Synthetic human secretin is a gastrointestinal peptide hormone. The primary action of secretin is to increase the volume and bicarbonate content of secreted pancreatic juices. Human secretin is an acetate salt of a synthetic 27 amino acid polypeptide. The structural formula for human secretin is presented below:



The structure of human secretin was elucidated by a variety of analytical and spectrophotometric techniques,

Human secretin has and is

The product is

Conformation of secretin has been investigated by a variety of techniques, including CD, NMR, and molecular dynamic. The results have appeared in the literature. These studies indicate that the molecule is highly structured in the solvents known to support secondary structure. The data show that secretin adopts a conformation consisting of an N-terminal irregular strand (residue 1-6) followed by two helices (residue 7-13 and 17-25) connected by a "half-turn" (residue 14-16); the last two residues (26-27) are again irregular.

The major impurities in human secretin are These impurities are in fact products with secretin. This affected by several factors, including pH and temperature.

REVIEW NOTE

The proposed release specifications include appearance, _____

_____ The proposed regulatory methods have been validated. The impurity and degradation profiles have been investigated. Reference standards for API have been developed and characterized.

Based on stability data from Lot # _____ HSEC0001, human secretin is stable for at least 6 months at -20°C when stored in _____ vial, _____ cap with tape seal.

During drug development, human secretin manufactured by _____ was used for clinical and non-clinical studies. Since the drug substance, manufactured by _____ was not manufactured with adequate controls, the material manufactured by _____ is used for the commercial product.

The human secretin and porcine secretin comprise the same amino acid sequence except at positions 15 and 16 [Glu-Gly for human secretin and Asp-Ser for porcine secretin]. Because of the difference in amino acid residuals between these two peptides, the molecule of human secretin is assigned an NME designation by the ONDC management (see the e-mail attachment). However, the final decision whether the orphan drug status should be granted to human secretin will be made by the clinical division (see the attached 1/21/04 Memo to File for NDA 21-256).

DRUG PRODUCT: The proposed commercial formulation for _____ is a white to off-white lyophilized powder. Each vial contains 16 µg of human secretin combined with mannitol, cysteine, and sodium chloride. Excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail. There is no provision for reprocessing.

Because of the _____ the formulation and manufacturing procedures were revised in the 10/10/03 NDA resubmission. _____ in the initial formulation was replaced with 0.9% sodium chloride solution and the _____ tube inserted for _____ was _____ after secretin human is added. Since changes in _____ in the new formulation can affect rate and extent of drug absorption, the bridging study between the old formulation and the new formulation may need to be considered by medical reviewer and biopharmacologist.

The drug product is currently manufactured by Bell-More Laboratories (Hampstead, MD) instead of _____ which was utilized to manufacture the clinical and non-clinical batches _____

The proposed release specifications included appearance, _____

_____ The proposed regulatory methods have been validated.

The drug product is packaged in a _____ vial _____ closed with a stopper _____ and sealed with a seal _____



REVIEW NOTE

Based on data from the three primary stability batches (0134589, 0134590, and 0134591), the batches fail to meet the acceptance criterion (—) during storage at -15 to -30°C, 2 to 8°C and 25°C for a period of — . In order to prevent these high assay values — , the Agency recommends to control manufacturing procedure to permit filling at target of — of label claim instead of — . Moreover, variations in the volume filled should be controlled to permit consistent fill of the target. In the mean time, the agency recommends to widen interim specification for assay of from — to — given consideration of orphan drug indication and usage of the product. However, the Agency requests the sponsor to commit to narrow the assay specification to — of label claim when new batches are manufactured with a filling target of — label claim.

The sponsor has cited a wrong regulation [21 CFR 25.31(e)] to claim a categorical exclusion from filling an environmental assessment.

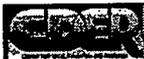
The sponsor's responses to the 11/21/01 discipline review letter have been reviewed and found satisfactory for most parts (See page 29 to 41 of this CMC review).

B. Description of How the Drug Product is Intended to be Used

The recommended dose of: — is 0.2 µg/kg for pancreatic function testing. For diagnosis of gastrinoma (—), the usual dose is 0.4 µg/kg. — is administered by intravenous injection over 1 minute.

C. Basis for Approvability or Not-Approval Recommendation

This application is **approvable** from a CMC viewpoint pending satisfactory responses. This recommendation is based upon several issues identified during the review. (1) General procedures for the synthesis of human secretin are outlined in DMF # — . All chemistry deficiencies have been addressed by the DMF holder, — , and found satisfactory. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Three primary stability batches with the new formulation have been manufactured by Bell-More Laboratories. Stability data indicate that no significant changes were observed in terms of appearance, — , when stored at -15° to -30°C, 2° to 8°C, and 25°C for — . However, the — for Lots 0134590 and 0134591 — during storage and fail to meet newly proposed specification — . and (4) Regarding the manufacturing sites for the drug product, the final recommendation by the Office of Compliance is still pending.



REVIEW NOTE

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./HFD-510/February 12, 2004

Chemistry Team Leader Name/Date: Liang Zhou, Ph.D., HFD-180

Project Manager Name/Date: Ryan, Baraco, HFD-180

C. CC Block

HFD-820: Dr. Eric Duffy/ Dr. Duu-Gong Wu

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confidential

commercial

information

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/s/

Chien-Hua Niu
2/12/04 03:52:47 PM
CHEMIST

Liang Zhou
2/12/04 04:57:07 PM
CHEMIST
Ryan: 1. DR letter 2. pending EER and other
consults. We need to set telecon with the
firm to facilitate to resolve these issues which
are considered as minor deficiencies.

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-256 **CHEM REVIEW #:** 1 **REVIEW DATE:** November 20, 2001

SUBMISSION TYPE	DATES		
DOCUMENT CDER	ASSIGNED	REVIEW	
RESUBMISSION	14-May-2001	25-May-2001	03-Jun-2001
AMENDMENT BZ	16-Jul-2001	17-Jul-2001	18-Jul-2001
IR LETTER	08-Aug-2001		
AMENDMENT BZ	10-Aug-2001	15-Aug-2001	20-Aug-2001
TELECON	20-Aug-2001		
AMENDMENT BZ	26-Sep-2001	27-Sep-2001	28-Sep-2001

NAME & ADDRESS OF APPLICANT: ChiRhoClin, Inc.

15500 Gallaudet Avenue

Silver Spring, MD 20905

DRUG PRODUCT NAME:

Proprietary: — **ACCEPTABLE** per OPDRA review 09/21/01

Nonproprietary: Synthetic Human Secretin

USAN: None See discussion below

CAS: None See discussion below

COMMENT1a: The applicant should provide a USAN and a CAS number for the drug substance.

Code Name/#: None

Chem.Type/Ther.Class: 1P

PHARMACOLOGICAL CATEGORY: hormone

INDICATIONS:

- 1) Diagnosis of exocrine pancreatic dysfunction,
- 2) Diagnosis of
- 3) For the facilitation of papilla during ERCP

DOSAGE FORM: INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION
(Lyophilized Sterile Powder)

STRENGTH: 16 µg **ROUTE OF ADMINISTRATION:** Intravenous

HOW DISPENSED: Rx OTC

SPOTS: None

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-
Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH₂

HSDGTFTSELSRLREGARLQRLLOGLV

C₁₃₀H₂₂₀N₄₄O₄₀ (CH₃COOH)_x (H₂O)_y

Since the acceptance criteria for the _____ are
not fixed (see Specification below), the unknown values for the _____
are appropriate.

Molecular Weight (Free base)

SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
—	III		—	3	Adequate	27-Dec-1999
—	II		Human Secretin	1	Inadequate	14-Sep-2001

RELATED DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-136	Synthetic Porcine Secretin for diagnosis of diagnostic use in pancreatic exocrine dysfunction
NDA	21-209	Synthetic Porcine Secretin for diagnosis of —

STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending See note below		
Biopharm	Acceptable	14-Nov-2001	Sandip Roy
OPDRA	Acceptable	21-Sep-2001	Hye-Joo Kim,
Microbiology	Acceptable	06-Nov-2001	Neal Sweeney

REMARKS/COMMENTS: This is a poorly organized and incomplete application. There are two sources for the drug substance,

— drug product has been manufactured from — drug substance. The — drug substance was manufactured under poorly controlled conditions and the plant was found unacceptable on inspection. The applicant states that — drug substance, which was used for the clinical trials, will not be used for the commercial product and is no longer being manufactured. Although the applicant has provided data to demonstrate that the — drug substances have the same sequence and *in vivo* biological activity, it is still important to obtain adequate manufacturing information and process controls to support the specifications for the — drug substance because:

- 1) The — drug substance was manufactured under conditions that were not compliant with cGMP.
- 2) Two of the clinical trials used less than thirty patients.
- 3) Only one batch of — drug substance has been manufactured.
- 4) — had a WH recommendation from the Office of Compliance in 1999 and — has a WH recommendation in this review cycle.

The manufacturing procedure for the drug product is poorly controlled, resulting in _____ during processing. There is no explanation for this and there is no specification for in-process testing used _____ per vial (16 µg) in _____

Without an in-process specification for the secretin content _____ the amount of excipients in the vial will vary to an unknown extent. The amount of excipients could have an effect on the stability of the finished drug product.

The assays for the finished drug product have not been shown to be capable of detecting impurities. There is no data to support the proposed acceptance criteria for impurities in the finished drug product. Once the assays have been shown to be capable of detecting and assaying impurities, then a toxicological and clinical assessment of their impact can be made. Stability studies performed using drug product manufactured from _____ drug substance are inadequate to establish an expiration date (proposed _____ months).

There is no basis for assessment of the adequacy of the finished drug product to be marketed because:

- 1) Only one batch of _____ drug substance and one batch of _____ drug substance have been manufactured.
- 2) The only batch of drug product that has been manufactured used drug substance manufactured at a plant that has a WH recommendation from the Office of Compliance
- 3) There is no information concerning the manufacture or specifications for drug product manufactured from _____ drug substance.
- 4) The manufacturing process for the drug product is poorly controlled in terms of process controls and specifications.
- 5) There is no stability data for drug product manufactured from _____ drug substance.
- 6) There is no adequate assay to assess the stability of the drug product.
- 7) The inadequacy of the stability data and the lack of a stability-indicating assay for the drug product manufactured from _____ drug substance does not permit extrapolation to future stability data for drug product manufactured from _____ drug substance.
- 8) DMF _____ for _____ has been found to be inadequate and the holder was informed in a letter dated September 14, 2001.

CONCLUSIONS & RECOMMENDATIONS: Not approvable. The applicant should be sent a Discipline Review Letter describing the deficiencies.

|S|

Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

|S|

Liang Zhou, Ph.D.
Team Leader, HFD-180

R/D Init by: LZhou 20-NOV-2001

ABS F/T/ 20-Nov-2001

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/s/

Arthur B. Shaw
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CHEMIST

Liang Zhou
11/20/01 02:55:26 PM
CHEMIST

See CMC review dated 3/18/04, pg. 19

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