therefore requires mannitol and cysteine HCl [redacted]

- Formulation and Drug Product Manufacturing: Very little product development was done to optimize the formulation. The manufacturing procedure has been amended to control for [redacted]

- Comparison of Preclinical and Marketing Formulations: The clinical, preclinical, and stability studies were done using drug product manufactured using one batch of drug substance manufactured by [redacted]. This drug substance was manufactured under poorly controlled conditions and [redacted] failed inspection. The applicant has not been able to measure impurities in the drug product and had proposed acceptance criteria of [redacted] label claim for secretin content. The stability data (secretin content only) for drug product manufactured using [redacted] drug substance does not support an expiration date assignment.

  [redacted] manufactured a new batch of drug substance, The [redacted] and [redacted] drug substances are comparable, although the [redacted] drug substance is purer. There is no accelerated stability data and limited real-time stability data for storage under the proposed storage conditions for drug product manufactured using [redacted] drug substance.

  The formulation has not changed.

- Additional Drug Product Information: The manufacture of [redacted] drug substance is described in DMF [redacted] There are some remaining issues concerning this DMF, but there is nothing to prevent approval of the NDA.
- All review issues have been addressed in the chemistry reviews for NDA 21-136, which is for the same drug product with different indications. The correspondence dated March 22, 2002 provides the right of reference to the March 13, 2002 submission to NDA 21-136, which was the subject of the final review recommending approval for NDA 21-136.

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

- Recommended dosage:

0.2 µg/kg = 15 µg for 75 kg patient = one vial
0.4 µg/kg = 30 µg for 75 kg patient = two vials

- The drug product is not intended for co-administration with another drug.
- Used as a diagnostic agent to be dosed only once.
- Expiration dating period and recommended storage conditions.

  — at -20°C with — of label claim and no impurity specification

III. Administrative

A. Reviewer's Signature: See DFS

B. Endorsement Block R/D/ init by Marie Kowblansky for Liang Zhou 03-Apr-2002

C. CC Block: See DFS

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Arthur B. Shaw
4/3/02 12:05:05 PM
CHEMIST

Marie Kowblansky
4/3/02 12:16:09 PM
CHEMIST

Marie Kowblansky is Acting Team Leader for Liang Zhou

FEB 3 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-209 **CHEM REVIEW #:** 1 **REVIEW DATE:** February 3, 2000

SUBMISSION TYPE	**DATES**			
	DOCUMENT	**CDER**	**ASSIGNED**	**REVIEW**
ORIGINAL	17-Aug-1999	17-Aug-1999	29-Oct-1999	

NAME & ADDRESS OF APPLICANT: ChiRhoClin, Inc.

DRUG PRODUCT NAME:

Proprietary: —

Nonproprietary: Synthetic Porcine Secretin

Chem.Type/Ther.Class: 3P

PHARMACOLOGICAL CATEGORY:

INDICATIONS: Diagnosis of gastrinoma

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

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

HOW DISPENSED: X **Rx** ___ **OTC**

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

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

SUPPORTING DOCUMENTS: NDA 21-136

RELATED DOCUMENTS: INDs 54,196, —
The first two INDs are for synthetic porcine and — — respectively and were reviewed earlier.

CONSULTS: See NDA 21-136

REMARKS/COMMENTS: This application was administratively split off from NDA 21-136 by the FDA when the applicant decided to file this indication (originally refused to file.) over protest. In a letter to NDA 21-136 dated January 28, 2000, the applicant granted right of reference to NDA 21-136 for the review of NDA 21-209. The CMC information in NDA 21-136 was found to be inadequate in Chem. Review #1, dated January 4, 2000.

CONCLUSIONS & RECOMMENDATIONS: Not approvable. See Chem. Review for NDA 21-136 Establishment Inspection not complete.

/S/ 03-Feb-00
Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

/S/ 2/4/00
Liang Zhou, Ph.D.
Acting Chemistry Team Leader, HFD-180

cc:
NDA # 21-209
HFD-180/LTalarico
HFD-180/Div File/NDA #21-209
HFD-180/LZhou
HFD-820/JGibbs
HFD-180/AShaw
HFD-181/CSO
R/D Init by: LZhou 03-Feb-2000
ABS **F/T/ ABS 03-Feb-2000**C:\WORD\NG\21-209 Synthetic Porcine Secretin Review #1.doc

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21209/000
Stamp: 17-AUG-1999
Regulatory Due: 09-APR-2002
Applicant: CHIRHOCLIN
15500 GALLAUDET AVE
SILVER SPRING, MD 209054176
Priority: 3P
Org Code: 180

Action Goal:
District Goal: 08-FEB-2002
Brand Name: SECREFLO(SYNTHETIC PORCINE SECRETIN) INJ
Estab. Name:
Generic Name: SYNTHETIC PORCINE SECRETIN
Dosage Form: (FOR INJECTION)
Strength: 16 MICROG/VIAL

Application Comment: I SENT AN EMAIL ON OCTOBER 19 1999 TO SHIRNETTE FERGUSON ALERTING HER TO THE NEW NDA (on 16-FEB-2000 by A. SHAW (HFD-180) 301-827-7310)
THIS NDA WAS SPLIT OFF FROM 21-136 ADMINISTRATIVELY IN OCTOBER AND EES WAS INFORMED IN AN E-MAIL. ALL THE SITES FOR 21-209 ARE THE SAME AS FOR 21-136 (on 16-FEB-2000 by A. SHAW (HFD-180) 301-827-7310)

FDA Contacts:

B. STRONGIN	(HFD-180)	301-827-7310	Project Manager
A. SHAW	(HFD-180)	301-827-7310	Review Chemist
L. ZHOU	(HFD-180)	301-827-7471	Team Leader

Overall Recommendation:
WITHHOLD on 11-FEB-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 07-AUG-2000 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 06-MAR-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 05-MAR-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 04-MAR-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 01-MAY-2000 by R. WOODS (HFD-324) 301-827-0062

Establishment: 1121526
CHESAPEAKE BIOLOGICAL LABORATORIES INC
1111 PACA STREET
BALTIMORE, MD 21230

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER
Profile: SVS OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-FEB-2000				SHAWA
SUBMITTED TO DO	16-FEB-2000	PS			DAMBROGIOJ
ASSIGNED INSPECTION	22-FEB-2000	GMP			BBARGO
ASSIGNED INSPECTION	22-FEB-2000	PS			BBARGO
INSPECTION SCHEDULED	22-FEB-2000				BBARGO
DO RECOMMENDATION	23-MAR-2000			ACCEPTABLE INSPECTION	BBARGO

ON 2/28-3/17/2000, A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED COVERING THE FIRM'S OPERATIONS. ALTHOUGH GMP DEFICIENCIES WERE NOTED, THE FIRM PROMISED CORRECTIONS.

OC RECOMMENDATION	27-MAR-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: 1123903
CHESAPEAKE BIOLOGICAL LABORATORIES INC
1111 SOUTH PACA ST
BALTIMORE, MD 212302591

DMF No: AADA:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-FEB-2002				SHAWA
OC RECOMMENDATION	11-FEB-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-FEB-2000				SHAWA
OC RECOMMENDATION	16-FEB-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: THIS SITE WAS INSPECTED FOR NDA 21-136. IT NEEDS TO BE RE-INSPECTED FOR BOTH NDA 21-136 AND 21-209 (on 03-AUG-2000 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-FEB-2000				SHAWA
SUBMITTED TO DO	16-FEB-2000	GMP			DAMBROGIOJ
INSPECTION PERFORMED	22-FEB-2000		18-FEB-2000		BBARGO
ON 2/16-18/2000, A GMP/PRE-APPROVAL ISPECTION WAS PERFORMED WHICH REVEALED MAJOR GMP VIOLATIONS.					
DO RECOMMENDATION	22-FEB-2000			WITHHOLD	BBARGO
EIR RECEIVED BY OC	21-MAR-2000				WOODSR
OC RECOMMENDATION	22-MAR-2000			WITHHOLD EIR REVIEW-CONCUR W/DISTRICT	WOODSR

OC RECOMMENDATION	06-MAR-2002	ACCEPTABLE	DAMBROGIOJ
		FIRM RESPONSE TO DEFIC. ADEQUA	

APPEARS THIS WAY
ON ORIGINAL

2 Page(s) Withheld

NDA 21-136

SecreFlo

Arthur B. Shaw, Ph.D.

Division of Gastrointestinal and
Coagulation Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-136
2. REVIEW #: 8
3. REVIEW DATE:
4. REVIEWER Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

ORIGINAL	14-May-99
IR LETTER	27-Jul-99
AMENDMENT BZ	13-Sep-99
AMENDMENT BZ	06-Oct-99
REVIEW #1	29-Dec-99
AMENDMENT BZ	29-Dec-99
REVIEW #2	08-Mar-00
AMENDMENT BZ	08-Mar-00
REVIEW #3	14-Mar-00
AMENDMENT BC	20-Mar-00
AE Letter	24-Mar-00
AMENDMENT AZ	08-May-00
AMENDMENT BZ	13-Jul-00
AMENDMENT BC	03-Aug-00
REVIEW #4	13-Sep-00
DR Letter	19-Sep-00
REVIEW #5	07-Nov-00
AE Letter	08-Nov-00
Meeting	06-Dec-00
AMENDMENT BZ	17-Sep-01
AMENDMENT AC	05-Oct-01
AMENDMENT BC	03-Dec-01
IR Letter	14-Dec-01
AMENDMENT BC	21-Jan-02
AMENDMENT BC	04-Feb-02
Meeting Minutes	12-Feb-02
AMENDMENT BL	13-Feb-02
Chem Review #6	01-Mar-02
Amendment BC	01-Mar-02
Amendment MR	21-Dec-01
Chem Review #7	07-Mar-02
DR Letter	08-Mar-02

APPEARS THIS WAY
ON ORIGINAL

6. SUBMISSION(S) BEING REVIEWED:

Telecon	02-Apr-02
Amendment BC	13-Mar-02
Amendment BC	02-Apr-02
Telecon (labeling)	03-Apr-02

7. NAME & ADDRESS OF APPLICANT:

Name: ChiRhoClin, Inc.

Address: 15500 Gallaudet Avenue
Silver Spring MD 20905

Representative: Edward Purich, Ph.D.

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SecreFlo
b) Non-Proprietary Name (USAN): Secretin
c) Code Name/# : N/A
d) Chem. Type/Submission Priority

- Chem. Type 3
- Submission Priority: 3

9. LEGAL BASIS FOR SUBMISSION: New drug

10. PHARMACOL. CATEGORY: Secretory hormone

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

12. STRENGTH/POTENCY: 16 µg/vial

13. ROUTE OF ADMINISTRATION Intravenous:

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. ___X_____Not a SPOTS product

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

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

MW= 3055.

$C_{130}H_{220}N_{44}O_{41}$

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[2]	DATE REVIEW COMPLETED
—	II	/	Synthetic Porcine Secretin	Adequate	03-Apr-2002
—	III		/	Adequate	27-Dec-1999

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-209	Same drug substance, different indication
NDA	21-256	Similar drug substance from same applicant
IND	54,196	Synthetic Porcine Secretin -
IND	[redacted]	
NDA	18-920	Biological porcine secretin

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Proposed expiration date not acceptable See review notes	13-Feb-2002	Milton Fan
EES	AC	04-Mar-2002	
Pharm/Tox	N/A		Independent review
Biopharm	N/A		Independent review
LNC	Secretin		Per USAN see below
Methods Validation	Not submitted See review notes		
DMETS	Secreflo Acceptable	07-Mar-2002	Alina R. Mahmud,
EA	N/A		Categorical Exclusion
Microbiology	Acceptable	16-Oct-2000	Carol Vincent

The Chemistry Review for NDA 21-136

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Approval

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

1. Phase IV Commitment:

Develop an assay to measure impurities in the drug product.

2. Additional Post-Approval Commitments:

II. Summary of Chemistry Assessments

A. Description of Drug Product and Drug Substance:

- Drug Product Description: Sterile lyophilized powder for injection at 16 µg per vial, to be reconstituted with 8 mL of 0.9% NaCl
- Drug Substance Description: Synthetic 27 amino acid peptide, whose sequence is the same as naturally occurring porcine secretin. The synthetic peptide has the same biological activity in a cat bioassay as the biological peptide. The synthetic peptide is
- Formulation and Drug Product Manufacturing: The manufacturing procedure has been amended to
- Comparison of Preclinical and Marketing Formulations: The clinical, preclinical, and stability studies were done using drug product manufactured using batch of drug substance manufactured by . This drug substance was manufactured under poorly controlled conditions and failed inspection. The applicant has not been able to measure impurities in the drug product and had proposed acceptance criteria of of label claim for secretin content. The stability data (secretin content only) for drug product manufactured using drug

substance does not support an expiration date assignment.

[redacted] manufactured a new batch of drug substance, The [redacted] drug substances are comparable, although the [redacted] drug substance is purer. There is no accelerated stability data and limited real-time stability data for storage under the proposed storage conditions for drug product manufactured using [redacted] drug substance.

The formulation has not changed.

- Additional Drug Product Information: The manufacture of [redacted] is described in DMF [redacted]. There are some remaining issues concerning this DMF, but there is nothing to prevent approval of the NDA.

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

- Recommended dosage:
  0.2 µg/kg = 15 µg for 75 kg patient = one vial
  0.4 µg/kg = 30 µg for 75 kg patient = two vials
- The drug product is not intended for co-administration with another drug.
- Used as a diagnostic agent to be dosed only once.
- Expiration dating period and recommended storage conditions.
  12 months at -20°C with [redacted] of label claim and no impurity specification

III. Administrative

A. Reviewer's Signature: See DFS

B. Endorsement Block R/D/ init by Marie Kowblansky for Liang Zhou 03-Apr-2002

C. CC Block: See DFS

22 Page(s) Withheld

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

/s/

Arthur B. Shaw
4/3/02 11:46:08 AM
CHEMIST

Marie Kowblansky
4/3/02 12:18:44 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

NDA 21-136

SecreFlo

Arthur B. Shaw, Ph.D.

Division of Gastrointestinal and
Coagulation Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-136
2. REVIEW #: 7
3. REVIEW DATE:
4. REVIEWER Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

ORIGINAL	14-May-99
IR LETTER	27-Jul-99
AMENDMENT BZ	13-Sep-99
AMENDMENT BZ	06-Oct-99
REVIEW #1	29-Dec-99
AMENDMENT BZ	29-Dec-99
REVIEW #2	08-Mar-00
AMENDMENT BZ	08-Mar-00
REVIEW #3	14-Mar-00
AMENDMENT BC	20-Mar-00
AE Letter	24-Mar-00
AMENDMENT AZ	08-May-00
AMENDMENT BZ	13-Jul-00
AMENDMENT BC	03-Aug-00
REVIEW #4	13-Sep-00
DR Letter	19-Sep-00
REVIEW #5	07-Nov-00
AE Letter	08-Nov-00
Meeting	06-Dec-00
AMENDMENT BZ	17-Sep-01
AMENDMENT AC	05-Oct-01
AMENDMENT BC	03-Dec-01
IR Letter	14-Dec-01
AMENDMENT BC	21-Jan-02
AMENDMENT BC	04-Feb-02
Meeting Minutes	12-Feb-02
AMENDMENT BL	13-Feb-02
Chem Review #6	01-Mar-02

APPEARS THIS WAY
ON ORIGINAL

6. SUBMISSION(S) BEING REVIEWED:

Amendment BC	01-Mar-02
Amendment MR	21-Dec-01

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: SecreFlo Under review
   b) Non-Proprietary Name (USAN): Synthetic Porcine Secretin (USAN applied for) INN = secretin
   c) Code Name/# : N/A
   d) Chem. Type/Submission Priority
      - Chem. Type 3
      - Submission Priority: 3
9. LEGAL BASIS FOR SUBMISSION: New drug
10. PHARMACOL. CATEGORY: Secretory hormone
11. DOSAGE FORM: INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (Lyophilized Sterile Powder)
12. STRENGTH/POTENCY: 16 µg/vial
13. ROUTE OF ADMINISTRATION Intravenous:
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. ___X_____Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

MW= 3055.

$C_{130}H_{220}N_{44}O_{41}$

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Synthetic Porcine Secretin	1	Inadequate	14-Feb-2001	Deficiencies can be corrected easily
	III			1	Adequate	27-Dec-1999	

The Chemistry Review for NDA 21-136

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
The conditions for approval, including post-approval commitments, include

1. The applicant should provide the adequate information before the application can be approved: as follows:
   a. Tighten the acceptance criteria for the drug substance (specific recommended values in draft letter).
   b. Provide a complete specification for the drug substance, including the [redacted] assay. Each test method, including assay(s) for secretin purity and impurity levels, should be completely and clearly described in a separate, uniquely numbered SOP.
   c. Amend the specification for the drug product to ensure adequate testing for identity, strength, quality, and purity (specific tests in draft letter. Each test method, including assay(s) for secretin purity and impurity levels, should be completely and clearly described in a separate, uniquely numbered SOP.
   d. The acceptance criterion for the secretin content in the drug product should be [redacted]
   e. Provide a stability protocol including testing for impurities as set in the specification.
   f. Provide an established name.
2. Post-approval Commitments

[redacted]

3. Post-Approval Commitments Made in March 1, 2002 Amendment:

II. Summary of Chemistry Assessments

A. Description of Drug Product and Drug Substance:

- Drug Product Description: Sterile lyophilized powder for injection at 16 µg per vial, to be reconstituted with 8 mL of 0.9% NaCl
- Drug Substance Description: Synthetic 27 amino acid peptide, whose sequence is the same as naturally occurring porcine secretin. The synthetic peptide has the same biological activity in a cat bioassay as the biological peptide. The synthetic peptide is
- Formulation and Drug Product Manufacturing:

  The manufacturing batch records show

  This is a problem that the applicant will address in future batches.
- Comparison of Preclinical and Marketing Formulations: The clinical, preclinical, and stability studies were done using drug product manufactured using batch of

drug substance manufactured by [redacted]
This drug substance was manufactured under poorly controlled conditions and [redacted] failed inspection. The applicant has not been able to measure impurities in the drug product and has proposed acceptance criteria of [redacted] of label claim for secretin content. The stability data (secretin content only) for drug product manufactured using [redacted] drug substance does not support an expiration date assignment.

[redacted] manufactured a new batch of drug substance, The [redacted] drug substances are comparable, although the [redacted] drug substance is purer. There is no accelerated stability data and limited real-time stability data for storage under the proposed storage conditions for drug product manufactured using [redacted] drug substance.

- Additional Drug Product Information: The manufacture of [redacted] is described in DMF [redacted] There are some remaining issues concerning this DMF, but there is nothing to prevent approval of the NDA.

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

- Recommended dosage:
  0.2 µg/kg = 15 µg for 75 kg patient = one vial
  0.4 µg/kg = 30 µg for 75 kg patient = two vials
- The drug product is not intended for co-administration with another drug.
- Used as a diagnostic agent to be dosed only once.
- Expiration dating period and recommended storage conditions.
  Requested: [redacted] at -20°C with [redacted] of label claim
  Recommended: 12 months at -20°C with [redacted] of label claim
  Rationale:
  (a) No test for impurities in drug product
  (b) Only [redacted] batch of drug product manufactured using new source of drug substance
  (c) In-process controls during manufacturing of the drug product were inadequate
  (d) No accelerated stability data for drug product using new source of drug substance

(e) Limited stability data at storage temperature for drug product using new source of drug substance
(f) Stability data for drug product using old source of drug substance do not support assignment of an expiration date

C. Basis for Not-Approval Recommendation
The application is not approvable at this time because there is insufficient data to ensure the consistent manufacture and quality control of the drug product. If the applicant provides the information requested and agrees to the post-approval commitments, the application can be approved.

III. Administrative

A. Reviewer's Signature: See DFS

B. Endorsement Block R/D/ init by Liang Zhou 07-Mar-2002

C. CC Block: See DFS

34 Page(s) Withheld

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

/s/

Arthur B. Shaw
3/7/02 02:47:10 PM
CHEMIST

Liang Zhou
3/7/02 03:20:37 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

NDA 21-136

SecreFlo

Arthur B. Shaw, Ph.D.

Division of Gastrointestinal and Coagulation Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-136
2. REVIEW #:
3. REVIEW DATE:
4. REVIEWER Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:

ORIGINAL	14-May-1999
IR LETTER	27-Jul-1999
AMENDMENT BZ	13-Sep-1999
AMENDMENT BZ	06-Oct-1999
REVIEW #1	29-Dec-1999
AMENDMENT BZ	29-Dec-1999
REVIEW #2	08-Mar-2000
AMENDMENT BZ	08-Mar-2000
REVIEW #3	14-Mar-2000
AE Letter	24-Mar-2000
AMENDMENT BC	20-Mar-2000
AMENDMENT AZ	08-May-2000
AMENDMENT BZ	13-Jul-2000
AMENDMENT BC	03-Aug-2000
REVIEW #4	13-Sep-2000
DR Letter	19-Sep-2000
REVIEW #5	07-Nov-2000
AE Letter	08-Nov-2000
Meeting	06-Dec-2000
IR Letter	14-Dec-2001

6. SUBMISSION(S) BEING REVIEWED:

AMENDMENT BC	01-Mar-2002
AMENDMENT BL	13-Feb-2002
AMENDMENT BC	04-Feb-2002
AMENDMENT BC	21-Jan-2002
AMENDMENT BC	03-Dec-2001
AMENDMENT AC	05-Oct-2001
AMENDMENT BZ	17-Sep-2001

APPEARS THIS WAY
ON ORIGINAL

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: SecreFlo
   b) Non-Proprietary Name (USAN): Synthetic Porcine Secretin (USAN applied for)
   c) Code Name/# : N/A
   d) Chem. Type/Submission Priority
      - Chem. Type 3
      - Submission Priority: 3
9. LEGAL BASIS FOR SUBMISSION: New drug
10. PHARMACOL. CATEGORY: Secretory hormone
11. DOSAGE FORM: INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION (Lyophilized Sterile Powder)
12. STRENGTH/POTENCY: 16 µg/vial
13. ROUTE OF ADMINISTRATION Intravenous:
14. Rx/OTC DISPENSED: _X_Rx ___OTC
15. __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

MW= 3055.

$C_{130}H_{220}N_{44}O_{41}$

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	Synthetic Porcine Secretin	1	Inadequate	14-Feb-2001	Deficiencies can be corrected easily
	III			1	Adequate	27-Dec-1999	

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-209	Same drug substance, different indication
NDA	[redacted]	Similar drug substance from same applicant
IND	54,196	Synthetic Porcine Secretin
IND	[redacted]	
NDA	18-920	Biological porcine secretin

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Expiration date not acceptable See review notes	13-Feb-2002	Milton Fan
EES	WH See review notes	25-Oct-2001	[redacted] withdrawn. This should relieve the WH
Pharm/Tox	N/A		Independent review
Biopharm	N/A		Independent review
LNC	Pending		
Methods Validation	Not submitted See review notes		
OPDRA	Pending		
EA	N/A		Categorical Exclusion
Microbiology	Acceptable	16-Oct-2000	Carol Vincent

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-136

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
Approvable

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

The conditions for approval, including post-approval commitments, include

1. The applicant should provide the adequate information before the application can be approved: as follows:
   a. Tighten the acceptance criteria for the drug substance (specific recommended values in draft letter).
   b. Provide a complete specification for the drug substance, including the new [redacted] assay. Each test method, including assay(s) for secretin purity and impurity levels, should be completely and clearly described in a separate, uniquely numbered SOP.
   c. Amend the specification for the drug product to ensure adequate testing for identity, strength, quality, and purity (specific tests in draft letter. Each test method, including assay(s) for secretin purity and impurity levels, should be completely and clearly described in a separate, uniquely numbered SOP.
   d. The acceptance criterion for the secretin content in the drug product should be [redacted]
   e. Provide a stability protocol including testing for impurities as set in the specification.
   f. Provide an established name.
2. Post-approval Commitments

[redacted]

II. Summary of Chemistry Assessments

A. Description of Drug Product and Drug Substance:

- Drug Product Description: Sterile lyophilized powder for injection at 16 µg per vial, to be reconstituted with 8 mL of 0.9% NaCl
- Drug Substance Description: Synthetic 27 amino acid peptide, whose sequence is the same as naturally occurring porcine secretin. The synthetic peptide has the same biological activity in a cat bioassay as the biological peptide. The synthetic peptide is .
- Formulation and Drug Product Manufacturing: ne manufacturing batch records show . This is a problem that the applicant should address.
- Comparison of Preclinical and Marketing Formulations: The clinical, preclinical, and stability studies were done using drug product manufactured using batch of drug substance manufactured by . This drug substance was manufactured under poorly controlled conditions and failed inspection. . The applicant has not been able to measure impurities in the drug product and has proposed acceptance criteria of of label claim for secretin content. The stability data (secretin content only) for drug product manufactured using drug substance does not support an expiration date assignment.

  manufactured a new batch of drug substance, The drug substances are comparable, although the drug substance is purer. There is no accelerated stability data and limited real-time stability data for storage under the proposed storage conditions for drug product manufactured using drug substance.
- Additional Drug Product Information: The manufacture of is described in DMF There are some remaining issues concerning this DMF, but there is nothing to prevent approval of the NDA.

B. Description of How the Drug Product is Intended to be Used:
- Recommended dosage:
  0.2:µg/kg and 0.4 µg/kg = 15 µg and 30µg for 75 kg patient = one vial and two vials
- The drug product is not intended for co-administration with another drug.
- Used as a diagnostic agent to be dosed only once.
- Expiration dating period and recommended storage conditions.
  Requested: at -20°C with of label claim
  Recommended: 12 months at -20°C with label claim
  Rationale:
  (a) No test for impurities in drug product
  (b) Only batch manufactured of drug product using new source of drug substance
  (c) In-process controls during manufacturing of the drug product are inadequate
  (d) No accelerated stability data for drug product using new source of drug substance

(e) Limited stability data at storage temperature for drug product using new source of drug substance
(f) Stability data for drug product using old source of drug substance do not support assignment of an expiration date

C. Basis for Not-Approval Recommendation
The application is not approvable at this time because there is insufficient data to ensure the consistent manufacture and quality control of the drug product. If the applicant provides the information requested and agrees to the post-approval commitments, the application can be approved.

III. Administrative

A. Reviewer's Signature: See DFS

B. Endorsement Block R/D/ init by Liang Zhou 01-Mar-2002

C. CC Block: See DFS

38 Page(s) Withheld

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

/s/

Arthur B. Shaw
3/1/02 08:19:41 PM
CHEMIST

This may need Eric's signature

Liang Zhou
3/4/02 09:00:59 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-136 CHEM REVIEW #: 5 REVIEW DATE: November 2, 2000

SUBMISSION TYPE		DATES
DOCUMENT TYPE	CDER	ASSIGNED
AMENDMENT BC	12-Oct-2000	13-Oct-2000
AMENDMENT BC	31-Oct-2000	02-Nov-2000
PREVIOUS DOCUMENT		
ORIGINAL	14-May-1999	
IR LETTER	27-Jul-1999	
AMENDMENT BZ	13-Sep-1999	
AMENDMENT BZ	06-Oct-1999	
REVIEW #1	29-Dec-1999	
AMENDMENT BZ	29-Dec-1999	
REVIEW #2	08-Mar-2000	
AMENDMENT BZ	08-Mar-2000	
REVIEW #3	14-Mar-2000	
AE Letter	24-Mar-2000	
AMENDMENT BC	20-Mar-2000	
AMENDMENT AZ	08-May-2000	
AMENDMENT BZ	13-Jul-2000	
AMENDMENT BC	03-Aug-2000	
REVIEW #4	13-Sep-2000	
DR Letter	19-Sep-2000	

APPEARS THIS WAY ON ORIGINAL

NAME & ADDRESS OF APPLICANT: ChiRhoClin, Inc.

DRUG PRODUCT NAME:

Proprietary: ——————(formerly ——— See discussion under "Labeling"

Nonproprietary: Synthetic Porcine Secretin

Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY: Hormone

INDICATIONS: 1) Diagnosis of pancreatic exocrine → and

[ ]

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

STRENGTH: 16 µg ROUTE OF ADMINISTRATION: Intravenous

HOW DISPENSED: X Rx ___OTC

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

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

MW= 3055.

$C_{130}H_{220}N_{44}O_{41}$

SUPPORTING DOCUMENTS:

Number	Item referenced	Holder	Status	Review Date
DMF [redacted]			Acceptable	27-Dec-1999
IND 54196				

RELATED DOCUMENTS: NDA 21-209

CONSULTS: Microbiology ACCEPTABLE

REMARKS/COMMENTS: Inspection of [redacted]; recommended WH. Only [redacted] lot of drug substance made. Assay for drug product is not sensitive enough to quantitate [redacted] impurities. Some issues in the amendments were not reviewed since they are not approvability issues.

CONCLUSIONS & RECOMMENDATIONS: Approvable.

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

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

cc:
NDA # 21-136
HFD-180/LTalarico
HFD/180/HGallo-Torres
HFD/180/VRaczkowski
HFD-180/LZhou
HFD-820/JGibbs
HFD-180/AShaw
HFD-181/CSO
R/D Init by: LZhou 06-Nov-2000
Abs F/T/ ABS 07-Nov-2000C:\WORD\NG\21-136 Synthetic Porcine Secretin Review #5.doc

56 Page(s) Withheld

/s/

Art Shaw
11/7/00 11:34:19 AM
CHEMIST

Joe Sieczkowski
11/7/00 11:48:44 AM
CHEMIST
Acting Team Leader for Liang Zhou, Ph D/Tuesday,Nov 7,2000.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-136 **CHEM REVIEW #:** 4 **REVIEW DATE:** August 11, 2000

SUBMISSION TYPE DOCUMENT TYPE	**CDER**	**DATES ASSIGNED**
AMENDMENT BC	20-Mar-2000	21-Mar-2000
AMENDMENT AZ	08-May-2000	09-May-2000
AMENDMENT BZ	13-Jul-2000	06-Sep-2000
AMENDMENT BC	03-Aug-2000	08-Sep-2000
PREVIOUS DOCUMENT		
ORIGINAL	14-May-1999	
IR LETTER	27-Jul-1999	
AMENDMENT BZ	13-Sep-1999	
AMENDMENT BZ	06-Oct-1999	
REVIEW #1	29-Dec-1999	
AMENDMENT BZ	29-Dec-1999	
REVIEW #2	08-Mar-2000	
AMENDMENT BZ	08-Mar-2000	
REVIEW #3	14-Mar-2000	
AE Letter	24-Mar-2000	

NAME & ADDRESS OF APPLICANT: ChiRhoClin, Inc.

DRUG PRODUCT NAME:

Proprietary: [redacted] See discussion under "Labeling"

Nonproprietary: Synthetic Porcine Secretin

Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY: Hormone

INDICATIONS: 1) Diagnosis of pancreatic exocrine [redacted] and 2)

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

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

HOW DISPENSED: X **Rx** ___ **OTC**

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

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

MW= 3055.

$C_{130}H_{220}N_{44}O_{41}$

APPEARS THIS WAY
ON ORIGINAL

SUPPORTING DOCUMENTS:

Number	Item referenced	Holder	Status	Review Date
DMF [redacted]			Acceptable	27-Dec-1999
IND 54196				

RELATED DOCUMENTS: NDA 21-209

CONSULTS: Micro pending

REMARKS/COMMENTS: Inspection recommended WH. Only [redacted] lot of drug substance made. Assay for drug product is not sensitive enough to quantitate [redacted] impurities.

CONCLUSIONS & RECOMMENDATIONS: Not approvable.

[/S/] Sept 13, 2000

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

[/S/] 9/15/00

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

cc:
NDA # 21-136
HFD-180/LTalarico
HFD/180/HGallo-Torres
HFD/180/SAurrechia
HFD-180/Div File/NDA #21-136
HFD-180/LZhou
HFD-820/JGibbs
HFD-180/AShaw
HFD-181/CSO
R/D Init by: LZhou 06-Sep-2000
Abs **F/T/ ABS 13-Sep-2000**C:\WORD\NG\21-136 Synthetic Porcine Secretin Review #4.doc

100 Page(s) Withheld

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-136 **CHEM REVIEW #:** 3 **REVIEW DATE:** March 14, 2000

SUBMISSION TYPE **DATES**

	DOCUMENT	CDER	ASSIGNED
AMENDMENT BZ	08-Mar-2000	08-Mar-2000	14-Mar-2000

PREVIOUS DOCUMENT

ORIGINAL	14-May-1999
IR LETTER	27-Jul-1999
AMENDMENT BZ	13-Sep-1999
AMENDMENT BZ	06-Oct-1999
REVIEW #1	29-Dec-1999
AMENDMENT BZ	29-Dec-1999
REVIEW #2	08-Mar-2000

NAME & ADDRESS OF APPLICANT: ChiRhoClin, Inc.

DRUG PRODUCT NAME:

Proprietary: None

Nonproprietary: Synthetic Porcine Secretin

Code Name/#:

Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY:

INDICATIONS: 1) Diagnosis of pancreatic exocrine

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

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

HOW DISPENSED: _X_ **Rx** ___ **OTC**

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

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

SUPPORTING DOCUMENTS: See Chem. Review #2

RELATED DOCUMENTS: See Chem. Review #2

CONSULTS: Microbiology Complete DMF ——— unacceptable

REMARKS/COMMENTS: This submission came in just after CHEM. REVIEW #2 was completed. The HPLC assay for release of the drug product still has not been shown to be stability-indicating.

CONCLUSIONS & RECOMMENDATIONS: Approvable. Establishment Inspection not complete

[/S/] 3/14/00
Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

[/S/] 3/14/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-80

cc:
NDA # 21-136
HFD-180/LTalarico
HFD-180/Div File/NDA #21-236
HFD-180/LZhou
HFD-820/JGibbs
HFD-180/AShaw
HFD-181/CSO
R/D Init by: Lzhou 14-Mar-2000
ABS F/T ABS 14-Mar-2000
C:\WORD\NG\21-136 Synthetic Porcine Secretin Review #3.doc

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-136 **CHEM REVIEW #:** 2 **REVIEW DATE:** March 8, 2000

SUBMISSION TYPE	**DATES**			
	DOCUMENT	**CDER**	**ASSIGNED**	**REVIEW**
AMENDMENT BZ	29-Dec-1999	30-Dec-1999	18-Jan-2000	

PREVIOUS DOCUMENT

ORIGINAL	14-May-1999
IR LETTER	27-Jul-1999
AMENDMENT BZ	13-Sep-1999
AMENDMENT BZ	06-Oct-1999
REVIEW #1	29-Dec-1999

NAME & ADDRESS OF APPLICANT: ChiRhoClin, Inc.

DRUG PRODUCT NAME:

Proprietary: None

Nonproprietary: Synthetic Porcine Secretin

Code Name/#:

Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY:

INDICATIONS: 1) Diagnosis of pancreatic exocrine disease

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

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

HOW DISPENSED: X **Rx** ___**OTC**

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

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date
[redacted]			Acceptable	27-Dec-1999

RELATED DOCUMENTS: INDs 54,196, 56,821, [redacted]
The first two INDs are for synthetic porcine and human secretin, respectively and were reviewed earlier.

CONSULTS: Microbiology Complete DMF [redacted] unacceptable

REMARKS/COMMENTS: This submission came in just after CHEM. REVIEW #1 was completed. A number of items that were considered deficiencies in the first review have been addressed in this submission. There are still many large deficiencies.

CONCLUSIONS & RECOMMENDATIONS: Approvable. Establishment Inspection not complete

[/S/] March 8, 2000
Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

[/S/] 3/8/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-80

cc:
NDA # 21-136
HFD-180/LTalarico
HFD-180/Div File/NDA #21-236
HFD-180/LZhou
HFD-820/JGibbs
HFD-180/AShaw
HFD-181/CSO
R/D Init by: Lzhou 08-Mar-2000
ABS F/T ABS 08-Mar-2000
C:\WORD\NG\21-136 Synthetic Porcine Secretin Review #2.doc

60 Page(s) Withheld

MEMORANDUM

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

Date: February 8, 2000

From: Arthur B. Shaw, Ph.D., Review Chemist, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

ES 2/8/00

Through: Liang Zhou, Ph.D., Acting Chemistry Team Leader, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

ES 2/8/00

To: NDA 21-136

Subject: Addendum to Chem. Review #1. Stability after Reconstitution

There is an additional item in the stability considerations for synthetic porcine secretin that was not addressed by the applicant, ChiRhoClin, and consequently was not reviewed. There is no information regarding the stability of the lyophilized drug product after reconstitution, particularly regarding —. In addition, there should be information concerning the stability of the drug in commonly-used syringes.

Draft of additional question for applicant:

Provide stability information for the reconstituted drug product. Data should be provided to support a label statement concerning acceptable time and temperature ranges for storage of the drug product after reconstitution. Particular attention should be paid to —.

/

Cc:
NDA 21-136
HFD-180/NDA 21-136
HFD-180/LTalarico
HFD-181/BStrongin
HFD-180/LZhou
HFD-180/AShaw
R/D init by:Lzhou 08-Feb-2000
ft/**ABS 08-Feb-2000** C:\WORD\NG\21-136 — Recon Stability Memo.doc

APPEARS THIS WAY ON ORIGINAL

JAN - 4 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-136 **CHEM REVIEW #:** 1 **REVIEW DATE:** December 29, 1999

SUBMISSION TYPE	**DATES**			
	DOCUMENT	**CDER**	**ASSIGNED**	**REVIEW**
ORIGINAL	14-May-1999	25-May-1999	03-Jun-1999	
IR LETTER	27-Jul-1999			
AMENDMENT BZ	13-Sep-1999	14-Sep-1999	21-Sep-1999	
AMENDMENT BZ	06-Oct-1999	07-Oct-1999	12-Oct-1999	

NAME & ADDRESS OF APPLICANT: ChiRhoClin, Inc.

DRUG PRODUCT NAME:

Proprietary: None

Nonproprietary: Synthetic Porcine Secretin

Code Name/#:

Chem.Type/Ther.Class: 3S

PHARMACOLOGICAL CATEGORY:

INDICATIONS: 1) Diagnosis of pancreatic exocrine —

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

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

HOW DISPENSED: X **Rx** ___ **OTC**

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

His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Asp-Ser-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date
—			Acceptable	27-Dec-1999

RELATED DOCUMENTS: INDs 54,196, 56,821—

The first two INDs are for synthetic porcine and human secretin, respectively and were reviewed earlier.

CONSULTS: Microbiology Pending

REMARKS/COMMENTS: This is a poorly organized and basically incomplete application. It appears that only — lot has been prepared so that an expiration date cannot be assigned.

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

[/S/] 1/4/00

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

[/S/] 1/4/00

Liang Zhou, Ph.D.
Acting Chemistry Team Leader, HFD-80

cc:
NDA # 21-136
HFD-180/LTalarico
HFD-180/Div File/NDA #21-236
HFD-180/LZhou
HFD-820/JGibbs
HFD-180/AShaw
HFD-181/CSO
R/D Init by: LZhou 04-Jan-2000
C:\WORD\NG\21-136 Synthetic Porcine Secretin Review #1.doc

114 Page(s) Withheld

DETAIL REPORT

Application: NDA 21136/000
Stamp: 25-MAY-1999
Regulatory Due: 09-APR-2002
Applicant: CHIRHOCLIN
15500 GALLAUDET AVE
SILVER SPRING, MD 209054176
Priority: 3S
Org Code: 180

Action Goal:
District Goal: 18-SEP-2001
Brand Name: SECREFLO(SYNTHETIC PORCINE SECRETIN) INJ
Estab. Name:
Generic Name: SYNTHETIC PORCINE SECRETIN LYOPHILIZED S

Dosage Form: (FOR INJECTION)
Strength: 16 MICROG/VIAL

Application Comment: NOTE THAT CONTACTS FOR TEAM LEADER AND PROJECT MANAGER HAVE CHANGED
THIS IS A RESUBMISSION FOLLOWING AE LETTER. — (DRUG SUBSTANCE MANUFACTURER THAT FAILED INSPECTION IN ORIGINAL) WILL NOT MAKE ANY MOTE DRUG SUBSTANCE. MADE NOW BY — on 22-OCT-2001 by A. SHAW (HFD-180) 301-827-7310)

FDA Contacts:
M. MCNEIL (HFD-180) 301-827-7310 , Project Manager
A. SHAW (HFD-180) 301-827-7310 , Review Chemist
L. ZHOU (HFD-180) 301-827-7471 , Team Leader

Overall Recommendation: WITHHOLD on 25-OCT-2001 by S. FERGUSON (HFD-324) 301-827-0062
WITHHOLD on 23-MAR-2000 by R. WOODS (HFD-324) 301-827-0062
WITHHOLD on 16-OCT-2000 by R. WOODS (HFD-324) 301-827-0062
ACCEPTABLE on 04-MAR-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 04-MAR-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1121526
CHESAPEAKE BIOLOGICAL LABORATORIES INC
1111 PACA STREET
BALTIMORE, MD 21230

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER

Profile: SVS OAI Status: NONE
Estab. Comment: FORMULATE DRUG PRODUCT AND FILL USING — PRODUCT IS THEN LYOPHILIZED (on 07-SEP-1999 by A. SHAW (HFD-180) 301-827-7310)
NOTE INCORRECT PCC SHOULD BE SVT (on 23-DEC-1999 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	02-SEP-1999				SHAWA
SUBMITTED TO OC	07-SEP-1999				SHAWA
SUBMITTED TO DO	13-SEP-1999	GMP			EGASM
ASSIGNED INSPECTION '	14-SEP-1999	GMP			BBARGO
SUBMITTED TO OC	23-DEC-1999				SHAWA
SUBMITTED TO DO	04-JAN-2000	GMP			DAMBROGIOJ
ASSIGNED INSPECTION '	04-JAN-2000	GMP			BBARGO
INSPECTION SCHEDULED	11-JAN-2000		28-JAN-2000		BBARGO
INSPECTION SCHEDULED	22-FEB-2000				BBARGO
INSPECTION PERFORMED	21-MAR-2000		17-MAR-2000		BBARGO
DO RECOMMENDATION	21-MAR-2000			ACCEPTABLE - INSPECTION	BBARGO
ON 2/28-3/17/2000, A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED COVERING THE FIRM'S OPERATIONS. ALTHOUGH GMP DEFICIENCIES WERE NOTED, THE FIRM PROMISED CORRECTIONS.					
OC RECOMMENDATION	21-MAR-2000			ACCEPTABLE	DAMBROGIOJ

			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	22-OCT-2001			SHAWA
SUBMITTED TO DO	22-OCT-2001	10D		DAMBROGIOJ
DO RECOMMENDATION	25-OCT-2001		ACCEPTABLE	BBARGO
			BASED ON FILE REVIEW INSPECTION	

ON 2/28-3/17/2000, A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED COVERING THE FIRM'S OPERATIONS. ALTHOUGH GMP DEFICIENCIES WERE NOTED, THE FIRM HAS CORRECTED THE ITEMS.

OC RECOMMENDATION	25-OCT-2001		ACCEPTABLE	FERGUSONS
			DISTRICT RECOMMENDATION	

Establishment: 1123903
CHESAPEAKE BIOLOGICAL LABORATORIES INC
1111 SOUTH PACA ST
BALTIMORE, MD 212302591

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: SVS OAI Status: NONE

Estab. Comment: THIS IS A NEW SITE FOR MANUFACTURE OF THIS DRUG PRODUCT. (on 28-JUL-2000 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JUL-2000				SHAWA
SUBMITTED TO DO	31-JUL-2000	10D			DAMBROGIOJ
ASSIGNED INSPECTION	31-JUL-2000	GMP			BBARGO
DO RECOMMENDATION	31-JUL-2000			ACCEPTABLE	BBARGO
				INSPECTION	

ON 2/28-3/17/2000, A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED COVERING THE FIRM'S OPERATIONS. THE MFG AND TESTING PROCEDURES WERE COVERED DURING THIS INSPECTION. ALTHOUGH GMP DEFICIENCIES WERE NOTED, THE FIRM'S WRITTEN RESPONSE WAS ADEQUATE.

OC RECOMMENDATION	31-JUL-2000		ACCEPTABLE	DAMBROGIOJ
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	22-OCT-2001			SHAWA
SUBMITTED TO DO	22-OCT-2001	10D		DAMBROGIOJ
DO RECOMMENDATION	25-OCT-2001		ACCEPTABLE	BBARGO
			BASED ON FILE REVIEW INSPECTION	

ON 2/28-3/17/2000, A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED COVERING THE FIRM'S OPERATIONS. ALTHOUGH GMP DEFICIENCIES WERE NOTED, THE FIRM CORRECTED THE ITEMS.

OC RECOMMENDATION	25-OCT-2001		ACCEPTABLE	FERGUSONS
			DISTRICT RECOMMENDATION	

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Estab. Comment: [redacted] 3-OCT-

DETAIL REPORT

1999 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-OCT-1999				SHAWA
OC RECOMMENDATION	20-OCT-1999			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	22-OCT-2001				SHAWA
OC RECOMMENDATION	22-OCT-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: THIS SITE PERFORMS (on 01-NOV-1999 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-NOV-1999				FERGUSONS
OC RECOMMENDATION	02-NOV-1999			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	22-OCT-2001				SHAWA
OC RECOMMENDATION	22-OCT-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:

Responsibilities:

Profile: CSN OAI Status: NONE

Estab. Comment: THIS FACILITY HAS BEEN FOUND ACCEPTABLE PER REVIEW OF DMF (on 28-JAN-2002 by A. SHAW (HFD-180) 301-827-7310)
THIS IS A (on 22-OCT-2001 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-OCT-2001				SHAWA
OC RECOMMENDATION	22-OCT-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: ALTHOUGH THIS NDA WAS FILED IN JULY, WE JUST RECEIVED THE ADDRESS ON OCTOBER 29. THIS FACILITY PERFORMS AN (on 01-NOV-1999 by A. SHAW (HFD-180) 301-827-7310)

DETAIL REPORT

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-NOV-1999				FERGUSONS
OC RECOMMENDATION	02-NOV-1999			ACCEPTABLE BASED ON PROFILE	EGASM
SUBMITTED TO OC	22-OCT-2001				SHAWA
OC RECOMMENDATION	22-OCT-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment:

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:) SEE COMMENT UNDER CONCERNING LATENESS OF EER (on 01-NOV-1999 by A. SHAW (HFD-180) 301-827-7310) NOTE ERROR IN ORIGINAL ENTRY. (on 23-DEC-1999 by A. SHAW (HFD-180) 301-827-7310)
THE SPONSOR HAS SUMITTED AN AMENDMENT (MAY 8, 2000) IN RESPONSE TO AE LETTER DATED MARCH 24, 2000. SPONSOR SAYS THIS SITE IS READY FOR INSPECTION. PLEASE SCHEDULE RE-INSPECTION (on 18-MAY-2000 by A. SHAW (HFD-180) 301-827-7310)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-NOV-1999				FERGUSONS
SUBMITTED TO DO	02-NOV-1999	GMP			EGASM
ASSIGNED INSPECTION	16-NOV-1999	GMP			BBARGO
SUBMITTED TO OC	23-DEC-1999				SHAWA
SUBMITTED TO DO	29-DEC-1999	GMP			EGASM
ASSIGNED INSPECTION	30-DEC-1999	GMP			BBARGO
INSPECTION PERFORMED	22-FEB-2000		18-FEB-2000		BBARGO
ON 2/16-18/00, A GMP INSPECTION WAS PERFORMED WHICH REVEALED MAJOR GMP ISSUES.					
DO RECOMMENDATION	22-FEB-2000				
EIR RECEIVED BY OC	21-MAR-2000				FERGUSONS
OC RECOMMENDATION	22-MAR-2000			WITHHOLD EIR REVIEW-CONCUR W/DISTRICT	WOODSR
EIR REVIEWED BY CSO MIKE GAVINI					
SUBMITTED TO OC	18-MAY-2000				SHAWA
SUBMITTED TO DO	19-MAY-2000	10D			FERGUSONS
ASSIGNED INSPECTION	19-MAY-2000	PS			BBARGO
INSPECTION SCHEDULED	20-SEP-2000		15-SEP-2000		BBARGO

DETAIL REPORT

INSPECTION PERFORMED	29-SEP-2000	15-SEP-2000	BBARGO
DO RECOMMENDATION	29-SEP-2000	WITHHOLD	BBARGO
		INADEQUATE QA FUNCTIONS INSUFFICIENT DEVELOPMENT DATA LACK OF/INADEQUATE SOPS	

ON 9/14-15/2000, A FOLLOW-UP GMP INSPECTION WAS PERFORMED WHICH REVEALED LACK OF DATA TO SUPPORT LOD & LOQ, FAILURE TO INVESTIGATE NDA OOS RESULTS, OOS SOP LACKING PROPER PROCEDURES, AND INCOMPLETE VALIDATION OF STABILITY TESTING METHOD.

EIR RECEIVED BY OC	02-OCT-2000		WOODSR
OC RECOMMENDATION	16-OCT-2000	[redacted]	WOODSR

NOTE - THAT THE FDA-483 OBSERVATIONS INCLUDE CHEMISTRY ISSUES THAT MAY BE SIGNIFICANT AND ARE REFERRED TO HFD-180 FOR EVALUATION. AND RE: THE FIRM'S RESPONSE -

- FIRM'S RESPONSE TO ONE GMP DEFICIENCY APPEARS ADEQUATE
- THE REMAINING GMP DEFICIENCY, BY ITSELF, IS NOT AT A LEVEL OF SIGNIFICANCE TO WARRANT WITHHOLDING THIS APPLICAITON.

SUBMITTED TO OC	22-OCT-2001		SHAWA
OC RECOMMENDATION	22-OCT-2001	[redacted]	DAMBROGIOJ
		BASED ON PROFILE	

APPEARS THIS WAY
ON ORIGINAL