CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-136
NDA 21-209

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

Dear Dr. Purich:

Please refer to your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SecreFlo™ (secretin) for Injection.

NDA 21-136 was dated May 14, 1999, received May 25, 1999, and NDA 21-209 was dated August 17, 1999, received August 17, 1999.

For NDA 21-136, we acknowledge receipt of your submissions dated September 17, October 5, November 2, November 26, December 3, December 21, 2001, January 21, February 4, February 13, February 14, February 27, March 1, March 13, April 2, April 3, and April 4, 2002. Your submission of October 5, 2001 constituted a complete response to our November 7, 2000 action letter.

For NDA 21-209, we acknowledge receipt of your submissions dated October 5, November 2, November 26, December 21, 2001, January 22, February 13, March 1, March 22, and April 2, April 3, April 4, 2002. Your submission dated October 5, 2001 constituted a complete response to our February 3, 2000 action letter.

NDA 21-136 provides for the use of SecreFlo (secretin) for Injection for: the use in secretin stimulation testing for stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction.

NDA 21-209 provides for the use of SecreFlo (secretin) for Injection for: the use in secretin stimulation testing for stimulation of gastrin secretion to aid in the diagnosis of gastrinoma.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert. The FPL for the immediate container and carton labels must be identical to the labeling text for the labels submitted April 3, 2002. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21136." Approval of this submission by FDA is not required before the labeling is used.

We remind you of the postmarketing commitments that you agreed to in your submission dated March 13, 2002 and in your April 2, 2002 teleconference with Dr. Art Shaw of this Division.

1. Develop an assay for impurities in the drug product

Final Report Submission: Within nine months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Your application does not address the pediatric study requirements. Submit your pediatric drug development plans or a request for a waiver, if you believe one is appropriate, within 120 days from the date of this letter. If you believe a waiver is justified, submit your request with supporting information and documentation.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

21 CFR 312.34 (a) allows access to an unapproved drug in certain situations by means of a treatment protocol. Upon commercial availability of SecreFlo, you will need to cease enrollment of patients into your treatment protocol under (b)(4)---------

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

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 03:54:54 PM
for Dr. Victor Raczkowski

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-136

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

Dear Dr. Purich:

Please refer to your new drug application (NDA) dated May 14, 1999, received May 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SecreFLo (synthetic porcine secretin) injection.

We acknowledge receipt of your submissions dated July 13, August 3, and August 31, 2000. Your submission of May 8, 2000 constituted a complete response to our March 24, 2000 action letter.

We also refer to your submissions dated October 12 and October 31, 2000. These submissions have not been completely reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues. The chemistry, manufacturing, and controls issues are substantial; if significant changes are made to the manufacturing process, to the drug substance, or drug product, additional clinical trials or clinical bridging studies may be needed to demonstrate that these changes have not altered the safety or effectiveness of your product.

I. Drug Substance

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

B. All future batches must be manufactured under CGMP conditions with adequate documentation provided.

C. Provide a determination of the precision of the assay for [redacted] by testing [redacted]

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

1. [redacted]

2. [redacted] assay;

3. [redacted] assay.

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

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

G. Provide information to identify and characterize the major impurity peaks seen in the [redacted] 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	[redacted]		
296	[redacted]		

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

H. Provide data to demonstrate that the [redacted] Assay is capable of detecting likely impurities, [redacted]

I. Provide data from stability studies of the drug substance using the [redacted] Assay, including evaluation of impurities, to determine the retest date.

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.

B. Add a specification (including acceptance criteria) for "Secretin Content (Assay)" in addition to "Content Uniformity" for the finished Synthetic Porcine Secretin Drug Product.

C. 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 — in forced stability studies.

D. 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.

2. An analysis to determine the validity of pooling the data from all batches, as requested in Question II.C.1.in our letter dated September 19, 2000. If the data from the batches cannot be pooled, then individual regression lines with 95% confidence intervals should be used to calculate the expiration date, using the shortest expiration date among the three regression lines. Submit the data on a diskette in either Excel or SAS format.

3. Stability data and statistical analysis for impurities collected using a validated assay.

E. Provide data, using a suitable HPLC assay, to demonstrate that there is not . [redacted] used to administer the drug.

F. Perform studies to demonstrate the stability of the drug product [redacted]

III Establishment Inspections

During recent inspections of the manufacturing facilities for your NDA ([redacted] Inc.), 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.

We will provide comments concerning your proposed labeling when we have received an acceptable response to the issues identified in this letter.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

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

6 Draft Labeling 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/

Joyce Korvick
4/4/02 03:54:54 PM
for Dr. Victor Raczkowski

APPEARS THIS WAY
ON ORIGINAL

/s/

Lilia Talarico
11/7/00 02:39:20 PM

APPEARS THIS WAY
ON ORIGINAL

NDA 21-136

Food and Drug Administration
Rockville MD 20857

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

MAR 24 2000

Dear Dr. Purich:

Please refer to your new drug application (NDA) dated May 14, 1999, received May 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (synthetic porcine secretin).

We acknowledge receipt of your submissions dated July 9, September 13, October 6, November 4, and December 29, 1999 and January 28, and March 8, 2000.

We also refer to your submissions dated February 18 and March 8, 2000. These submissions have not been reviewed in the current review cycle. You may incorporate them by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, with draft labeling. The indication for "diagnostic use in pancreatic exocrine dysfunction" is approvable. ———— ———— Before this indication can be approved, adequate and well-controlled studies showing the diagnostic advantage associated with the use of ——— in this setting are necessary. Alternatively, you may withdraw this indication from the NDA and submit a supplemental application after approval of the NDA.

Before this application may be approved for the indication specified in the enclosed draft labeling, however, it will be necessary for you to address the following:

Chemistry, Manufacturing, and Controls

I. Drug Substance

A. Description and Characterization

1. Provide a "full description of the physical and chemical characteristics of the drug substance" [e.g., pI value (isoelectric pH), solubility profile, and solution pH], as specified in the "Guideline For Submitting Supporting Documentation In Drug Applications For The Manufacture Of Drug Substances" (February, 1987).

13 Page(s) Withheld

Carton

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

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

Sincerely,

[/S/] for

Lilia Talarico, M.D. 3/24/00
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

6 Draft Labeling Page(s) Withheld

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-209

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

Dear Dr. Purich:

Please refer to your new drug application (NDA) dated August 17, 1999, received August 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SecreFlo (synthetic porcine secretin) injection

We acknowledge receipt of your submission of May 26, 2000 that constituted a complete response to our May 16, 2000 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit acceptable responses to the chemistry, manufacturing, and controls issues listed in our November 7, 2000 approvable letter for NDA 21-136.

We will provide comments concerning your proposed labeling when we have received acceptable responses to the issues identified in this letter.

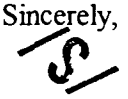
Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information that you will have regarding your new drug. Please provide updated information covering all studies and uses of the drug including those involving indications not being sought in the present submission, and other dose levels.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,



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

/s/

Lilia Talarico
11/28/00 05:47:08 PM

APPEARS THIS WAY
ON ORIGINAL

SECRETIN

NDA 21-209

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

MAY 16 2000

Dear Dr. Purich:

Please refer to your new drug application (NDA) dated August 17, 1999, received August 17, 1999 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for . synthetic porcine secretin) Injection.

We acknowledge receipt of your submissions dated February 3 and 18, March 8, 16, and 31, and April 14, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following:

1. all information, including identification, case report forms, and primary source documents for subjects number 5 and number 6 in the study report entitled, "A Randomized, Controlled, Crossover Study Evaluating Synthetic Porcine Secretin, Synthetic Human Secretin, and Biologically Derived Porcine Secretin for the Diagnosis of Gastrinoma. Pooled analysis of CRC 99-8 and CRC 97-2 (with 2-Way Crossover Amendment) studies", submitted April 14, 2000;

2. identification of the assays for serum gastrin used in the database including the apparent outside laboratory associated with subject #3 ( ) from Study CRC 97-2;

3. adequate responses to the chemistry, manufacturing and controls, microbiology, clinical pharmacology and biopharmaceutics, and labeling issues listed in our March 24, 2000 approvable letter for NDA 21-136.

Labeling for this application will be considered in conjunction with the labeling for NDA 21-136 when responses to items 1 and 2 above have been received and reviewed.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

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7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

Sincerely,

/S/

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

cc:
Archival NDA 21-209
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/Reviewers and Team Leaders
HFD-002/ORM
HFD-103/ADRA
HF-35/Orphan Drugs
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

5!-15-15-00

Drafted by: BKS/May 12, 2000
Initialed by: KJ/May 15, 2000
LG/May 15, 2000
HGT/May 15, 2000
SA/May 15, 2000 5/16/00
final: BKS/May 15, 2000
filename: 21209005.0

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL