US

FERRING
PHARMACEUTICALS

April 3, 2001

ARCHIVE

Susan Allen, M.D.
Director
Division. of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: OVANEX, NDA 21,289 Amendment #005

Dear Dr. Allen:

This amendment responds to queries received by Ferring from Drs. Al Habet and Parekh concerning the Pharmacokinetic report for Purified Human FSH. The enclosed NDA amendment contains:

- A revised and more detailed Table of Contents for the Pharmacokinetic report beginning with Volume 6B. Each table and figure is identified with its relevant section in the report. Please note the organization of the Table of Contents reflects the report format which describes Single Dose SC Administration first, then Multiple Dose SC followed by Single and Multiple Dose IM. Within each section, the raw individual data are presented first, e.g., Tables 1, 4, 9, 12, followed by observed mean values for the PK parameters, e.g., Figures 3, 4, 5 and 6 and Tables 2, 5, 10 and 13 and finally values derived from the P-Pharm fit models for Single Dose, Multiple Dose and combined Single and Multiple Doses, e.g., Tables 3, 6, 7, 11, 14 and 16.

  We believe this organization is logical and clear but will be happy to reorganize the report in any way you direct to assist in your review.

- Complete annotated PK section from the original package insert with each PK value reference specific to Volume, Page and Table in Reference Map 1. This provides you with the precise origin of each value in the original labeling as a point of reference. Per our discussion you requested we revise certain of these PK values from ones derived from the P-Pharm program models to actual observed values. This is represented in the next bullet point.

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

- Complete revised PK section for the package label with selected PK values changed to reflect observed values rather than model fits, wherever possible as you requested. These 13 revised PK values are annotated by Volume, Page and Table in Reference Map 2. The subsection entitled Excretion has been revised with the header "Elimination" and the stated half-lives for SC and IM are observed mean values for Single Dose Administration, consistent with Table 1 in the Label.

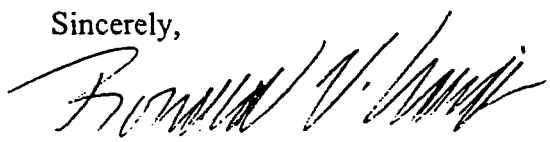
- As described above, Reference Maps 1 and 2 are provided to specifically annotate each original and revised PK value in the labeling.

Please refer only to Volumes 6B, C and D in Section 6 of the NDA which constitute the formal PK Report. Volume 6A is the clinical report meant for the medical reviewer which contains only highly excerpted summary PK results.

We believe these revisions reflect your preferences as stated during the teleconference but are prepared to incorporate whichever values you think most appropriate and revise the labeling to reflect your preference. Please let us know.

Finally we trust this package of revisions and references is fully responsive to the questions posed and to your reviewing requirements. Please contact us immediately with any remaining questions.

Sincerely,



Ronald V. Nardi, Ph.D.
Vice President, Regulatory & Scientific Affairs

APPEARS THIS WAY
ON ORIGINAL

US

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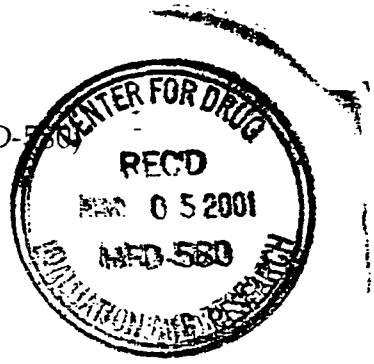
March 1, 2001



Susan Allen, MD
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Ovanex™ NDA# 21,289 -S004

Dear Dr. Allen:

Enclosed is amendment S004 to NDA# 21,289 for Ovanex™. This document contains:

- The final clinical study report for FPI FSH 99-05 – An Open Label, Multi-Center Efficacy Study of Purified FSH Given Subcutaneously To Female Patients Participating in a Donor Egg IVF Program.
- Pharmacokinetic report on the population pharmacokinetic data and modeling requested by the biopharmaceutics division
- Updated summaries for efficacy and safety reflecting the data from the FSH 99-05 study
- Pregnancy outcome data for the ovulation induction and IVF studies
- Revised package insert reflecting additional clinical data

Please note that the 99-05 study report has appropriate submissions for the statistics, data listings, and case report form sections of the NDA.

Please contact me at 914-333-8932 with any questions.

Thank you.

Sincerely,

Ronald V. Nardi, Ph.D.
Vice President,
Scientific & Regulatory Affairs

914-333-8932

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900 Telefax: (914) 631-1992

CONTENTS

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ARCHIVE

February 15, 2001

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-289, Ovanex™ (urofollitropin for injection)
Amendment No. 003

Dear Dr. Allen:

Enclosed please find our response to the third point raised by Dr. Rhee in the Information Request Letter of January 24, 2001 (we responded to the first two points in Amendment 002, February 9, 2001).

3. **Based on the maximum recommended product dose of 450 IU and the release specification of not more than —— endotoxin/IU FSH, the resulting patient endotoxin dose exceeds the recommended —— kg/hr (based on a 70 kg adult) maximum endotoxin dose. Therefore, the maximum endotoxin specification for this product should be decreased.**

   The release specification of —— endotoxin/IU FSH is changed to ——/IU FSH. We trust this fully responds to the points raised in the Information Request Letter of January 24, 2001.

We are also including revised drug substance analytical methods for ——. Although these are submitted in Spanish we are translating them into English should you need English versions. If you have any questions regarding this amendment you may contact me at (914) 333-8958 or Dr. Ronald Nardi at (914) 333-8932.

Sincerely,

Michael Bernhard

Michael I. Bernhard, Ph.D.
Senior Director, Regulatory Affairs

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

US

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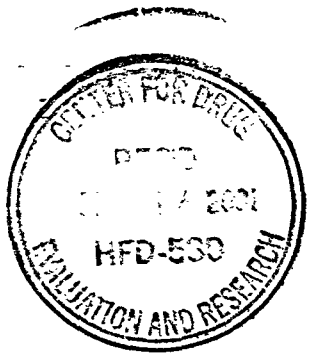
PHARMACEUTICALS

February 9, 2001



Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

Re: NDA 21-289, [redacted] (urofollitropin for injection)
Amendment No. 002

Dear Dr. Allen:

Enclosed please find our responses to the microbiology comments raised by Dr. Rhee in the Information Request Letter of January 24, 2001.

1. **Descriptions and data demonstrating the endotoxin removal efficacy of the stopper washing process should be provided. Alternatively, if the stoppers are purchased "endotoxin-free" from the vendor, this should be stated. In this case, limits for endotoxin remaining on the stoppers as received should be specified. A schedule for testing incoming stoppers and data demonstrating the amount of residual endotoxin on the stoppers, as received, should also be provided.**

The stoppers are not purchased "endotoxin-free" from the vendor. Therefore, they are cleaned and validated for endotoxin removal at SP Pharmaceuticals via validation protocols. The stoppers are washed and validated in the [redacted]

The process is validated once every year on SP Pharmaceuticals' worst case stopper following the Performance Qualification.
A validation protocol was initiated for the [redacted] The purpose of the test was to document that the [redacted] wash cycle will reduce the endotoxin burden on this type of closure. There were two acceptance criteria:

1. At least a three log reduction of the endotoxin challenge on the closures based on recovery values and
2. A record of the [redacted] of unwashed closures, for information only.

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
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SP Pharmaceuticals passed these criteria with a log reduction greater than — and of less than — The raw data are provided in Attachment A.

The procedure for implementing the validation protocol is as follows:

e

2. **Since the goal of any media fill should be the absence of contamination, we recommend that any positive container be investigated to determine possible causes of the contamination.**

All positive media containers are investigated per SOP 05-999 "Visual Inspection of Media-Fill Units for Fill Line Validations". This SOP is included as Attachment B. Please also note that from November 1997 to May 1999, SP Pharmaceuticals did not register any positive media vials for room 252.

3. **Based on the maximum recommended product dose of 450 IU and the release specification of not more than —endotoxin/IU FSH, the resulting patient endotoxin dose exceeds the recommended — kg/hr (based on a 70 kg adult) maximum endotoxin dose. Therefore, the maximum endotoxin specification for this product should be decreased.**

The release specification of —endotoxin/IU FSH will be lowered. We are analyzing our data and will respond shortly with a lower specification.

If you have any questions regarding this amendment you may contact me at (914) 333-8932.

Sincerely,

Ronald V. Nardi, Ph.D.
Vice President, Regulatory and Scientific Affairs

Attachments A and B
cc: Ovanex™ correspondence file

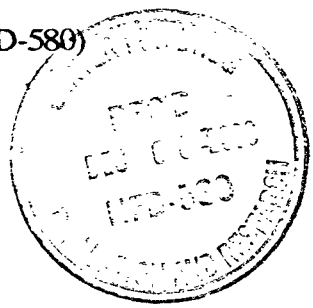
US

DUPLICATE

FERRING
PHARMACEUTICALS

December 6, 2000

Susan Allen, M.D.
Director,
Division of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA #21-289 OVANEX™ (Urofollitropin for Injection)
—— FSH (Urofollitropin)
Amendment #001– Electronic NDA Submission

NEW CORRESP

Dear Dr. Allen:

Please find enclosed a digital tape formatted at 35GB/70GB DLT 7000 containing our electronic submission for NDA #21-289 OVANEX™, which was submitted in paper form on September 29, 2000. The electronic files contained herein are exact duplicates of the paper version and only minor revisions to formatting of the document and Tables of Contents have been changed for clarity. No typographical or content changes have been made to these files in their electronic form.

All editorial and content changes will be submitted as an errata amendment in the near future both in paper and electronic form. If you have any questions concerning this electronic submission, please contact me at 914-333-8932.

Sincerely,

Ronald V. Nardi, Ph.D.
Vice President, Regulatory and Scientific Affairs

Enclosures: Digital Tape (35GB/70GB DLT 7000)
Attachments: FDA Form 356H
NDA Table of Contents

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

FERRIN(
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November 9, 2000

ORIGINAL

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

N/C

RE: NDA # 21-289 OVANEX™ (Urofollotripin for Injection)
FSH (Urofollitropin)
Amendment # 001 - Electronic NDA Submission

Dear Dr. Allen:

Enclosed please find a digital tape containing the Archive copy of our electronic submission for NDA #21-289, OVANEX™, which was submitted in paper form on September 29, 2000. The electronic files contained herein are exact duplicates of the paper version and only minor revisions to formatting of the document and Tables of Contents have been changed for clarity. No typographical or content changes have been made to these files in their electronic form.

All editorial and content changes will be submitted as an errata amendment in the near future both in paper and electronic form. If you have any questions concerning this electronic submission, please contact me at 914-333-8933.

Sincerely,

Ronald V. Nardi

Ronald V. Nardi, Ph.D
Vice President, Regulatory and Scientific Affairs

Enclosures: Digital Tape
Attachments: FDA Form 356H
NDA Table of Contents

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

ED 11/21/00
CSO INITIALS DATE

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

ORIGINAL

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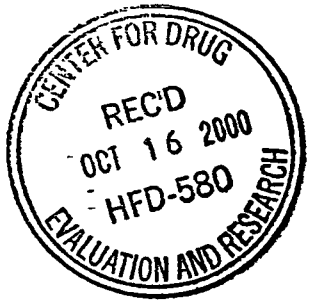
October 13, 2000



Ms. Eufrecina DeGuia
Food and Drug Administration
Division of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857-1706

NEW CORRESP
NIC

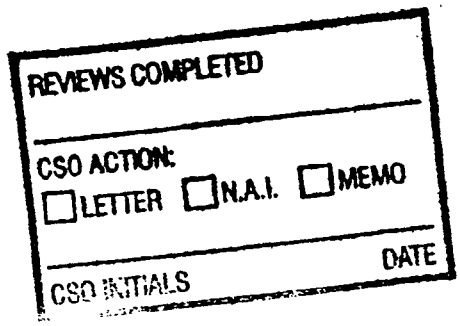
Dear Ms. DeGuia:

As per our conversation regarding our recent NDA submission, NDA 21-289, I am enclosing several items which you requested:

* Four (4) Staff Copies of our Volume 1A including the additional materials (Sections 13-19),
* Original (signed) FDA Form 3454 which was omitted in our original submission and is now incorporated into Volume 1A Section 19A (Financial Disclosure), and
* Four (4) copies of the [redacted] letter which was omitted from our CMC section and should be inserted in Volume 4B (Name/Address, Manufacturer(s) as page 130A, following the [redacted]).

If I can be of additional assistance, please contact me at 914-333-8930.

Sincerely,



Michele G. Cobham
Manager, Regulatory Documentation

nclosures

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

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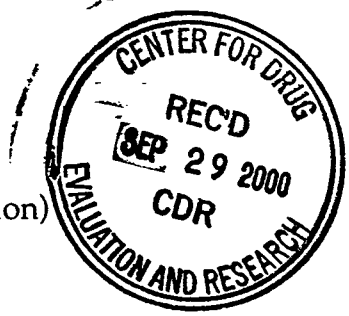
September 28, 2000

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA # 21-289 Ovanex™ (urofollitropin for injection)
[redacted], FSH (urofollitropin)

Dear Dr. Allen,

Enclosed please find NDA #21-289, which is respectfully submitted, for your review as a 505 (b)(1) application. Ovanex is a preparation of Follicle Stimulating Hormone (FSH) purified to near homogeneity from the urine of postmenopausal women. The data contained in this application demonstrate that Ovanex is safe and effective therapy for women being treated for infertility.

Per the agreements at the pre-NDA meeting this application seeks the approval of a new product based on data from clinical trials in the United States. Controlled trials in the US compared Ovanex administered via subcutaneous and intramuscular routes to Follistim® (an approved recombinant FSH product) administered via a subcutaneous route. The studies were parallel group, randomized, open-label trials. The study in the *in vitro* fertilization patients (FPI 99-04) demonstrated Ovanex:

- was at least therapeutically equivalent to Follistim
- had a significant advantage over Follistim with respect to injection site tolerance
- had a benefit/risk ratio similar to or better than Follistim.

The study in ovulation induction (FPI 99-03) demonstrated that Ovanex had:

- an efficacy profile equal to the efficacy of Follistim
- a safety profile similar to the safety of Follistim.

The study in oocyte donor patients is continuing. An interim report is included in this application. We commit to providing timely updates to this study. Per the agreements at the pre-NDA meeting, we are not requesting a separate indication for this patient population.

Pharmacokinetic data from a US study in normal volunteers are presented in Section 6. These data are descriptive. They were not intended to demonstrate bioequivalence of the different routes of administration. They do demonstrate pharmacokinetic profiles consistent with the literature for other FSH containing products.

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

Data in Section 4 demonstrate that both drug substance and drug product can be made under appropriate control and with acceptable reproducibility. Per our agreements at the pre-NDA meeting please note the following:

- The oxidation issue has been investigated and the oxidized species identified. Interestingly, mild oxidation does not appear to alter the biological activity. A ——— method has been added to the analytical methods and the proportion of oxidized protein has been characterized. The method is applicable to both drug substance and drug product. Some stability data are included and this test has been added to the ongoing stability programs.
- Characterization of the carbohydrate content of the drug substance is included in this submission.
- Sequencing of the FSH is nearing completion although the submission only contains the data previously submitted. For both the α and β chains one internal peptide remains to be sequenced before confirming that the complete sequences agree with the expected amino acid sequence for the FSH subunits.
- Specifications have been established consistent with the requests of the Chemistry reviewers

Please note that the application contains a total of 58 volumes. Volume numbers correspond to each of the Sections of the NDA (i.e.1-19). Within a Section volumes are identified further with letters in alphabetical sequence (e.g. Volumes 8a, 8b, etc. correspond to Section 8 items). Individual reviewing disciplines have appropriately color-coded volumes including the administrative Sections 1-3. Each page of the original has a unique two-part page number that includes both the volume number and page number within that volume (e.g. Vol. 8a page 010).

A User Fee Cover Sheet is also attached. User fee payments were made using user fee #4033.

We acknowledge the requirement for periodic updates during the review of this application. If you need any other information please feel free to contact me at 914-333-8932 or by fax at 914-631-5120. If you have specific questions concerning the clinical data you may also contact Dr. Seymour Fein at 914-333-8947 or by fax at 914-631-5120.

Sincerely,

Ronald V. Nardi

Ronald V. Nardi, Ph.D.
Vice President, Scientific and Regulatory Affairs

Enclosures: NDA #21-289
Attachments: User Fee Cover sheet

ORIGINAL

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noted
9/23/00
RLB

September 14, 2000

N 004- PC, PE

AJ 9/26/00

Susan Allen, M.D.
Acting Director
Division of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: ——— Amendment No. 004, FSH (urofollitropin)

Dear Dr. Allen:

Enclosed is a submission amending ——— for Ferring's purified FSH. The submission consists of the following:

- Two statistical modifications to Protocol # FPI FSH 99-03 dated March 29, 2000 and June 6, 2000.
- Two statistical modifications to Protocol # FPI FSH 99-04 dated March 29, 2000 and June 6, 2000.
- One protocol amendment to Protocol # FPI FSH 99-05 dated June 5, 2000.
- Required regulatory documentation for study FPI FSH 99-05: Dr. Crain (FDA form 1572 & CV), Dr. Kaufmann (revised FDA Form 1572 & CV).

The statistical modifications for studies FPI FSH 99-03 and FPI FSH 99-04 dated March 29, 2000 were made prior to the pre-NDA meeting held on April 24, 2000. At that meeting the FDAs biostatistician and Ferring's consulting biostatistician agreed to further modifications in the statistical plans for these studies which became the amendments dated June 6, 2000 and which supercede the March 29, 2000 versions. All these amendments received IRB approvals.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS 1/3/01 DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-289

INFORMATION REQUEST LETTER

Ferring Pharmaceuticals
Attention: Ronald Nardi, Ph.D.
Vice President, Scientific and Regulatory Affairs
120 White Plains Road
Suite 400
Tarrytown, New York 10591
USA

Dear Dr. Nardi:

Please refer to your September 28, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bravelle (urofollitropin for injection, purified).

We also refer to your submissions dated February 9 and 15, March 1 and 3, April 3, 5, 20 23 and 25, May 1, 15, 14 and 24, June 8, 14, and 29, 2001.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

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/s/

Moo-Jhong Rhee
7/9/01 02:52:09 PM

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TELEFAX

TO: Dr. Nardi
Chem IR letter

FAX: 914 631 5120

PHONE: 914 333-8932

FROM: Dorothe Spell-LeSane

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267
PHONE: (301) 827-4260

DATE: 7/9/01

PAGES: 7 (Inclusive)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-289

INFORMATION REQUEST LETTER

Ferring Laboratories, Inc.
Attention: Ronald Nardi Ph.D.
Vice President, Scientific and Regulatory Affairs
120 White Plane's Road, Suite 400
Tarrytown, NY 10591

Dear Dr. Nardi:

Please refer to your September 28, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bravelle ™ (urofollitropin for injection).

We also refer to your April 25 and May 24, 2001 draft labeling amendments.

We have completed the review of this draft labeling and have several comments. Revisions have been incorporated directly into the enclosed Physician Package Insert. Additions have been noted in double underline, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in bracketed **[14 pt bold face type]**.

Please submit your revised package insert as soon as available so that we can continue the evaluation of your NDA.

If you have any questions, please contact Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble, B.S.N., RN,
Chief, Regulatory Project Management Staff
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Revised Physician Insert

Number of Pages Redacted 11

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/s/

Terri F. Rumble
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********** -COMM. JOURNAL- ********** DATE JUN-05-2001 ***** TIME 12:35 *********

MODE = MEMORY TRANSMISSION START=JUN-05 12:31 END=JUN-05 12:35

FILE NO.=679

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-FDA/DRUDP

********** -FDA/DRUDP - ***** - 301 827 4267- **********

TELEFAX

TO: Michael Bernhard

re Labeling Comments

FAX: 914-631-5120

PHONE: 914-333-8932

FROM: Donnette Spell-LeSane

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267
PHONE: (301) 827-4260

DATE: 6/5/01

PAGES: 14 (Inclusive)

TELEFAX

TO: Michael Bernhard

re Labeling Comments

FAX: 914-631-5120

PHONE: 914-333-8932

FROM: Dorothe Spell-LeSane

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267
PHONE: (301) 827-4260

DATE: 6/5/01

PAGES: 14 (Inclusive)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-289

INFORMATION REQUEST LETTER

Ferring Laboratories, Inc.
Attention: Ronald Nardi Ph.D.
Vice President, Scientific and Regulatory Affairs
120 White Plane's Road, Suite 400
Tarrytown, NY 10591

Dear Dr. Nardi:

Please refer to your September 28, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ovanex™ (urofollitropin for injection).

We also refer to our January 24, 2001, information request letter and your response dated February 9, 2001.

We have reviewed your submission regarding the microbiological issues concerning sterility assurance and the following issue was not completely addressed.

Please provide the new final product endotoxin specification for this drug product.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
HFD-580
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Moo-Jhong Rhee
5/11/01 04:04:06 PM

TELEFAX

TO: Ronald Nardi
N21-289 IR Letter

FAX: 914-631-5120

PHONE: 914-333-8932

FROM: Dornette Spell-LeSane

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267
PHONE: (301) 827-4260

DATE: 5/14/01

PAGES: 3 (Inclusive)

recd

/s/

NDA 21-289

INFORMATION REQUEST LETTER

Ferring Pharmaceuticals, Inc.
Attention: Ronald Nardi
Vice President, Scientific and Regulatory Affairs
120 White Plains Road, Suite 400
Tarrytown, NY 10591

Dear Dr. Nardi:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ovanex™ (urofollitropin for injection).

We are reviewing the Microbiology section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA. The submission was reviewed for microbiological issues concerning sterility assurance and the following issues were not completely addressed:

1. Descriptions and data demonstrating the endotoxin removal efficacy of the stopper washing process should be provided. Alternatively, if the stoppers are purchased "endotoxin-free" from the vendor, this should be stated. In this case, limits for endotoxin remaining on the stoppers as received should be specified. A schedule for testing incoming stoppers and data demonstrating the amount of residual endotoxin on the stoppers, as received, should also be provided.

2. Since the goal of any media fill should be the absence of contamination, we recommend that any positive container be investigated to determine possible causes of the contamination.

3. Based on the maximum recommended product dose of 450 IU and the release specification of not more than [redacted] the resulting patient endotoxin dose exceeds the recommended 5 EU/kg/hr (based on a 70 kg adult) maximum endotoxin dose. Therefore, the maximum endotoxin specification for this product should be decreased.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Moo-Jhong Rhee
1/24/01 03:16:21 PM

APPEARS THIS WAY
ON ORIGINAL

DeGuia

NDA 21-289

OCT 4 2000

Ferring Pharmaceuticals, Inc.
Attention: Ronald Nardi, Ph.D.
Vice President, Scientific and Regulatory Affairs
120 White Plains Road, Suite 400
Tarrytown, NY 10591

Dear Dr. Nardi:

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

Name of Drug Product:	Ovanex™ (urofollitropin for injection)
Therapeutic Classification:	Standard (S)
Date of Application:	September 28, 2000
Date of Receipt:	September 29, 2000
Our Reference Number:	NDA 21-289

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 2, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 29, 2001, and the secondary user fee goal date will be September 29, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 10/3/00

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-289
HFD-580/Div. Files
HFD-580/E.DeGuia/TRumble
HFD-580/SSlaughters/RBennett/MRhee/AParekh/SAllen/DShames/AJordan/Kammerman
HFD-510/DWu/MHaber
DISTRICT OFFICE

Drafted by: ED/10.03.00
Initialed by: EDeGuia
final: EdEGuia
filename: ACKLTR.DOC

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

DRAFT

MEMORANDUM OF TELECONFERENCE

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

DATE: **June 21, 2001**

BETWEEN:

Name: **Ronald Nardi, Ph.D., Vice President, Regulatory Affairs, Ferring Pharmaceuticals**

AND:

Name: **Duu-Gong Wu, Ph.D., Chemistry Team Leader, Division of Metabolic and Endocrine Drug Products (HFD-510)**

SUBJECT: **USAN name**
NDA 21-289, Bravelle (urofolitropin, purified)

Discussion:

- the Agency has decided that a totally different USAN name is not acceptable; we will permit the use of "urofollitropin for injection, purfied" for now in conjunction with the NDA review
- it is possible that a modifier may be used within the context of USP monograph in the future, depending on the additional data we received and analyzed
- Dr. Nardi indicated that the USAN name application will not go forward, he further indicated that a alfa or beta system to type A or B would be prefered

MEMORANDUM OF TELECONFERENCE

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

DATE: **June 15, 2001; 11:00 a.m.**

BETWEEN:

Name: **Ronald Nardi, Ph.D., Vice President, Regulatory Affairs, Ferring Pharmaceuticals**

AND:

Name: **Duu-Gong Wu, Ph.D., Chemistry Team Leader, Division of Metabolic and Endocrine Drug Products (HFD-510)**

SUBJECT: **USAN name**
NDA 21-289, Bravelle (urofolitropin, purified)

Background:
The telephone call was initiated by Ferring following an earlier inquiry concerning Ferring's approach to obtain an USAN name for their urofollitropin product. Ferring has approached USAN and was told that unless an identical CAS number was assigned, their product will not be given an identical name "urofollitropin". Ferring subsequently went to get a CAS number and verbally informed the person who handled the CAS number that Ferring's product has a different specific biological activity. They were told that possibly a different CAS number would be given. With this, Ferring apparently is expecting a different name other than urofollitropin from USAN. The Agency was not told these activities until last week.

Discussion:

- the Agency has requested that Ferring provide a side-by-side comparison on ——— for Serono's Fertinex and Ferring's product so that the data can be used by the Agency to consider the name issues; these issues will be communicated to both USAN Council and USP at a later date
- in addition, Dr. Nardi was informed that:
  - the agency would be holding an internal meeting to discuss the issues related to the established name for their product; the initial thinking was that the Agency prefers not to have a completely different name for their product
  - a specification for the ——— needs to be established for the release and the acceptance criteria for the oxidized form should be re-calculated only for the alfa subunit

Dr. Nardi agrees that they will try to do all these as soon as possible.

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

/s/

Dornette Spell-LeSane
7/31/01 09:14:09 AM
CSO

Duu-gong Wu
8/1/01 12:21:08 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: March 26, 2001

APPLICATION NUMBER: NDA 21-289, Ovanex (urofollitropin, purified)

BETWEEN:

Name: Ronald Nardi, Ph.D., Vice President, Regulatory Affairs
Seymour Fein, M.D., Clinical Head

Representing: Ferring Pharmaceuticals

AND

Name: Eufrecina DeGuia, Regulatory Project Manager
Ameeta Parekh, Ph.D., Team Leader
Sayed Al-Habet, Ph.D., Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Pharmacokinetic (PK) Data clarification

The sponsor was asked to clarify and resolve the following issues:

1. On Volume 6B, Page 29: There are no individual data for C_{max}, T_{max}, and AUC for SC single. A table similar to that in page 23 is missing.

2. Table in labeling: The K_{el}, V_d, and K_a data do not match with the data in the reports. For example, page 23 for SC single dose.

3. On Volume 6B, pages 23 and 27 (Tables 2 and 5): Please check the calculation of the half-life calculation. For examples:
   - Half life = $0.693/K_{el}$ = 0.693/0.0362 = 19 hours not 24 hours
   - Labeling (Vol 3A, page 2): The half-lives in the Table do not match to the statement under "Excretion"

4. Page 31 (Volume 6B, Table 9): AUC is 331 but in labeling (page page 2, vol 3A), in summary report (Vol 3A page 39), and in page 33 (Vol 6B) is 343. Also note the differences in C_{max} and T_{max} among these tables.

5. Volume 6 B (page 31): The mean data for single dose SC IM do not match with the data in the labeling. For example, C_{max}, T_{max}, and AUC are 8.8, 17.4, and 331 in page 31 (vol. 6B) whereas in labeling are: 7, 17.8, and 343. However, they do match to those shown in PK summary report (see page 39 in volume 3A) and computer output (volume 6C pages 14-16).

6. Computer generated data for SC multiple dose for C_{max}, T_{max}, and AUC are missing (see page 158, vol. 6B)

7. Unless we know the absolute bioavailability of the drug after SC and IM, the clearance and volume of distribution should be referred to as "apparent" parameters. The absolute bioavailability of the drug is important that can be used for correction factor to estimate the clearance and volume of distribution.

Conclusion:

- The sponsor explained that a lot of discrepancy may be due to the Vol. 6A, as well as Vol. 6B that contain information for the Biopharmaceutics reviewer. Vol. 6A is purely clinical (integrated clinical report) and explicitly refer to appropriate appendix. Although the Vol. 6A follows the ICH format, it created some confusion in the review. The reviewer was advised to concentrate review on Vol. 6B, C, D which contain the full PK report and ignore Volume 6A for the purpose of primary review.
- The sponsor agreed to provide the clarification and information for the above requests.
- Annotated labeling will also be provided; the location of where every number comes from will be indicated.

(See appended electronic signature page)

Eufrecina DeGuia
Regulatory Project Manager

Ameeta Parekh, Ph.D.
Team Leader, OCPB @ DRUDP

Ameeta Parekh, Ph.D.
Team Leader

/s/

Eufrecina deGuia
4/4/01 09:45:02 AM
CSO

Ameeta Parekh
4/5/01 11:49:04 AM
BIOPHARMACEUTICS
I concur

TELEFAX

TO: ___Dr. Ronald Nardi__

___Vice President, Scientific and Regulatory Affairs___

___Ferring Pharmaceuticals, Inc.____

FAX: ___(914) 631-5120___

PHONE: ___(914) 333-8932___

FROM: ___Freshnie DeGuia, Regulatory Project Manager_____

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267

PHONE: (301) 827-4260

DATE: _____April 12, 2001_____

PAGES: __4__ (Inclusive)

Comments: Memorandum of Telecon on March 26, 2001

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane-HFD-580
Rockville, Maryland 20857-1706

Approved for telefacsimile_____

MINUTES of TELECONFERENCE

Date: December 4, 2000 **Time**: 11:30 AM– 12:00 PM **Location**: Parklawn; Ms. DeGuia's Office

NDA: 21-289 **Drug Name:** Ovanex (urofollitropin, purified)

External Participant: Ferring Pharmaceuticals, Inc.

Type of Meeting: Information Request (Clinical Pharmacology and Biopharmaceutics)

FDA Lead: Dr. Ron Kavanagh **External Participant Lead:** Dr. Ronald V. Nardi

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Ron Kavanagh, B.S. Pharm., Pharm.D., Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Constituents:
Ronald V. Nardi, Ph.D. – President, Scientific and Regulatory Affairs
Seymore Fine, M.D. – Medical Director
Michele Cobham – Manager of Scientific Information
[redacted] – Consultant

Meeting Objectives: To clarify FDA request of Ferring to provide pharmacokinetic data at the upper end of the proposed dose range, including population data with sparse sampling, if desired.

Background Information: On December 1, 2000, Ferring Pharmaceuticals provided the Division, via telefacsimilie, copies of the data sheet with individual FSH plasma levels post-FSH dosing in patients from Study FPI FSH 99-04, a published paper describing formal PK profiles for a single-dose of 450 IU of FSH (in Pergonal) administered IM and SC, and the synopsis of the final study report for Study FPI REP 97-01 which analyzed single- and multiple-dose pharmacokinetics and population pharmacokinetics for FSH in patients receiving Repronex intramuscular (IM) or subcutaneous (SQ) for ovulation induction.

Discussion Points:
- Section 8 of the NDA submission for Ovanex did not include complete pharmacokinetic (PK) study reports as claimed; they should be submitted as an amendment to both Section 8 and Section 6; data interpretation should also be included in the study report
- in the Pre-NDA meeting minutes, it was suggested that the sponsor could use sparse sampling from the Phase 3 studies to address some of the pharmacokinetic parameters in the NDA review; complete study reports were requested by the Division
- Study report 9902, that was submitted to the NDA, did not address dose linearity and time invariance issues

- the company did not submit the PK study report initially because the company felt that a coherent report would be difficult with the small amount of data obtained from the PK study; in addition, the sponsor felt that the Division would be requesting the information during the NDA review
- the sponsor noted that a complete validation report from [redacted] was submitted to the NDA; the sponsor feels that the same validation should apply to the requested information because the same assays and laboratory were used in PK Study 9902 as were used in the data submitted by [redacted]
- the sponsor is planning to run a single-dose study utilizing the 450 IU strength; the Division noted that some parameters e.g., time invariance, would not be addressed in a single-dose, 450 IU study

Decisions reached:

- the literature reference to Pergonal can be added to the NDA as supportive data
- the sponsor should complete a study report on the available data and submit it; the report should include complete bioanalytical validation on the drug substance, subject information, timing of doses, and sampling; whether these values were in the expected ranges compared with other doses should be evaluated
- once the reports have been submitted to the NDA, the sponsor may request a follow-up teleconference for verification as to whether the submitted reports are acceptable
- a population analysis should be included in the study reports
- if the information for the assay validation has been submitted to the NDA, it could be cross-referenced when the sparse study report is submitted
- a pharmacokinetic review will not be initiated until all requested information has been received

Action Items:

Item:	**Responsible Person**:	**Due Date**:
• provide the Division with the timeline for study report submission	Ferring Pharmaceuticals	1-week
• provide meeting minutes	Ms. Moore	1-month

Signature, minutes preparer

Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/December 4, 2000/NDA 21-289TC12400.doc

cc:
NDA Arch:
HFD-580
HFD-580/SAllen/DShames/DMoore/TRumble/RKavanagh/AParekh

Concurrences:
T.Rumble 12.19.00/RKavanagh 1.2.01

/s/

Diane V. Moore
1/8/01 01:40:28 PM

Ron Kavanagh
1/8/01 04:02:44 PM

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: May 1, 2000 **Time:** 10:00-11:00 AM **Location:** PKLN; 17B-45

IND: [redacted] **Drug Name:** FSH (urofollitropin, purified) Injection

Indication: ovulation induction and stimulation of follicular development in women undergoing *in-vitro* fertilization

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: Guidance (Chemistry)

Meeting Chair: Dr. Moo Jhong Rhee **External Participant Lead:** Dr. Ronald Nardi

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Eufrecina De Guia - Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Duu Gong Wu, Ph.D. – Chemistry Team Leader, Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)
Martin Haber, Ph.D. – Chemist, DMEDP; HFD-510

External Participants:
Ronald Nardi, Ph.D. – Vice-President, Scientific and Regulatory Affairs
Michele Cobham – Manager, Scientific Information Systems

Meeting Objectives: To clarify and continue discussion of the CMC issues related to the two Phase 3 protocols, FPI FSH 99-03 and FPI FSH 99-04 that were not discussed at the face-to-face meeting on April 24, 2000 between the Division and Ferring Pharmaceuticals.

Background: These Phase 3 protocols of this IND were submitted on November 4, 1999.

Decisions reached:
- regarding the range of the specific activity of the drug substance; the Division indicated that the sponsor propose a range of the limits for the specific activity of the drug substance, not just the lower limit, should be set based on the sponsor's experience with as many batches as possible by the time of the NDA submission
- [redacted]
- [redacted]

come with the excipient, lactose, the Division will accept specifications only for drug substance based on analysis of clinical lots and the oxidation analysis of the drug product may be waived

- if sponsor can provide data on the full sequencing of the alpha and beta chains that is currently on-going then the Division not need peptide mapping to be included in the characterization of the drug substance
- sponsor will attempt to perform , of the drug substance for oxidation products and results will be discussed further with the Division
- the sponsor was asked to clarify what they mean by 95% purity; how is it determined; the purity profile needs to be better defined; is hCG present; the sponsor replied that hCG was not detected immunochemically and that it is difficult to determine protein purity absolutely; the Division stated that this should be discussed in detail in another submission

General Comments:

- characterization of protein structure in the IND is inadequate; not adequately identified;
- the following tests were recommended:

Also, additional information regarding the specificity of monoclonal antibodies used for western blots and should be provided.
Additional testing to establish purity profile is also required (i.e., is hCG present in the drug substance?) The sponsor noted their test was negative but more data needs to be provided

Action Items: none

Signature, minutes preparer

Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

APPEARS THIS WAY
ON ORIGINAL

drafted: EDeGuia/05.09.00
cc:
NDA Arch:
HFD-580/Division File
HFD-580/DeGuia/Rhee
HFD-510/DWu/MHaber
Concurrences: MRhee,MHaber,DWu05.10.00
Final: EDeGuia

Teleconference Minutes

Meeting Minutes

Date: April 24, 2000 **Time**: 2:30 – 4:15 PM **Location:** Conference Room "K"

Drug Name: FSH (urofollitropin, purified) Injection

Indication: ovulation induction (OI) and stimulation of follicular development in women undergoing *in- vitro* fertilization

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: pre-NDA meeting

Meeting Chair: Dr. Shelley Slaughter **Participant Lead:** Dr. Ronald Nardi

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Susan Allen, M.D., M.P.H. – Acting Director, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D., Team Leader, Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)
Ridgely Bennett, M.D. – Medical Officer, DRUDP (HFD-580)
Eufrecina De Guia - Regulatory Project Manager, DRUDP (HFD-580)
Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, OCPB @DRUDP (HFD-580)
David Hoberman, Ph.D. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Martin Haber, Ph.D. - Chemistry Reviewer, Division of Metabolic and Endocrine Drug Products, DMEDP (HFD-510)
Duu Gong Wu, Ph.D. – Chemistry Team Leader, DNDC II @ DMEDP (HFD-510)
Laurie McLeod, Ph.D. – Pharmacologist, DRUDP (HFD-580)

Ferring Pharmaceuticals Attendees:
Ronald Nardi, Ph.D. – Vice President, Scientific and Regulatory Affairs
Seymour Fine, M.D. – Medical Director
Michael Zudiker, Ph.D. – Executive Director, Manufacturing
Michael Bernhard, Ph.D. – Senior Director, Regulatory Affairs

Meeting Objectives: To determine whether the Agency agrees that the studies that are in progress will provide data required to assess the efficacy and safety of the product and to initiate discussions regarding the NDA preparation to make sure that the Agency's requirements are met.

Background: Purified Follicle stimulating hormone (FSH) is extracted from urine of postmenopausal women and has undergone multiple purification steps. It has been shown that FSH is effective in stimulating follicular development. It has also been shown to be effective in stimulating multiple follicular development in ovulatory women undergoing Assisted Reproductive Technology (ART) such as *in-vitro* fertilization. The intended routes of administration for purified FSH are subcutaneous and intramuscular. The sponsor expects to be done with data collection in June or July 2000 and anticipates submission of the NDA in electronic format in late August or early September 2000. The sponsor provided some slides with additional CMC data for drug substance and product.

Decisions reached:

CMC Drug Substance

1. **Does the Agency agree that the test methods proposed to set release specifications are adequate?**

- no, additional methods for identification and purity determination, such as [redacted] should be developed
- other safety tests such as monitoring for the Hepatitis A and C antibody, (sponsor is already doing Hepatitis B and HIV) pyrogens, and total microbial count should also be added
- the sponsor needs to define a range (upper and lower limits) of specific activity (IU FSH/mg), not just the lower limit and add it to the tests and specifications
- the sponsor argued that [redacted] shows many peaks that are difficult to interpret so it was not used but agreed to provide more data on batches of drug substance and to continue to develop the method
- the Division noted that urofollitropin because of its nature as a urinary product, has a significant amount of oxidation products (which are known to have reduced biological activity) the amount of these products is a critical factor for determining batch-to-batch consistency
- sponsor emphasized their proposal to use [redacted] as fingerprinting for [redacted], to show batch to batch consistency; the test is sensitive to changes in the charge of very large molecules
- the Division indicated that [redacted] nly detects the degree of [redacted] f protein molecules, not other changes in the polypeptide backbone
- the sponsor was asked to test oxidized products from clinical batches, determine the stability and submit a proposal for the Division to review
- further discussion between the chemists and the sponsor will continue after the meeting to resolve issues related to test methods and oxidation products

2. **We believe the drug substance stability protocol is suitable to determine the retest interval of the drug substance and to extend the retest interval as supported by data. We propose to [redacted] -8° stability becomes the accelerated storage condition. Currently available data show no loss of potency when the drug substance is stored at [redacted] 8° for [redacted] By the end of the NDA review period, we anticipate having 24-month stability data at the accelerated conditio[redacted] -8°) and more than [redacted] Assuming these data support continued drug substance stability and that extrapolation of the data permit, we anticipate a [redacted] Do you agree?**

- it will depend on the data; NDA should have 12 months of normal stability data and at least 6 months of accelerated data at time of submission
- 2-8° C storage condition is acceptable; stress testing for further degradation of proteins should be performed (i.e., degradation occuring at room temperature or upon forced oxidation)

3. **As described in the summary, we plan to prepare a single reference standard for use in all assays that require a reference standard, including the bioassay. The primary reference standard will be**

stored at [redacted] as a lyophilized powder and the secondary standards will be frozen at [redacted] Do you agree?

- one reference standard for all test is acceptable, storage conditions will depend on the data available to demonstrate stability

CMC Drug Product

1. **Do you agree that the test methods proposed to set release specifications are adequate?**

- no, additional identification methods, such as [redacted] are needed; [redacted] is not specific enough for identification since other macromolecules co-elute on [redacted] several tests together may provide more assurance; the sponsor expressed concern that the small amount of protein in the drug product may make it difficult to develop accurate tests

2. **We believe the drug product stability protocol is suitable to determine the expiration dating of the drug product and to extend the expiration dating as supported by data. We anticipate having [redacted] month stability data at the time the NDA is submitted and [redacted] month data by the end of the review period. Assuming the data show the drug substance is stable for 21 months at 5° C and 25° C and for 6 months at 30° C and that extrapolation of the data permit, we anticipate [redacted] expiration dating. Do you agree?**

- real-time data is required (12-month real-time data at time of submission) to set expiration date
- submission of stability data during the review cycle is considered a major amendment; it should be submitted three months before the goal date; if after that, it will extend the review clock for three more months

Pre-Clinical Pharmaceuticals/Tox

1. **Based on the fact that Purified FSH is derived from the menotropin drug substance for Repronex, the two single dose toxicology studies in rats and dogs and the single dose cardiovascular study dogs are adequate to support NDA approval? Do you agree?**

- The data from the studies described would support NDA filing; the Division would need to review data and QA statements; no additional animal studies are required

Clinical/Biopharmaceutics

1. **The single and multiple dose PK study in normal female subjects is adequate to support NDA approval. Do you agree?**

- sponsor needs to consider sparse blood sampling trough levels for FSH pharmacokinetics (PK) over the dose range of 75 to 450 IU
- complete bioanalytical assay report with assay validation report for FSH should be provided
- complete final PK reports with synopses should also be provided
- electronic PK and PD data in ASCII format with user guide should be submitted
- in the studies performed, OI patients have higher higher Body Mass Index (BMI) than ART patients and the analysis of this data will be submitted (dose in relation to weight of patients)

2. **The Ovulation Induction and IVF studies totaling approximately 300 patients are adequate to demonstrate the efficacy and safety of FSH SC and IM and to support NDA approval? Do you agree?**

- this is sufficient for filing the NDA

3. **The open label, non-comparative Donor IVF in 40 patients is adequate to support NDA labeling for the use of Purified FSH SC in Donor IVF programs. Do you agree?**

- the Division does not view the proposed study as evidence for a new indication but as supportive data for the IVF indication
- depending upon the review of the data, it may be appropriate to include some information in the clinical studies portion of the label

Statistics:

- the sponsor must explicitly describe primary analyses for both trials; if covariates are used, they should be specified in the sponsor's next protocol submission
- in general, the sponsor should state what statistical hypotheses and propose methodology for testing those hypotheses that are consistent with the way they are formulated

Note: The Division understands each trial's (99-03 and 99-04) purpose to be the demonstration of the non-inferiority of either delivery method (IM and SC) of the sponsor's product (FSH) compared to Follistim. These should not be trials which simply test for a difference between the treatment groups and then regard a non-statistically significant result as informative. In trial 99-03, the Division takes the 35% relative difference in ovulation incidence (favoring Follistim) to be worse case scenario to be ruled out by either a properly constructed hypothesis tests or confidence intervals for the ratio of the incidences in the two groups. A simple Chi-Square test will not be adequate. Logistic regression is not useful for estimating the incidence ratio, but would be useful for an analysis based on the odds ratio. In order to control for the two comparisons to Follistim, the Division mentioned one possibility for a hypothesis test in conjunction with Hochberg's procedure for controlling the Type I error at 5%, since Hochberg's procedure does not facilitate construction of confidence intervals; use the estimate of the log-odds ratio from a logistics regression model to construct a z-test by subtracting the log-odds ratio of the worse case scenario, then dividing by the standard error of the estimate. However, the sponsor is free to use any other adequate procedure to demonstrate non-inferiority. Similarly, in trial 99-04, the Division takes the worse case scenario to be that Follistim produces mean of at least 1.2 more oocytes than either delivery method of FSH.

Additional Comments:

- more emphasis will be given to clinical (not chemical) and on-going pregnancies
- incidence of Ovarian Hyperstimulation Syndrome (OHSS) and severity should be included in Adverse Events; analysis of multiple gestation should also be reported
- the sponsor is not asking for a male indication
- the sponsor noted that race will not be analyzed if enrollment of women of more than one ethnic group is not possible

Action Items:

- a teleconference between the Chemistry team and the sponsor will be scheduled
- a teleconference between the Statistician and the sponsor will also be scheduled after the sponsor submits a revised statistical plan
- minutes will be provided to the sponsor in 30 days

_____ _____

Signature, minutes preparer Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.
drafted: EDeGuia/04.28.00

cc:
NDA Arch:
HFD-580/Division File
HFD-580/SSlaughter/DHoberman/RBennett/SAllen/MRhee/LMcLeod/AParekh/Jlau
HFD-510/DWu/MHaber
Concurrences: TRumble05.01.00/DHoberman05.02.00/JLau,AParekh05.03.00/DWu,MHaber05.08.00
LMcLeod05.02.00/SSlaughters05.10.00/SAllen05.12.00

NDA 21-289

An Advisory Committee meeting was not held to discuss this application.

NDA 21-289

No Federal Register Notices were published for this application.

DIVISION FILE

NDA 21289

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 13 2001

Richard P. Dickey, M.D.
Fertility Institute of New Orleans
6020 Bullard Avenue
New Orleans, Louisiana 70128

Dear Dr. Dickey:

Between March 5 and March 9, 2001, Ms. Dana Daigle representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol FPI FSH #99-04; NDA 21,289) of the investigational drug, urofollitropin, performed for Ferring Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. Specifically:

1. You failed to conduct your study in accordance with the approved protocol.

   -Laboratory tests were not performed as required by the protocol for several subjects:

   -Early follicular phase prolactin, testosterone, and DHEA-S were not performed for Subject 03S015. In your March 22 response to the observations in FDA Form 483 you noted that these tests were obtained, only 4 days earlier than specified in the protocol.

   -Semen analyses for the partners of subjects 03S033 and 03S040 were not performed within 6 months prior to the baseline visit. You note in your response that these analyses were obtained, only outside of the time limitation specified in the protocol.

   -A urinalysis was not performed for subject 03S040 prior to treatment with leuprolide. You note in your response that the urinalysis was performed, but not until the day of egg retrieval.

   -Rubella screening tests were not performed within 60 days prior to leuprolide treatment for 3 of 8 subjects reviewed (03S003, 03S014, 03S017). You note in your response that the sponsor, at initiation of the study, had approved this deviation.

At the conclusion of the inspection, Ms. Daigle discussed her findings with you and Ms. Susie White, study coordinator.

We appreciate the cooperation shown Ms. Daigle during the inspection and your prompt written response to her observations. Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-269

Food and Drug Administration
Rockville MD 20857

Melvin Thornton, M.D.
23861 McBean Parkway, Suite C-6
Valencia, California 91355

Dear Dr. Thornton:

Between March 22 and March 29, 2001, Mr. Ronald Koller representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #FPI FSH 99-04) of the investigational drug, urofollitropin, performed for Ferring Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. Specifically:

1. You failed to conduct your study in accordance with the approved protocol.

One subject (013), who did not meet inclusion criteria, was enrolled in the study.

2. You failed to maintain adequate and accurate records.

No source documents could be located for subject 001.

At the conclusion of the inspection, Mr. Koller discussed his findings with [redacted] and Ms. Nanette Bahl, Clinical and Office Manager.

We appreciate the cooperation shown Mr. Koller during the inspection. Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855cc:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

D/F

Doc Rm N21-28

APR - 4

Paul B. Miller, M.D.
880 West Faris Street
Greenville Hospital Systems
Greenville, South Carolina 29605

Dear Dr. Miller:

Between February 27 and 28, 2001, Ms. Myla Chapman representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #99-03) of the investigational drug, urofollitropin, performed for Ferring Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects, with the exception of one minor objectionable condition involving a transcription error from a subject's laboratory results into the case report form. At the conclusion of the inspection, Ms. Chapman discussed her findings with you.

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

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

D/F

DOC RM N2 1259

APR - 4

John E. Nichols, M.D.
890 West Faris St.
Greenville Hospital Systems
Greenville, South Carolina 29605

Dear Dr. Nichols:

Between February 28 and March 2, 2001, Ms. Myla Chapman representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #99-04) of the investigational drug, urofollitropin, performed for Ferring Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects, with the exception of one minor objectionable condition involving transcription errors from study subject records into the case report form. At the conclusion of the inspection, Ms. Chapman discussed her findings with you.

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

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: November 28, 2000

To: Roy Blay, GCPB Reviewer/HFD-46

From: Eufrecina DeGuia, Regulatory Project Manager, HFD-580

Subject: **Request for Clinical Inspections**
NDA 21-289
Ferring Pharmaceuticals
Ovanex (urofollitropin for injection)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Assisted Reproductive Technology (ART)	99-04	Richard Dickey, M.D. Fertility Institute of New Orleans 6020 Bullard Ave. New Orleans, LA 70128 Tel: (504) 246-8971 Fax: (504) 246-9778
Assisted Reproductive Technology (ART)	99-04	Melvin Thornton, M.D. Center for Reproductive Health and Gynecology 23861 McBean Parkway Suite C-6 Valencia, CA 91355 Tel: (661) 254-0545 Fax: (661) 254-3221

Assisted Reproductive Technology (ART)	99-04	Benjamin Gocial, M.D. Penn Reproductive Associates 5217 Militia Hill Road Plymouth Meeting, PA 19462 Tel: (610) 834-1140 Fax: (610) 834-0962
Assisted Reproductive Technology (ART)	99-04	John Nichols, M.D. Greenville Hospital Division of Reproductive Endocrinology and Infertility 890 West Faris Road, Suite 470 Greenville, SC 29605 Tel: (864) 455-8487 Fax: (864) 455-8489

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **June 29, 2001**. We intend to issue an action letter on this application by (action goal date) **July 29, 2001**.

Should you require any additional information, please contact Eufrecina DeGuia at (301) 827-4260.

Concurrence: (if necessary)
Shelley Slaughter, M.D., Ph.D., Medical Team Leader
Ridgely Bennett, M.D., Medical Reviewer

APPEARS THIS WAY
ON ORIGINAL

/s/

Eufrecina deGuia
11/28/00 04:00:09 PM

APPEARS THIS WAY
ON ORIGINAL

Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: NDA 21-289

Name of Drug: Ovanex (purified urofollitropin) 75 IU Injectable

Sponsor: Ferring Pharmaceuticals

Material Reviewed:

Submission Date: September 28, 2000

Receipt Date: September 29, 2001

Filing Date: December 2, 2000

User-Fee Goal Date(s): July 29, 2001 (10-month goal date)
September 29, 2001 (12-month goal date)

Proposed Indication: Ovulation Induction and Multiple follicular maturation

Other Background Information: Related IND: ——

Review

PART I: OVERALL FORMATTING[a]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Vol. 1A
2. Form FDA 356h (original signature)	X		Vol. 1A
a. Reference to DMF(s) & Other Applications			Vol. 1A
3. Patent information & certification	X		Vol. 13A and 14A
4. Debarment certification (note: must have a definitive statement)	X		Vol. 16A
5. Financial Disclosure	X		Vol. 18A
6. Comprehensive Index	x		Vol. 1A, 2A, 3A

7. Pagination	x		Vol. 1A, 2A, 3A
8. Summary Volume	x		Vol. 1A, 2A, 3A
9. Review Volumes	x		Vol. 1.0 – Vol. 58
10. Labeling (PI, container, & carton labels)	x		Vol. 2A and 3A
a. unannotated PI	x		Vol. 2A, p. 2-12
b. annotated PI	x		Vol. 3A p. 1-11
c. immediate container	x		Vol. 2A p. 22
d. carton	x		Vol. 2A, p. 14
e. foreign labeling (English translation)		x	
11. Foreign Marketing History	x		Vol. 3A, p. 13
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	x		Vol. 11A- HA- Vol. 12B
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	x		Vol. 12

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Vol. 3A p. 12
2. Summary of Each Technical Section	X		Vol. 3A
a. Chemistry, Manufacturing, & Controls (CMC)	X		Vol. 3A p. 14-21
b. Nonclinical Pharmacology/Toxicology	X		Vol. 3A p. 31
c. Human Pharmacokinetic & Bioavailability	X		Vol. 3A p. 34-40
d. Microbiology	X		Vol. 3A p. 41-45
e. Clinical Data & Results of Statistical Analysis	X		Vol. 3A p. 46-62
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Vol. 3A p. 73-78
4. Summary of Safety	X		Vol. 9
5. Summary of Efficacy	X		Vol. 9

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS

			(list volume & page numbers)
1. List of Investigators	X		Vol. 8 and Vol. 19A
2. Controlled Clinical Studies	X		Vol. 3A p. 48 (summary)
a. Table of all studies	X		Vol. 8
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		
c. Optional overall summary & evaluation of data from controlled clinical studies	X		
3. Integrated Summary of Efficacy (ISE)	X		Vol. 8
4. Integrated Summary of Safety (ISS)	X		Vol. 8
5. Drug Abuse & Overdosage Information	X		Vol. 9 p. 10
6. Integrated Summary of Benefits & Risks of the Drug	X		Vol. 8
7. Gender/Race/Age Safety & Efficacy Analysis Studies		X	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)

1. Written Documentation Regarding Drug Use in the Pediatric Population			Statement is in the label
2. Diskettes			
a. Proposed unannotated labeling in MS WORD 8.0	X		
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format		X	
d. Biopharmacological information & study summaries in MS WORD 8.0		X	
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt	X		Vol. 18A

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments: Filing meeting was held on September 19, 2000.

Conclusions: This NDA is fileable.

Regulatory Health Project Manager

Concurrence, Chief, Project Management Staff

cc:
Original NDA
HFD-580/Div. Files
HFD-580/DeGuia/Rumble
HFD-580/Allen/DShames/Bennett/Slaughter/Rhee/RKavanagh/Parekh/Jordan/Raheja
final: DeGuia

ADMINISTRATIVE REVIEW

APPEARS THIS WAY
ON ORIGINAL

/s/

Eufrecina deGuia
2/20/01 01:09:07 PM
CSO

Terri F. Rumble
2/20/01 01:22:39 PM
CSO

APPEARS THIS WAY
ON ORIGINAL