CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-484

Administrative Documents

13.0 PATENT INFORMATION

Reference is made to NDA # 21-289, Volume 13A., submitted to FDA on September 29, 2000.

14.0 A PATENT CERTIFICATION

Reference is made to NDA # 21-289, Volume 14A., submitted to FDA on September 29, 2000.

EXCLUSIVITY SUMMARY for NDA # 21-484 SUPPL #
Trade Name Bravelle™ Generic Name
Urofollitropin for Injection, Purified 75. I.U.
Applicant Name Ferring Pharmaceuticals
HFD- 580
Approval Date December 17, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

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

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

   YES /_X__/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

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

Three years

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

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

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

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

YES /___/ NO /_X_/

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

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

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

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

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

YES /_X_/ NO /___/

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

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

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

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

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

YES /_X_/ NO /___/

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

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

YES /__/ NO /_X__/

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

YES /___/ NO /_X_/

If yes, explain:

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

YES /___/ NO /_x__/

If yes, explain:

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

Investigation #1, Study # FPI-FSH-2001-01

Investigation #2, Study #

Investigation #3, Study #

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

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

Investigation #1	YES /___/	NO /_X__/
Investigation # 2	YES /___/	NO /___/
Investigation # 3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA in which each was relied upon:

NDA # _____ Study # _____

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

Investigation #1	YES /___/	NO /_X__/
Investigation # 2	YES /_ __/	NO /___/
Investigation # 3	YES /_ __/	NO /___/

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

NDA # _____ Study #

NDA # _____Study

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

Investigation #_1_, Study # _FPI-FSH-2001-01_____

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1

IND # _____ YES /_X__/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

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

Investigation #1

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

_____ ! _____

_____ ! _____

Investigation #2

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

_____ ! _____

_____ ! _____

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Archana Reddy, M.P.H. 12/17/02

Signature of Preparer Date

Title: Regulatory Project Manager

Daniel Shames, M.D. 12/18/02

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- 580/Division File
HFD- 580/RPM/Reddy
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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/s/

Daniel A. Shames
12/19/02 01:34:09 PM

16.0 DEBARMENT CERTIFICATION

Reference is made to NDA # 21-289, Volume 16A, submitted to FDA on September 29, 2000.

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

"Draft"

MEMORANDUM OF TELECON

DATE: September 18, 2002

APPLICATION NUMBER: NDA 21-289, 21-484; Bravelle (urofollitropin injection, purified)

BETWEEN:

Name: Ms. Josephine Torrente
Phone: 202-737-7554
Representing: Ferring Pharmaceuticals, Inc.

AND

Name: Florence Houn, M.D., Director, Office of Drug Evaluation III
Bronwyn Collier, Associate Director for Regulatory Affairs, ODE III

SUBJECT: August 19, 2002, Request for dispute resolution

Background: NDA 21-289 originally proposed two indications, ovulation induction in patients who have previously received pituitary suppression (OI) and multiple follicular development (controlled ovarian stimulation (IVF)). Ferring was issued a not approvable letter on July 27, 2001, for NDA 21-289 that cited deficiencies relating to adequacy of manufacturing facilities, chemistry, manufacturing and controls (CMC), and clinical issues for the IVF indication. Subsequently, the deficiencies relating to the manufacturing facilities and CMC were resolved, Ferring withdrew the IVF indication from NDA 21-289, and the Division of Reproductive and Urologic Drug Products (DRUDP) approved the NDA on May 6, 2002, for the use of Bravelle only for the OI indication. The information submitted to address the clinical deficiencies regarding the indication for the use of Bravelle for IVF was submitted and is being reviewed separately under NDA 21-484. A request for formal dispute resolution was submitted asking that we address four issues related to review of the IVF indication. The purpose of this call was to provide a summary of the decisions made on the issues requested to be addressed under formal dispute resolution.

Call:

1. Whether the Division's proposed, post-hoc analysis of FPI FSH 2001-01 should be considered for the primary analysis.

We acknowledge that there was a delay by the division in sending comments on study 2001-01. The comments had been finalized in January and sent to Ferring on February 5, 2001. The first draft of the protocol sent in September 2001 was followed later by a revised protocol in October leading the division to think that the protocol was still under development. The division was not aware that the study had already been completed until January 20, 2002. The records do not appear to show that agreement on the statistical approach was ever reached. However, the issue of whether the division's February 2002 statistical approach should be used to analyze Study 2001-01 is not ripe for dispute because the study is still under review (NDA 21-484) and no decision on the study has been made. The dispute resolution process is not meant to circumvent the division's review of the data or the decision process for determining efficacy. If the study is approved (NDA 21-484 approved) the issue is moot.

Ms. Torrente stated that they considered this a procedural issue and that Ferring may wish to pursue it again following a decision on the IVF indication (NDA 21-484). She acknowledged that the division and Ferring seemed to be "talking past each other" on earlier communications on this issue.

2. Whether Ferring prespecified a 30% difference of the mean oocytes retrieved in the reference group as the lower limit of the confidence interval (CI) for the primary endpoint in FPI FSH 99-04.

Two power calculations were specified in the protocol for study 99-04. Neither was identified as the hypothesis to be tested to determine non-inferiority. The E-mails between Drs. —— and Hoberman documented agreement on the hypothesis for study 99-03, which addressed the OI indication rather than IVF. The OI indication was ultimately approved without the need for further clinical data. For the IVF indication, Ferring decided to conduct another study (2001-01) in response to clinical deficiencies for that indication which was submitted to NDA 21-484. The agency must first respond to Ferring's decision to submit Study 2001-01 in response to the July 27, 2001 not approvable action. Should FDA approve this application (study), the issue of what was prespecified as the appropriate power calculation is moot.

Ms. Torrente stated that if the IVF indication were not approved, Ferring would likely want to revisit this issue. In addition, Ferring does not want submission of a new study (2001-01) to be considered their acceptance of the analysis of study 99-04. She acknowledged that a better time to appeal this issue would have been following the not approvable action but before submission of study 2001-01. Dr. Houn stated that the labeling, if the product is approved, may be a way to address Ferring's views on Study 99-04.

3. Determination of a clinically relevant lower limit of the CI for the primary endpoint in a non-inferiority study when comparing IVF drug products.

All FDA reviews of Repronex and Follistim and the comments on IND —— used numeric endpoints rather than percentages. We acknowledge that these numbers have varied, however, it is a numeric endpoint that is currently used. FDA could have been clearer in its letter of October 12, 2001 by stating Ferring needed to state the number, "(not percentage)" of oocytes that the study hypothesis should exclude as the lower limit of the 95% confidence interval as clinically and statistically relevant. The division has been asked to hold an advisory committee meeting next year to get public input on this topic of endpoints as part of the Good Guidance Practice process in order to develop a guidance on efficacy standards for products for assistive reproductive technology.

4. Whether the Division's request that the results of FPI FSH 2001-01 be submitted as an "Administrative" NDA rather than as a Class 2 resubmission affects the time of the review.

Ferring's letter of September 10, 2001, conveyed a proposal designed to go forward with attaining approval on the OI indication and then submitting a supplemental application (to an approved NDA 21-289) for the IVF indication. Implicit in this proposal is their withdrawal of the IVF indication in order to have submission of chemistry, manufacturing, and controls information and correction of cGMP issues at the manufacturing facilities be accepted as a complete response to the July 27, 2001, not approvable letter. The division's letter of October 12, 2001 stated that the proposal was acceptable. This statement also addressed the implied withdrawal of the IVF indication. Once withdrawn, the IVF indication could only be submitted for review prior to approval of NDA 21-289 as an original new NDA, or as a supplemental application to an approved NDA 21-289. Both of these types of applications would receive the 10-month review clock applied to original NDAs and efficacy supplements.

See appended electronic signature page

Bronwyn Collier

Associate Director for Regulatory Affairs
Office of Drug Evaluation III

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/s/

Bronwyn Collier
9/24/02 07:18:10 AM
CSO

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
- oxidation product on the dosage form; sponsor should analyze and propose maximum content of oxidation products in the drug product at the time of submission of NDA; the [redacted] can only detect

- the sponsor will make an effort to try to determine the amount of oxidation products in the drug product; if this is not feasible due to the low amount of protein present and the interference from other proteins that

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 ——— analysis of the drug substance for oxidation products and results will be discussed further with the Division
-

General Comments:

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

  Peptide mapping is not necessary as the sponsor is already doing complete amino acid sequencing
  Amino acid sequencing (both N and C terminal with enough internal sequence to confirm identity for both α and β subunits)
  Carbohydrate structure determination
  Disulfide bonds structure, if possible
  Presence of oxidized and/or deaminated forms
  Also, additional information regarding the specificity of monoclonal antibodies used for and should be provided.

Action Items: none

/S/

Signature, minutes preparer

/S/

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.

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

Teleconference Minutes

Date: January 21, 2000 **Time:** 2:30 – 2:45 PM **Location:** PKLN; 17B-43

IND: —— **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 (clinical and Statistical)

Meeting Chair: Dr. Shelley Slaughter

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
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)
David Hoberman, Ph.D. – Statistical Reviewer, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants:
Ronald Nardi, Ph.D. – Vice-President, Scientific and Regulatory Affairs
Michael Bernhard, Ph.D. – Senior Director, Regulatory Affairs
Seymour Fine, M.D. – Medical Director
Linda Cheng - Project Manager
Michele Cobham – Manager, Scientific Information Systems

Meeting Objectives: To clarify some statistical issues related to the analysis plan for the two Phase 3 protocols, FPI FSH 99-03 and FPI FSH 99-04.

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

Decisions reached:
- the sponsor clarified that the sample size was calculated based on 70% power to detect a relative (not absolute) difference of 35% in ovulation rate
- Dunnet's procedure should be used for the two (FSH) comparisons to Follistim

/S/ /S/

Signature, minutes preparer Concurrence, Chair

drafted: EDeGuia/01/28/00

cc:
NDA Arch:
HFD-580/Division File
HFD-580/SSlaughter/DHoberman/RBennett
Concurrences: TRumble02.18.00/DHoberman,RBennett02.22.00/SSlaughter02.23.00

MEETING MINUTES

Date: October 15, 2002 **Time:** 11:00 – 11:20 AM **Location:** Conf. Rm. 17B-43

NDA: 21-484 **Drug Name:** Bravelle™ (urofollitropin for injection, purified)

Sponsor: Ferring Pharmaceuticals, Inc.

Indication: Assisted Reproductive Technologies (ART)

Type of Meeting: Eight-month Status Meeting

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Ridgely Bennett, M.D., Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, OCPB @ DRUDP (HFD-580)
Archana Reddy, M.P.H, Project Manager, DRUDP (HFD-580)
David Hoberman, M.D., Biostatistician, Division of Anesthetic and Critical Care Drug Products (HFD-170)

Background:
The sponsor received a not approvable action on July 27, 2001 for NDA 21-289. In response to this NA action, a type A meeting to discuss the NDA action was held with the sponsor on August 22, 2001. On September 10, 2001, a general correspondence was received with the sponsor's proposals to resubmit the NDA. The sponsor withdrew the indication of multiple follicular development from NDA 21-289 and resubmitted the NDA for ovulation induction o November 6, 2001. The primary user fee goal date was May 6, 2002. A new NDA, NDA 21-484, with the indication of multiple follicular development during ART was received on February 19, 2002 and the PDUFA goal date is December 19, 2002.

Discussion:
Statistics
- Draft statistical review is with Biostatistics Team Leader for review
- Bravelle is within 2.2 oocyte lower bound confidence interval limit
- No approvability issues

Clinical
- Review is ongoing
- Bravelle is within 2.2 oocyte lower bound confidence interval limit

Chemistry

- sponsor is cross-referencing chemistry information from NDA 21-289

Biopharmaceutics/Clinical Pharmacology

- sponsor is cross-referencing information from NDA 21-289
- full PK/PD profile provided by sponsor
- issue of whether dose can be administered by IM route of administration for the ART indication has been addressed
- no new data submitted by sponsor; referencing original NDA 21-289
- draft of biopharm review with Clinical Pharmacology Team Leader for review

Pharmacology

- draft review is complete

Microbiology

- Review is complete and in DFS; recommend approval

Regulatory Issues

- Financial disclosure review is complete.
- No tradename review needed as the tradename Bravelle™ has already been approved by OPDRA on April 25, 2001.
- DSI inspections are complete and acceptable according to DSI report dated October 2, 2002.

Decision Reached:

All reviews will be forwarded to the Medical Team Leader by November 1, 2002.

Cc:
Arch NDA 21-484
HFD-580/Division Files
HFD-580/Reddy/Shames/Bennett/Slaughter/McLeod/Jordan/Parekh/Al-Habets/Lin
HFD-510/Haber/Wu

Created by: Archana Reddy, December 1, 2002
Concurrence: ss/December 12, 2002,
Finalized: ar/December 13, 2002, 2002
File Path: C:Data/My Documents/NDAs/n21484/7monthstatusminutes.doc

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/s/

Shelley Slaughter
12/13/02 01:01:01 PM
I concur.

MEETING MINUTES

Date: September 5, 2002 **Time:** 1:00 – 1:20 AM **Location:** Conf. Rm. 17B-43

NDA: 21-484 **Drug Name:** Bravelle™ (urofollitropin for injection, purified)

Sponsor: Ferring Pharmaceuticals, Inc.

Indication: Assisted Reproductive Technologies (ART)

Type of Meeting: Seven-month Status Meeting

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley R. Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (HFD-580)
Ridgely Bennett, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H, Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, OCPB @ DRUDP (HFD-580)

Background:
The sponsor received a not approvable action on July 27, 2001 for NDA 21-289. In response to this NA action, a type A meeting to discuss the NDA action was held with the sponsor on August 22, 2001. On September 10, 2001, a general correspondence was received with the sponsor's proposals to resubmit the NDA. The sponsor withdrew the indication of multiple follicular development from NDA 21-289 and resubmitted the NDA for ovulation induction o November 6, 2001. The primary user fee goal date was May 6, 2002. A new NDA, NDA 21-484, with the indication of multiple follicular development during ART was received on February 19, 2002 and the PDUFA goal date is December 19, 2002.

Discussion:
Statistics -
- review is underway

Clinical
- review is ongoing

Chemistry
- sponsor is cross-referencing chemistry information from NDA 21-289
- sponsor has met criteria for non-inferiority
- review is underway

Biopharmaceutics/Clinical Pharmacology

- sponsor is cross-referencing information from NDA 21-289
- full PK/PD profile provided by sponsor
- issue of bioequivalence between the subcutaneous and IM forms of the drug product needs to be addressed by clin pharm/biopharm group
- no new data submitted by sponsor; referencing original NDA 21-289
- draft of biopharm review with Clinical Pharmacology Team Leader for review

Pharmacology

- review is underway

Regulatory Issues

- Financial disclosure review is complete.
- No tradename review needed as the tradename Bravelle™ has already been approved by OPDRA on April 25, 2001.
- DSI inspections are pending.

Decision Reached:

All reviews will be forwarded to the Medical Team Leader by November 1, 2002.

Cc:
Arch NDA 21-484
HFD-580/Division Files
HFD-580/Reddy/Shames/Bennett/Slaughter/McLeod/Jordan/Parekh/Al-Habets/Lin
HFD-510/Haber/Wu

Created by: Archana Reddy, December 1, 2002
Concurrence: ap/, 2002, ss/December 3, 2002
Finalized: ar/December 13, 2002
File/Path: C:Data/My Documents/NDAs/n21484/7monthstatusminutes.doc

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/s/

Shelley Slaughter
12/13/02 12:57:23 PM
I concur.

MEETING MINUTES

Date: July 17, 2002 **Time:** 10:00 – 10:20 AM **Location:** Conf. Rm. 17B-43

NDA: 21-484 **Drug Name:** Bravelle™ (urofollitropin for injection, purified)

Sponsor: Ferring Pharmaceuticals, Inc.

Indication: Assisted Reproductive Technologies (ART)

Type of Meeting: Six-month Status Meeting

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (HFD-580)
Ridgely Bennett, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H, Project Manager, DRUDP (HFD-580)
Laurie McLeod, Ph.D., Pharmacologist, DRUDP (HFD-580)
Sayed Al-Habet, Ph.D., Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCBP) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, OCPB @ DRUDP (HFD-580)
Duu-Gong Wu, Ph.D., Associate Director, Office of New Drug Chemistry II (ONDC II)

Background:
The sponsor received a not approvable action on July 27, 2001 for NDA 21-289. In response to this NA action, a type A meeting to discuss the NDA action was held with the sponsor on August 22, 2001. On September 10, 2001, a general correspondence was received with the sponsor's proposals to resubmit the NDA. The sponsor resubmitted the NDA on November 6, 2001, and stated their intent to withdraw the ART indication from NDA 21-289 in response to Agency advice. The primary User Fee goal date for this application is May 6, 2002. To administratively split the two indications, the sponsor was advised to submit a new NDA for the ART indication. NDA 21-484 was received on February 19, 2002 for the ART indication and the PDUFA goal date is December 19, 2002.

Discussion:
Statistics
- review is underway

Clinical
- sponsor has completed another IVF study using only the SubQ form of the drug product

Chemistry

- sponsor ~~is~~ cross-referencing chemistry information from NDA 21-289
- sponsor has met criteria for non-inferiority
- review is underway

Biopharmaceutics/Clinical Pharmacology

- sponsor is cross-referencing information from NDA 21-289
- full PK/PD profile provided by sponsor
- issue of bioequivalence between the subcutaneous and IM forms of the drug product needs to be addressed by clin pharm/biopharm group
- no new data submitted by sponsor; referencing original NDA 21-289
- review is underway

Pharmacology

- review is underway

Regulatory Issues

- Financial disclosure review is complete.
- No tradename review needed as the tradename Bravelle™ has already been approved by OPDRA on April 25, 2001.
- DSI inspections are pending.

Decision Reached:

All reviews will be forwarded to the Medical Team Leader by November 1, 2002.

Addendum to Meeting Minutes

The Project Manager called Seymour Fein of Ferring Pharmaceuticals on July 24, 2002, to request that they provide data on the bioequivalence between the SubQ and IM forms of Bravelle for the IVF indication. The sponsor indicated that they did not have this data. A response from the sponsor regarding this issue was received on July 29, 2002 (letter date of July 25, 2002) regarding this issue.

Cc:
Arch NDA 21-484
HFD-580/Division Files
HFD-580/Reddy/Shames/Bennett/Slaughter/McLeod/Jordan/Parekh/Al-Habets/Lin
HFD-510/Haber/Wu

Created by: Archana Reddy
Concurrence: lm/September 29, 2002, ap/August 29, 2002, ss/October 28, 2002, rb/August 29, 2002
Finalized: ar/November 14, 2002
File/Path: C:Data/My Documents/NDAs/n21484/6monthstatusminutes.doc

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/s/

Shelley Slaughter
11/19/02 10:58:37 AM
Concur

MEETING MINUTES

Date: April 10, 2002 **Time:** 11:00 – 11:30 AM **Location:** Conf. Rm. 17B-43

NDA: 21-484 **Drug Name:** Bravelle™ (urofollitropin for injection, purified)

Sponsor: Ferring Pharmaceuticals, Inc.

Indication: Assisted Reproductive Technologies (ART)

Type of Meeting: Filing Meeting

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (HFD-580)
Ridgely Bennett, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H, Project Manager, DRUDP (HFD-580)
Laurie McLeod, Ph.D., Pharmacologist, DRUDP (HFD-580)
Sayed Al-Habet, Ph.D., Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCBP) @ DRUDP (HFD-580)
David Hoberman, Ph.D., Statistician, Division of Biometrics II (DB II) @ Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)

Background:
The sponsor received a not approvable action on July 27, 2001 for NDA 21-289. In response to this NA action, a type A meeting to discuss the NDA action was held with the sponsor on August 22, 2001. On September 10, 2001, a general correspondence was received with the sponsor's proposals to resubmit the NDA. The sponsor resubmitted the NDA on November 6, 2001, and stated their intent to withdraw the ART indication from NDA 21-289 in response to Agency advice. The primary User Fee goal date for this application is May 6, 2002. To administratively split the two indications, the sponsor was advised to submit a new NDA for the ART indication. NDA 21-484 was received on February 19, 2002 for the ART indication and the PDUFA goal date is February 19, 2002.

Discussion:
Statistics
- NDA is fileable

Clinical
- draft labeling is inadequate; labeling revisions sent to sponsor on June 5, 2001; sponsor has not addressed these labeling changes

- NDA is fileable

Chemistry
- sponsor is cross-referencing chemistry information from NDA 21-289
- NDA is fileable

Biopharmaceutics/Clinical Pharmacology
- sponsor is cross-referencing information from NDA 21-289
- NDA is fileable

Pharmacology
- NDA is fileable

Regulatory Issues
- Financial disclosure review is complete.
- No tradename review needed as the tradename Bravelle™ has already been approved by OPDRA on April 25, 2001.
- The PM will forward request for inspections to the Division of Scientific Investigations if it is determined inspections are needed.

Decision Reached:
NDA is fileable

Addendum to Meeting Minutes
On February 5, 2002, DRUDP sent an advice letter to the sponsor in response to their amendment dated October 23, 2001 containing their proposal to
the efficacy of Follistim. The sponsor intends to appeal this decision based upon the fact that this advice letter was received two weeks before NDA 21-484 was filed.

Cc:
Arch NDA 21-484
HFD-580/Division Files
HFD-580/Reddy/Shames/Bennett/Slaughter/McLeod/Jordan/Parekh/Al-Habets/Lin
HFD-510/Haber/Wu

Created by: Archana Reddy
Concurrence: lm/April 26, 2002/mh, April 26, 2002, ss/May 3, 2002, rb/May 2, 2002
Finalized: ar/May 3, 2002
File/Path: C:Data/My Documents/NDAs/n21484/filing minutes.doc

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/s/

Shelley Slaughter
5/15/02 12:47:47 PM
Concurrence provided 5-3-02.

Meeting Minutes

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

IND: —— **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

—
—
—
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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 in anovulatory women. 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 —— 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 —— 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 —— as fingerprinting for —— to show batch to batch consistency; the test is sensitive to changes in the charge of very large molecules
- the Division indicated that —— only detects ——
- 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 store the drug substance becomes the accelerated storage condition. Currently available data show no loss of potency when the drug substance is stored at 2°-8° for 12 months. By the end of the NDA review period, we anticipate having stability data at the accelerated condition (2°-8°) and more than nonths under conditions. Assuming these data support continued drug substance stability and that extrapolation of the data permit, we anticipate a month retesting interval. 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. ——— as a lyophilized powder and the secondary standards will be. ——— 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 ——— are needed; — is not specific enough for identification since other macromolecules co-elute on ——— 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 9-month stability data at the time the NDA is submitted and 21-month data by the end of the review period. Assuming the data show the drug substance is stable for ——— and that extrapolation of the data permit, we anticipate — 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

/S/

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/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA: 21-484	Efficacy Supplement Type SE-	Supplement Number: N/A
Drug: Bravelle™ (urofollitropin for injection, purified) 75 I.U.		Applicant: Ferring Pharmaceutical, Inc.
RPM: Archana Reddy	HFD- 580	Phone #: 7-7514
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): 21-289 (Bravelle)	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3s
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	December 19, 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception: This is an administrative NDA to NDA 21-289 for Bravelle, which is indicated for ovulation induction and NDA 21-484 is indicated for mutiple follicular development in ART/*in-vitro* fertilization.	( ) Orphan designation ( ) No-fee 505(b)(2) (X) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X (Project Manager)

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (12/13/02)
• Most recent applicant-proposed labeling	X (12/18/02)
• Original applicant-proposed labeling	X (2/15/02)
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (ODS; see NDA 21-289) (DRUDP revised label sent on 12/13/02)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Bravelle, Repronex
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	N/A (See NDA 21-289)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	April 24, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Clinical, CMC Guidance, Status Meetings
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical Team Leader Memo (12/18/02)
❖ Clinical review(s) *(indicate date for each review)*	10/31/02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	5/17/02
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Medical Officer's Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	11/7/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	12/03/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	10/08/02
• Bioequivalence studies	N/A
❖ CMC review(s) *(indicate date for each review)*	10/31/02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (See NDA 21-289 review)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	5/17/02
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed: 10/22/02 (X) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11/20/02.
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Archana Reddy
12/18/02 12:47:59 PM

18.0 USER FEE COVER SHEET

This is an administrative NDA (#21-484) requested by the reviewing Division of CDER (Reproductive and Urologic Drug Products) to reinitiate its review of the Assisted Reproductive Technologies/In Vitro Fertilization (ART/IVF) clinical indication for Bravelle™.

The Division has determined that this administrative NDA is exempt from User Fees. Please contact Terri Rumble, Chief, Project Management Staff, Office of Drug Evaluation III for confirmation..

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

Microbiology Efficacy Review

This new drug application did not require a micro efficacy review.

cvr 12/08/02

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

Abuse Liablity Review

This new drug application is not the subject of an abuse liability review.

CVR 12/08/02

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secret and/or

confidential

commercial

information

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

DSI Memo (GLP Inspection)

No DSI memo since no GLP inspection was requested for this new drug application.

OR 12/08/02

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

Press Office Information

This new drug application was not the subject of any press releases.

cm 12/08/02

NDA REGULATORY FILING REVIEW

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type): NDA 21-484, Bravelle (urofollitropin for injection, purified) 75 I.U.

Applicant: Ferring Pharmaceuticals, Inc.

Date of Application: 12/15/02
Date of Receipt: 2/19/02
Date of Filing Meeting: 4/10/02
Filing Date: 4/19/02

Indication(s) requested: Multiple follicular development in ART/*in-vitro* fertilization

Type of Application: Full NDA __X_____ Supplement _____
(b)(1) _____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S____X___ P_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.)__3s____
Other (orphan, OTC, etc.)__N/A_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid _____
Waived (e.g., small business, public health) ___X (administrative NDA to NDA 21-289_____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES_____ NO_____
User Fee ID#_____
Clinical data? YES _____ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: _____

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES NO
- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO NA

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES; If yes, ___3___years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:
  Waiver for all pediatric populations; this drug is not indicated for pediatric patients
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: IND ——

End-of-Phase 2 Meeting? Date_____ NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) 4/24/00 NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO NA

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

Archana Reddy, M.P.H.
Regulatory Project Manager, HFD-580