

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21047

ADMINISTRATIVE DOCUMENTS

NDA 21-047

Repronex® (Menotropins for Injection, USP) 75 or 150 IU

Ferring Pharmaceuticals, Inc.

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

**Group Leader Memorandum
Repronex Original NDA**

NDA: 21-047

Drug: Repronex

Dosage Form/Route: Lyophilized powder or pellet in vials for reconstitution.
Subcutaneous or intramuscular administration.

Applicant: Ferring Pharmaceuticals

Original Submission Date: October 26, 1998
March 24, 1999

Date of Memorandum: August 12, 1999

This application was submitted on October 26, 1998 (amended March 24, 1999) and in the cover letter the Sponsor indicated that with this 505 (b)(2) application a new subcutaneous route of administration for Repronex was being sought based on clinical trials conducted in the US and Europe. Repronex IM is an approved drug under ANDAs 73-598 and 73-599 for the indications of induction of ovulation, multiple follicular development in ovulating women for IVF, and stimulation of spermatogenesis in men. These ANDAs conclude that Repronex IM is equivalent to Pergonal for these indications.

Two trials were submitted in support of the new route of administration, Studies 97-01 and 97-02, in which Repronex IM and Repronex SC were compared to each other and to Pergonal IM. These trials were designed to demonstrate that the subcutaneous administration of Repronex is safe and effective for the indications listed above for Repronex IM and Pergonal IM. The trials were small (36 subjects per treatment arm in Study 97-01 and 65, 60 and 61 subjects for Repronex IM, Repronex SC and Pergonal IM, respectively, for Study 97-02). There were no statistically significant or clinically meaningful differences in the primary endpoint (the number and percentage of subjects who ovulated in Study 97-01 and the number of oocytes retrieved in Study 97-02).

The primary safety issues with the use of menotropins are multiple gestation and the Ovarian Hyperstimulation Syndrome (OHSS). The differences in the incidence of OHSS were felt not to be statistically significant among the three treatment groups for both studies and the rates of OHSS were not substantially different from the rate of OHSS reported in the literature with menotropin use. The rate of multiple pregnancy was approximately 50% for both Repronex IM and Repronex SC (based on small numbers). This is higher than the 17% multiple pregnancy rates in the original Pergonal studies conducted in oligo-anovulatory patients. The final label presents the multiple pregnancy

rates as the numbers of multiple pregnancies per total pregnancies and gives clear direction that the patient and her partner should be advised of the risk of multiple births before starting treatment. One additional point on the safety of Repronex, administration of Repronex SC did result in a higher incidence of injection site reactions compared to Repronex IM. This is clearly addressed in the label under Adverse Reactions. The review of the medical officer concluded that Repronex SC is safe and effective for the induction of ovulation and multiple follicular development in IVF and recommended approval for this route of administration. I concur with the recommendation of the primary clinical reviewer.

This submission also contained three pharmacokinetic studies (Meno 96/02/NL [with Menogon, a product similar to Repronex marketed in Europe], FPI Rep 97-01 and FPI Rep 97-02) which were conducted to determine the pharmacokinetic profile(s) of single and multiple doses of Repronex SC, Repronex IM, and Pergonal IM. The pharmacokinetic data was not intended to demonstrate bioequivalence of Repronex SC to Repronex IM (as a number of studies had previously documented that the subcutaneous and intramuscular routes were not bioequivalent). The biopharmacology reviewer found that the human pharmacokinetic and bioavailability data were supportive of this NDA. A significant review finding was that the injection site for subcutaneous administration appears to affect the FSH PK. A recommendation was made that the dosage and administration section of the label clearly stipulate the site of injection for SC administration as the lower abdomen (alternating sides). This was the site used for the two clinical safety and efficacy studies.

The Sponsor cross-referenced ANDAs 73-598 and 73-599 for pharmacology/toxicology, CMC, and microbiology data. Cross-referenced data was accepted by the pharmacology/toxicology, chemistry, and microbiology review teams, respectively.

The DSI audit revealed that one of the two audited sites had 6 protocol violations and the site was classified as OAI (official action indicated). The site will be issued a warning letter to correct these types of violations. However, the clinical team has reviewed these protocol violations and concluded that most of these violations were minor, consistent with usual infertility practice, and did not affect the ability to evaluate these subjects.

One aspect of this application's approval merits further comment. During labeling negotiations, the Sponsor indicated their intent to rewrite the Repronex label to reflect not only the data from Studies 97-01 and 97-02 as supportive of the subcutaneous route of administration for Repronex, but also to revise the labeling of Repronex IM based on these studies as well. The Sponsor's rationale for pursuing this labeling change was that Studies 97-01 and 97-02 reflect the current state of infertility practice for controlled ovarian stimulation and ovulation induction (with the use of GnRH pituitary suppression prior to beginning menotropin therapy) and that the data in the current label for Repronex administered intramuscularly is outdated. As this was a departure from the original intent of the NDA, to gain an indication for the SC route only, the labeling review involved in-depth discussions with the Sponsor, FDA General Counsel, and the Office of Generic Drugs. The Division review team felt that revising the label based solely on the data

from these studies was reasonable given the 30 year history of safe and effective use of menotropins (including 2 years of Repronex IM use). The representative from the Office of Generic Drugs stated that the Sponsor needed to be informed that they would not have an "AB" rating (to Pergonal in the publication, Approved Drug Products with Therapeutic Equivalence Evaluation) for Repronex IM or SC as a result of a new label based solely on the results of studies submitted in this NDA. The FDA General Counsel felt that it was acceptable to reference the ANDA for CMC and pharmacology/toxicology data.

In a teleconference held 8/3 /99, the Sponsor was informed that if the new label was to be based solely on Studies 97-01 and 97-02 in support of the intramuscular route of administration as well as a subcutaneous route, then the label would have to clearly reflect the population in which both routes of administration were studied (i.e. women with GnRH analog pituitary suppression [down regulation]), the indication for males would need to be withdrawn, and the "AB" rating as equivalent to Pergonal would be withdrawn. The Sponsor indicated clear acceptance of all of these conditions. The Agency agreed to accept a label for Repronex IM and Repronex SC based solely on the clinical trial data from Studies 97-01 and 97-02. The label as agreed upon is included in this action package

The registered name Repronex will be used for both the intramuscular and subcutaneous routes of administration.

/S/
Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader, HFD-580

M.D. Ph.D. 8/13/99

cc:

NDA 21-047

HFD-580/L.Rarick/M. Mann/R. Bennett/S.Slaughter

Addendum to Group Leader Memorandum

NDA: 21-047
Date: August 17, 1999
Re: Phosphate Buffer in Repronex

Dr Rhee, chemistry team leader, brought to my attention today that the final label as proposed by the Sponsor contained in the Description section the following sentence which was not present in the original proposed label: *The final product may contain sodium phosphate buffer (sodium phosphate tribase and phosphoric acid).* }

Upon discussion with the Sponsor, it was learned that the clinical trials submitted in this NDA were performed with a drug product that did not contain the sodium phosphate buffer. Subsequent to these trials, the Sponsor obtained approval on May 21, 1999 of the drug product containing the phosphate buffer in a supplement to the ANDA. The Sponsor notes that the phosphate buffer was added in response to a request from FDA to tighten the pH specifications.

The clinical trials submitted in this NDA demonstrated that there was no clinically meaningful difference in the efficacy of the IM and SC routes of administration. The drug product containing the phosphate buffer has been approved in a supplemental ANDA. Therefore, after consideration of this information and discussions with Dr. Rhee (who has accepted the change in drug product from a chemistry consideration), the clinical reviewing team has determined that the addition of phosphate buffer to the drug product would have little or no impact on the safety and efficacy of this drug. It is recommended that approval be granted.

JS
Shelley R. Slaughter, MD, Ph.D. - 8/17/99
Reproductive Medical Team Leader

cc:
NDA 21-047
HFD-580/L.Rarick/M.Mann/R.Bennett/M.Rhee/S.Slaughter

Memorandum

To: NDA 21-047

From: Moo-Jhong Rhee, Ph.D., Chemistry Team Leader

Date: 08/17/99

Re: Phosphate Buffer in Repronex

JS/8/17/99

This NDA was submitted with cross-reference to the previously approved ANDAs, 73-598 and 73-599 for CMC information. Because of the nature of the drug substance (protein), CMC review was consulted to Dr. Martin Haber in HFD-510, who did the consult review for those ANDAs previously.

Based on his review and recommendation, this NDA can be approved from CMC point of view. However, when the final labeling was submitted, it was noted that the sponsor added the following sentence in the Description section of the package insert as well as in the carton labels,

The final product may contain sodium phosphate buffer (sodium phosphate tribase and phosphoric acid).

After communication with the sponsor, it was learned that they got approval of supplements for those ANDA on May 21, 1999, for adding phosphate bufer to their product in order to adjust the pH during the manufacturing process, and this was for tightening the pH specification.

This was notified to Drs. Ridgely Bennett (MO) and Shelly Slaughter (Team Leader) whether this will have any clinical implication or not.

However, from chemistry point of view, it is deemed acceptable since it was approved for the ANDAs.

CC: NDA 21-047

HFD-580/Division File

HFD-580/MRhee/DMoore

HFD-510/MHaber/DWu

EXCLUSIVITY SUMMARY for NDA # 21-047 SUPPL # _____

Trade Name Repronex® Generic Name (Menotropins for Injection, USP) 75
or 150 mIU

Applicant Name Ferring Pharmaceuticals Inc. HFD-580 _____

Approval Date, if known _____

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 question 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 / / NO / /

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 / / OTC Switch / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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# 17-646 Pergonal

NDA# 20-328 Humegon

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 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

- (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 / / 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 8:

YES / / NO / /

- (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 / /

- (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 / /

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 independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

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:

FPI Rep 97-01

FPI Rep 97-02

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 / /

Investigation #2 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:

- 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 / /
Investigation #2 YES / / NO / /

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

- 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"):

FPI Rep 97-01

FPI Rep 97-02

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 / <input checked="" type="checkbox"/> /	! NO / <input type="checkbox"/> / Explain: _____
	!
	!
Investigation #2	!
IND # _____ _____ YES / <input checked="" type="checkbox"/> /	! NO / <input type="checkbox"/> / Explain: _____
	!
	!

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21047</u>	Trade Name:	<u>REPRONEX (MENOTROPINS/INJ) 75/150IU VIAL</u>
Supplement Number:		Generic Name:	<u>MENOTROPINS/INJ</u>
Supplement Type:		Dosage Form:	<u>FIJ</u>
Regulatory Action:	<u>PN</u>	Proposed Indication:	<u>Repronex, in conjunction with hCG, is indicated for multiple follicular development (controlled ovarian stimulation) and ovulation induction in patients who have previously received pituitary suppression.</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
August 13, 1999

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, DIANE MOORE

DS
Signature

8/13/99
Date

NDA 21-047

Repronex® (Menotropins for Injection, USP) 75 or 150 IU

Ferring Pharmaceuticals, Inc.

Microbiology Review

No microbiology review is required. The microbiology reviewers returned the consult as no action indicated. They have no problem with approval from the standpoint of product quality microbiology.

NDA 21-047

Repronex® (Menotropins for Injection, USP) 75 or 150 IU

Ferring Pharmaceuticals, Inc.

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 21-047

Repronex® (Menotropins for Injection, USP) 75 or 150 IU

Ferring Pharmaceuticals, Inc.

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 21-047

Repronex® (Menotropins for Injection, USP) 75 or 150 IU
Ferring Pharmaceuticals, Inc.

Advertising Material

No advertising material has been submitted.

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21047
To: HFD-580
Place: 17B43
Compound: Menotropins (Repronex™)
Sponsor: Ferring Pharmaceuticals, Inc.
Date: December 7, 1998
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background:

Menotropins are human menopausal gonadotropins containing equal amounts (75 IU) of follicular stimulating hormone (FSH) and leutinizing hormone (LH). Intramuscular injection (IM) Repronex™ is approved (ANDA 73598/599) as equivalent to IM Pergonal® for the treatment of ovulation induction, in vitro fertilization, and spermatogenesis. The sponsor submitted this 505 (b)(2) NDA on October 26, 1998 to seek approval of subcutaneous injection (SC) Repronex™ with the same indications as IM Repronex™. IM Repronex™ is marketed as IM Menogon® in Europe by the same sponsor. Menogon® and Repronex™ are sourced from the same bulk active drug product. However, Menogon® has less lactose (5 mg/vial) than Repronex™ (20 mg/vial) and is manufactured at different facilities (Kiel, Germany). The innovator IM Pergonal® has 10 mg of lactose per ampule.

Comments:

1. The sponsor conducted 2 clinical pharmacology studies for this NDA. The 1st study (Meno 96/02/NL) is a single dose study to compare the bioavailability (BA) of SC Menogon® to IM Menogon® in healthy female subjects. The 2nd study is a multiple dose study (FPI REP 97-01) to compare the single dose and steady-state pharmacokinetics (PK) of SC Repronex™ to IM Repronex™, and IM Pergonal® in oligoovulatory infertile patients.
2. A final report for the single dose (1st) study is provided. This study monitored only serum FSH concentrations but not serum LH concentrations. SC Repronex™ results in higher FSH C_{max} (↑35%) and AUC (↑22%) than those for IM Repronex™.
3. The multiple dose (2nd) study is still ongoing.
4. No bioanalytical assay validation is provided for the multiple dose study.
5. Based on the interim population PK analyses for the multiple dose study on 20 patients, the sponsor claims that no differences exist for FSH and LH PK parameters among the 3 treatment groups.
6. The sponsor claims that the formulation tested in this clinical pharmacology study is the same as the to-be-marketed formulation. The formulation used in the 1st study is the European Menogon®.
7. Since SC Repronex™ is lyophilized and reconstituted for injection as a solution, lack of dissolution data in this NDA is acceptable.

Telephone Conference Minutes*

NDA: 21047

Compound: Menotropins (Repronex™)

Date and time: December 4, 1998, 9:45 a.m.

Sponsor: Ferring Pharmaceuticals, Inc.

Sponsor's representative (responder): Ronald V. Nardi, Ph.D. (914-333-8932)

FDA's representative (caller): FDA, Office of Clinical Pharmacology and Biopharmaceutics (OCPB), Division of Pharmaceutical Evaluation II, Ameeta Parekh, Ph.D. and S.W. Johnny Lau, R.Ph., Ph.D.

JL
Purpose of telephone conference: obtain information on NDA 21047 to determine its filability

Dr. Nardi provided the following information:

1. The single dose study (Meno 96/02/NL) was originally meant to estimate the bioavailability of subcutaneous injection (SC) of Menogon® to intramuscular injection (IM) of Menogon®. This study was not meant to assess bioequivalence, even though it showed that SC Menogon® is not bioequivalent to IM Menogon®.
2. Study (#9701) compared the clinical efficacy of SC Repronex™, IM Repronex™, and IM Pergonal®. Forty nine out of 56 subjects completed the study and the PK data can be submitted by the beginning of 1999.
3. The lactose content of IM Menogon®, IM Repronex™, and IM Pergonal® is 5, 20, and 10 mg/vial, respectively.
4. Study #9702 (no PK portion) has the same design as study #9701 and is completed.
5. Both clinical efficacy study #9701 and #9702 used the to-be-marketed Repronex™ formulation.

* Project manager (Ms. D. Moore; HFD-580) consented to the direct contact of Sponsor by OCPB staff.

Teleconference Minutes

Date: August 17, 1999

Time: 2:15-2:25 p.m.

Location: Parklawn;17B45

NDA 21-047

Type of Meeting: Information Request

Meeting Chair: Dornette Spell-LeSane

External Lead: Dr. Nardi

Meeting Recorder: Dornette Spell-LeSane

FDA Attendees

Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

External Attendees:

Dr. Nardi, Ferring Pharmaceuticals, Inc.

Meeting Objectives:

Request for information to clarify chemistry issues discovered in the description section of the label.

Background:

After review of the draft labeling faxed from the Sponsor, 8/17/99, Chemistry information was requested.

Discussion:

Question to the Sponsor: Does the drug product used in the clinical trials contain sodium phosphate and if so how does it differ from the current drug product?

Response: The current drug product contains sodium phosphate buffer (sodium phosphate tribase and phosphoric acid). This was approved in supplement to the ANDA on May 19, 1999. The clinical trials, FPI REP 97-01 and FPI REP 97-02, were conducted prior to approval of the sodium phosphate buffer containing drug product. The drug product used for the clinical trials did contain some sodium phosphate, however, the buffer method used to assure consistent pH was not utilized.

Action Items:

Sponsor will Fax by COB today:

1. A copy of the approval letter from the submission by which approval was granted for the change in the use of the phosphate buffer for Repronex
2. Supporting documentation that provides for bioavailability.
3. A desk copy of the submission relating to this issue.

/S/

~~Minutes Preparer: /Meeting Chair~~

cc:

Original NDA 21-047

HFD-580/Div. Files

HFD-580/Rarick/Slaughter/Rhee/Moore

Drafted by: Spell-LeSane August 25, 1999

Concurrences: Pauls for Rumble, 8.26.99

final: Spell-LeSane, 8.26.99

MEETING MINUTES

MINUTES of TELECONFERENCE

Date: August 3, 1999 **Time:** 11:30 – 11:50 AM **Location:** Parklawn; Dr. Rarick's Office

NDA: 21-047 **Drug Name:** Repronex (menotropins for injection, USP)

External Participant: Ferring Pharmaceuticals, Inc.

Type of Meeting: Internal policy discussion

FDA Lead: Dr. Lisa Rarick

External Participant Lead: Dr. Ronald V. Nardi

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

External Constituents:

Wayne Anderson CEO, Ferring

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

Background: This NDA is a 505(b)(2) which references the chemistry and pharmacology sections of the sponsor's approved ANDA. The ANDA referenced Pergonal as the innovator drug.

Meeting Objectives: To discuss the proposed labeling for NDA 20-047.

Discussion Points:

- the sponsor is seeking 3-year exclusivity for the subcutaneous route of administration
- except for the clinical trials section of the label, the current labeling retains the boilerplate from the referenced ANDA including the descriptions in the WARNINGS and PRECAUTIONS sections
- historical items have been supplemented with trial data
- the previous clinical trial sections would be deleted and replaced with the data from the clinical trials submitted in this application on the basis that the old data is dated with regards to the current standard of practice in infertility therapy
- the sponsor intends to later file a supplemental NDA for a purer product; this will contain appropriate chemistry information
- data from the innovator product may need to be deleted from the tables in the current labeling

Decisions reached:

- the clinical data that was submitted to this application appears to be sufficient to support both the IM and SC routes of administration in the labeling
- the instructions for usage should be revised to begin with 75 IU or 150 IU doses of Repronex with adjustment to higher doses during the treatment cycle

NDA 21-047

Minutes of Telecon – August 3, 1999

- *in vitro* fertilization (IVF) indication should recommend a dose of up to 225 IU Repronex in the **DOSAGE and ADMINISTRATION** section; this section should be revised to reflect the true data from the 186-patient study data
- the labeling text should specifically describe the patient population studied in the subcutaneous trial as down-regulated women
- when the labeling is revised to include data from the IM and SC routes of administration, the generic AB rating will not be retained
- the following sections should be revised: **Clinical Trials, INDICATIONS and USAGE, DOSAGE AND ADMINISTRATION**
- the male indication will not be included in the labeling

Action Items:

Item:	Responsible Person:	Due Date:
• submit revised labeling	Ferring Pharms.	2 days

Signature, minutes preparer

Concurrence, Chair

drafted: dm/August 11, 1999/NDA 21047TC72899.doc

cc:

NDA Arch:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/DMoore/TRumble/JLau/AParekh/LKammerman

HFD-580/AJordan

HFD-715/MNg

Concurrence:

TRumble 08.13.99

MEETING MINUTES

Date: August 3, 1999

Time: 9:00 – 10:30 AM

Location: Parklawn; Rm. 17-B43

NDA: 21-047

Drug Name: Repronex (menotropins for injection, USP)

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: Internal policy discussion

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (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., M.P.H. - Medical Officer, DRUDP (HFD-580)

Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Jeanine Best – Project Manager, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Moh-Jee Ng, Ph.D. – Statistician, Division of Biometrics II (DBII; HFD-715)

Barbara Stradling, Esq, General Attorney, General Counsel (GCF-1)

Don Hare – Consumer Safety Officer, Office of Generic Drugs (OGD; HFD-604)

Kim Duddleback, Esq, General Counsel (GCF-1)

Background: This NDA references the chemistry and pharmacology sections of the sponsor's approved ANDA which makes it a 505 (b) (2) application. The ANDA referenced Pergonal as the innovator drug.

Meeting Objectives: To discuss the regulatory aspects of the sponsor's labeling proposal for NDA 20-047.

Discussion Points:

- the original proposed intent for this submission was to add data from the clinical trials for the subcutaneous (SC) route of administration to the currently approved labeling for Repronex; the original labeling contained only data for the intramuscular (IM) route of administration; the sponsor has subsequently requested that the clinical data for the IM route of administration for Repronex submitted in this application replace the approved IM labeling from the ANDA which consisted of class labeling from the Pergonal label
- Patent
 - Pergonal has been approved for many years and the patent has probably expired

NDA 21-047

Minutes of Telecon – August 3, 1999

- if an NDA sponsor references an ANDA application, they must notify the innovator within 45 days for litigation if patents are not expired
- AB rating
 - if the labeling is changed, the application is no longer an ANDA; a suitability petition would be needed for the Orange book and the therapeutic route would not be given
 - a generic drug product cannot add a new route of administration to the same label without jeopardizing the AB status
- the new data for the intramuscular (IM) administration of Repronex, albeit small, is more current than the Pergonal data

Decisions reached:

- because this is a 505(b)(2) application, the sponsor must assert reference to Pergonal and certify that the patents are expired (see CFR 314.54)
- if the clinical data for IM and SC submitted to this application is deemed sufficient for approval, the new IM and SC data could be incorporated into the Repronex labeling; the B rating would be lost
- class labeling from the Pergonal label for safety could be retained in the labeling
- the referenced innovator drug (Pergonal) has only the IM route of administration; Repronex could therefore, be eligible for 3-years of exclusivity for the subcutaneous route of administration upon approval

Action Items:

Item:	Responsible Person:	Due Date:
• request patent certification from sponsor	Ms. Moore	1 week

Signature, minutes preparer

Concurrence, Chair

drafted: dm/August 11, 1999/NDA 21047TC72899.doc

cc:

NDA Arch:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/DMoore/TRumble/JLau/AParekh/LKammerman

HFD-580/JBest

GCF-1/BStradling/KDuddlebach

HFD-604/DHare

Concurrence:

TRumble, SSlaughter 08.13.99

DRAFT

MEETING MINUTES

Date: July 27, 1999

Time: 10:00 – 10:40 AM

Location: Parklawn; Rm. 17-B43

NDA: 21-047

Drug Name: Repronex (menotropins for injection, USP)

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: Labeling discussion

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (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., M.P.H. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Moh-Jee Ng, Ph.D. – Statistician, Division of Biometrics II (DBII; HFD-715)

M. Saito, Ph.D. - Fellow

Meeting Objectives: To discuss the status of the labeling for NDA 20-047.

Discussion Points:

- as a result of the Biopharmaceutics briefing, the Biopharmaceutics discipline has concerns regarding the linearity of the follicle stimulating hormone (FSH) PK data
- the most recent label was updated based on two patients who received the highest studied dose; the reviewers are working on obtaining the actual observed values
- revising the data in the IM label may be problematic; a separate subcutaneous label could be written as an alternative; a meeting with General counsel should help answer internal questions

Decisions reached:

- no covariates were detected with FSH PK parameters
- data generated from small numbers should be expressed as percentages
- the labeling should be submitted on electronic disc
- discuss changes in labeling further with General Counsel

Action Items:

- | Item: | Responsible Person: | Due Date: |
|--|----------------------------|------------------|
| • invite Don Hare from OGD to internal discussion with General Counsel | Ms. Moore | ASAP |
| • request electronic version of labeling from sponsor | Ms. Moore | 1-2 days |

Signature, minutes preparer

Concurrence, Chair

drafted: dm/August 11, 1999/NDA 21047TC72899.doc

cc:

NDA Arch:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/DMoore/TRumble/JLau/AParekh/LKammerman

HFD-580/MSaito

HFD-715/MNg

Concurrence:

TRumble, SSlaughter 08.13.99

MINUTES of TELECONFERENCE

Date: July 20, 1999 **Time:** 1:30 – 2:05 PM **Location:** Parklawn; Dr. Mann's Office

NDA: 21-047 **Drug Name:** Repronex (menotropins for injection, USP)

External Participant: Ferring Pharmaceuticals, Inc.

Type of Meeting: Labeling discussion

FDA Lead: Dr. Marianne Mann

External Participant Lead: Dr. Ronald V. Nardi

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (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., M.P.H. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Constituents:

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

Wayne Anderson - CEO, Ferring Pharmaceuticals, Inc.

Dennis Marshall, M.D. - Head of Medical Affairs

Michele Cobham - Manager of Scientific Information

Meeting Objectives: To discuss the clinical section of the labeling for NDA 20-047.

Discussion Points:

- the original application was submitted for a new (subcutaneous) route of administration
- the application for the subcutaneous route of administration was not filed for the male indication
- the original package insert was from the ANDA which referenced the clinical data from the innovator drug trials; subcutaneous administration data from the comparative trial was added
- one clinical study compared the Repronex IM and SC routes of administration and the Pergonal IM route of administration
- the sponsor is proposing to use the clinical data for the Repronex IM route of administration from the comparative trial in the labeling instead of clinical data derived from the comparator drug from the approved ANDA; general reference to the comparator data is preferred over specific data from the referenced innovator drug

Decisions reached:

- there should be a separate **DOSAGE AND ADMINISTRATION** section for each route of administration which recommends an optimal dose for each route of administration
- additional data from the literature data should be referenced for the IM route of administration

- the tables in the package insert should include data from the SC route of administration
- since the IM route of administration has been approved for the male indication, it is the sponsor's option whether to retain that section in the labeling, however, the subcutaneous route of administration should not include the male indication
- the agency will discuss regulatory aspects to determine whether the clinical trial data for the IM and SC routes of administration is adequate to support labeling different from the "class labeling" currently in the ANDA and convey answers to the sponsor
- the sponsor should submit their proposed labeling for review

Action Items:

Item:	Responsible Person:	Due Date:
• submit proposed labeling revisions	Ferring	1 week
• schedule internal meeting	Ms. Moore	1-2 days
• set up Telecon to discuss decision	Ms. Moore	1 week
• provide meeting minutes	Ms. Moore	1 month

Signature, minutes preparer

Concurrence, Chair

drafted: dm/August 11, 1999/NDA 21-047TC72099.doc

cc:

NDA Arch:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/RBennett/DMoore/TRumble/JLau/AParekh

Concurrence:

TRumble, SSlaughter 08.13.99

MINUTES of TELECONFERENCE

Date: July 14, 1999

Time: 1:00 – 1:50 PM

Location: Parklawn; 17B-45

NDA: 21-047

Drug Name: Repronex (menotropins for injection, USP)

External Participant: Ferring Pharmaceuticals, Inc.

Type of Meeting: Labeling

FDA Lead: Ms. Marianne Mann

External Participant Lead: Dr. Seymore Fine

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (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., M.P.H. - Medical Officer, DRUDP (HFD-580)

Diane Moore - 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)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

S. W. Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Constituents:

Seymore Fine, M.D. – Medical Director

Dennis Marshall, M.D. – Head of Medical Affairs

Michele Cobham – Manager of Scientific Information

Meeting Objectives: To convey revisions to be made in the labeling for NDA 20-047 in response to the June 1999 amendment to the NDA.

Discussion Points:

- the numbers are misleading when using patients who ovulated as the denominator rather than induction of pregnancies; subcutaneous (SC) administration and intramuscular (IM) administration should be 50%
- >1% multiple pregnancy rate was obtained with Pergonal (5 of 7)

Decisions reached:

- the indication for induction of ovulation should be separated from the IVF indication throughout the labeling
- DESCRIPTION section is acceptable as proposed

- **DOSAGE AND ADMINISTRATION** section
 - there should be a separate **DOSAGE AND ADMINISTRATION** section for each route of administration which refers to the site used in the respective clinical trials
 - the optimal dose for each route of administration should be recommended
 - the injection site should be stipulated because the SC and IM administration sites studied in the sponsor's study, "Meno 96/02/NL" and that of Dobbs et al, Fertility and Sterility, 1994, Vol. 62, pg 978) differ and result in conflicting observations; namely, FSH C_{max} and AUC are higher with SC than with IM (Meno 96/02/NL) and the published reference study found that FSH C_{max} and AUC are higher with IM than SC
 - a text statement is needed in the **DOSAGE AND ADMINISTRATION** section to describe that the dosage used in the study was 225 IU and that after five days it was individualized; data from the trials should be used
 - if a patient has not been down-regulated, the dosage for induction of ovulation should be 75-450 IU/day for 7-12 days; if a patient has been down-regulated, the starting dose should be 150 IU/day
- the **Drug-Drug interaction** subsection should be placed in the **CLINICAL PHARMACOLOGY** section
- the **Drug-Food** subsection does not apply to this drug product; a comment should be included that states that no drug-drug interaction studies have been conducted for Repronex
- the Biopharmaceutics reviewer has revised the single- and multiple-dose studies under the **PHARMACOKINETICS** section
- in Table 1, under PK parameter, the '___' should be '___' and '___' should be deleted
- the AUC units are incorrect in the table
- **Clinical Comments regarding labeling**
 - the IM administration information was based on the Pergonal studies; these should be retained in the labeling; the data for the subcutaneous route of administration is marginal
 - all references to men have been deleted and is acceptable; if it is to be retained, it must be specified that the information is for IM use only
 - the first paragraph under **CLINICAL STUDIES** subsection that begins, "Women: The results of . . ." should be retained
 - efficacy results should be based on ITT population; the total oocytes retrieved and mature oocytes retrieved for all three arms are not ITT; the figures should be corrected
 - standard deviations should be included in the tables
 - the parameters of the last two items (Pts w/Clinical Pregnancy and Pts w/Continuing Pregnancy) in the table entitled, "For Patients in IVF Protocol" should be in percentages
 - in the table entitled, "For Patients in Ovulation Induction Protocol (One cycle of treatment)", the parameter entitled, "Received hCG(%)" under "Repronex IM" that reads ___ should read, ___
- the following items should be added to the second table (Ovulation Induction Protocol)
 - number aborted
 - number of multiple pregnancies of three or more
 - number of twins conceived
 - incidence of hyperstimulation syndrome
- the response to the FDA request for information regarding multiple births for ovulation induction trial has been reviewed and the information is incorrect; multiple gestation rates are based on the number of deliveries or pregnancies; rates should be shown as ratios for both trials
- the original wording for congenital abnormalities from the Pergonal labeling should be retained; the statement, "no reports of congenital abnormalities" should be deleted

MINUTES of TELECONFERENCE

Date: July 6, 1999

Time: 11:30 AM– 12:00 PM

Location: Parklawn; 17B-45

NDA: 21-047

Drug Name: Repronex (menotropins for injection, USP)

External Participant: Ferring Pharmaceuticals, Inc.

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

FDA Lead: Dr. Ameeta Parekh

External Participant Lead: Dr. Ronald V. Nardi

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

S. W. Johnny Lau, R. Ph., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Michael Fossler, Pharm. D., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DMEDP (HFD-510)

External Constituents:

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

Seymore Fine, M.D. – Medical Director

Dennis Marshall, M.D. – Head of Medical Affairs

Ed Purich, Ph.D. – Consultant

Meeting Objectives: To convey comments regarding the proposed labeling for NDA 20-047 from the Clinical, Clinical Pharmacology and Biopharmaceutics review disciplines.

Discussion Points:

- the Agency has reviewed the data for the population pharmacokinetics analyses of study FPI REP 97-01
- an effect on pharmacokinetics by demographic variables was not demonstrated by the data from study Meno 96/02/NL
- the PK data from the IM and subcutaneous arms are contradictory and the effects are not clinically relevant

Decisions reached:

- the population analysis regarding the covariates described in the labeling are not adequate and should be deleted
- the labeling should reflect the lack of covariates associated with pharmacokinetics of menotropins (or FSH, to be more specific)
- the Division will send a copy of proposed revisions to the **CLINICAL PHARMACOLOGY** section to the sponsor via telefacsimile

Meeting Minutes

Date: June 18, 1999

Time: 11:30 AM - 12:50 PM

Place: Parklawn; Rm. 17B-43

NDA: 21-047

Drug Name: Repronex (menotropins)

Indications: 1) induction of ovulation and pregnancy, and
2) stimulation of the development of multiple follicles for *in vitro* fertilization in women who are ovulating.

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: Labeling

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:

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)

Gerald Willett, M.D. – Medical Officer, DRUDP (HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

S. W. Johnny Lau, R.Ph., Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Moh-Jee Ng, Ph.D. – Statistician, Division of Biometrics II (DBII; HFD-715)

Meeting Objective:

To discuss the proposed labeling for NDA 21-047, dated June 16, 1999.

Background: This NDA is being submitted to obtain a new subcutaneous (SC) route of administration. It was filed for the female indications only. The 10-month goal date is August 28, 1999.

Discussion Items:

- **Chemistry and Manufacturing**
 - the **DESCRIPTION** section should include how the standardization of the bioactivities of LH and FSH are obtained; the historical topic will be discussed internally by the chemists to determine whether the labeling statement should be revised
- **Clinical Pharmacology and Biopharmaceutics**
 - the analysis of the population pharmacokinetics (PK) has been completed; this analysis indicates that the FSH data is too contradictory to be included in the labeling; all label references should be deleted
 - the **Absorption, Distribution, Metabolism, Excretion (ADME)** sections should be revised to indicate that the respective studies have not been performed

Decisions Reached:

• **CLINICAL PHARMACOLOGY** section

- the heading for the first paragraph should be **Pharmacodynamics**; the first paragraph may be retained
- the second paragraph should be **Pharmacokinetics**
- all label references should be deleted
- Table 1 entitled, _____

_____ should be deleted; a new table will be proposed by the

Pharmacokinetic reviewer

- the **CLINICAL PHARMACOLOGY** section will be revised by the Biopharmaceutics reviewer to include to the European single-dose study data; the ADME sections will also be revised
- a teleconference is scheduled with the sponsor to convey the population pharmacokinetics findings
- **Clinical Studies** subsection
 - a description of the studies is needed
 - the patient numbers do not agree with the numbers in the NDA for the intent-to-treat (ITT) population; only primary responders are listed in the clinical studies section
 - standard deviations should be included in the tables
 - the parameters of the last two items (Patients w/Clinical Pregnancy and Patients with/Continuing Pregnancy) in the table entitled, "For Patients in IVF Protocol" should be in percentages
 - in the table entitled, "For Patients in Ovulation Induction Protocol (One cycle of treatment)", the parameter entitled, "Received hCG(%)" under "Repronex IM" that reads ' _____' should read, _____
 - the following items should be added to the second table (Ovulation Induction Protocol)
 - number aborted
 - number multiple pregnancies of three or more
 - number of twins conceived
 - incidence of hyperstimulation syndrome
- **DRUG-DRUG INTERACTIONS** section
 - a comparison of the drug-drug interactions between Gonal F or Follistim with this menotropin could be included
- **WARNINGS** section
 - references should be included in the discussion under **Overstimulation of the Ovary During Repronex™ Therapy** subsection
 - **Multiple Births** subsection
 - the numbers should be verified from the clinical trials data
 - **Hypersensitivity/Anaphylactic Reactions** subsection
 - the hypersensitivity reactions should be verified by the sponsor
- **PRECAUTIONS** section
 - **Laboratory Tests** subsection
 - in the first sentence that begins, "In most instances, . . ." the term, _____ should be replaced with the term, _____
- **ADVERSE REACTIONS** section
 - in the section following item number 12 that begins, "The following medical events . . ." item number 2, entitled, _____ should be deleted and the previous labeling from the Pergonal labeling should be retained

Meeting Minutes – June 18, 1999

- the numbers in the Adverse Event table should include results from both studies 97-01 and 97-02; only numbers from 97-02 are currently included
- **DOSAGE AND ADMINISTRATION** section
 - the dosage should be revised in accordance to the data from the clinical trials; different regimens should be delineated according to:
 - patients who are down-regulated with agonists
 - IVF patients
 - ovulation reduction patients

Action Items:

Item	Responsible Party	Due Date
• discuss gonadotropin standardization	Drs. Rhee and Haber	July 8, 1999
• convey Biopharmaceutics revisions to sponsor in telecon	Drs. Lau and Parekh	July 6, 1999
• verify numbers of multiple births for different arms in the clinical trial	Dr. Bennett	July 8, 1999

 IS/ *8/9/99*
Signature, recorder

 IS/
Signature, Chair

8/9/99

Note: The above action items were completed on July 6, 1999.

drafted: dm/07.16.99/N21047LM61899.doc

Concurrence:

TRumble 07.20.99/MNg 08.03.99/RBennett 08.03.99/SSlaughter 08.04.99/JLau 08.06.99

Concurrence not received from GWillett/LKammerman

cc:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/SAllen/RBennett/MRhee/AJordan

HFD-580/LKammerman/MNg/JLau/AParekh/DMoore/TRumble

HFD-510/MHaber

Meeting Minutes

Date: June 9, 1999 **Time:** 2:30 - 3:00 PM **Place:** Parklawn; Rm. 17B-43

NDA: 21-047 **Drug Name:** Repronex (menotropins)

Indications: 1) induction of ovulation and pregnancy, and
2) stimulation of the development of multiple follicles for *in vitro* fertilization in women who are ovulating.

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: 8-month Status

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Shelley Slaughter, M.D., Ph.D. - Team Leader, DRUDP (HFD-580)

Ridgely Bennett, M.D. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader ONDC @ DRUDP (HFD-580)

Martin Haber, Ph.D. - Chemist, ONDC @ Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)

S. W. Johnny Lau, R. Ph., Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective:

To discuss the status of reviews for NDA 21-047.

Background: This NDA is being submitted to obtain a new subcutaneous (SC) route of administration. It was filed for the female indications only. The 10-month goal date is August 28, 1999.

Discussion Items:

- **Clinical**
 - review ongoing
- **Chemistry**
 - review almost complete
 - final manufacturing inspection report is pending
 - the drug substance manufacturing audit report is unknown; apparently previous problems have been addressed
 - LNC has not responded to the tradename issue of whether the same name can be used for a NDA and a generic at the same time; no law prohibits the use of the same tradename for both

cc:

HFD-580

HFD-580/LRarick/MMann/SSlaughter/SAllen/RBennett/MRhee/AJordan

HFD-580/LKammerman/MNg/JLau/AParekh/DMoore/TRumble/LPauls

HFD-510/MHaber

Div

Meeting Minutes

Date: May 17, 1999

Time: 1:00 - 1:20 PM

Place: Parklawn; Rm. 17B-43

NDA: 21-047

Drug Name: Repronex (menotropins)

Indications: 1) induction of ovulation and pregnancy, and
2) stimulation of the development of multiple follicles for *in vitro* fertilization in women who are ovulating.

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: 7-month Status

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Ridgely Bennett, M.D. - Medical Officer, DRUDP (HFD-580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

Moo-Jhong-Rhee, Ph.D. - Chemistry Team Leader ONDC @ DRUDP (HFD-580)

Martin Haber, Ph.D. - Chemist, ONDC @ Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)

S. W. Johnny Lau, R. Ph., Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II (DBII; HFD-715)

Meeting Objective:

To discuss the status of reviews for NDA 21-047.

Background: This NDA is being submitted to obtain a new subcutaneous (SC) route of administration. It was filed for the female indications only. The 10-month goal date is August 28, 1999.

Decisions Reached:

- Clinical
 - review pending; completion is targeted for July 15, 1999
- DSI
 - reports pending
- Chemistry/Regulatory
 - review pending; review completion targeted for late May, 1999
 - EER inspection reports pending
 - the trademark "Repronex" was submitted to the LNC for review; review pending
- Microbiology
 - ANDA data is referenced for this NDA; Microbiology review is not necessary

Ms. E

Teleconference Minutes

Date: May 14, 1999

Time: 2:45 p.m.

Location: Parklawn; Rm. 17B-45

NDA: 21-047

Drug: Repronex (Menotropins/Inj)

Indication: Induction of ovulation and pregnancy

Sponsor: Ferring Pharmaceuticals

Type of Meeting: Information Request

Meeting Chair: Ameeta Parekh, Ph.D.

External Lead: Dr. Nardi, Ph.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB DPE II; HFD-870) @ DRUDP (HFD-580)

S.W. Johnny Lau, R.Ph., Ph.D. Pharmacokinetic Reviewer, OCPB (HFD-870) @ DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Ronald V. Nardi, Ph.D., Ferring Pharmaceuticals

Meeting Objective: To discuss outstanding Biopharmaceutical data

Background:

Dr. Nardi requested a teleconference to discuss the assay method validation report submitted May 11, 1999. The information was provided by the [redacted] and Dr Nardi wanted to confirm that the information was satisfactory.

Discussion:

The submitted assay method validation reports concerning FSH and LH were reviewed by the Clinical Pharmacology and Biopharmaceutics Reviewer; the information that remains outstanding is as follows:

1. The corresponding QC samples that were run with the unknown samples should be provided.
2. Raw data for samples that resulted in plasma FSH and LH concentrations should be provided.

Unresolved decisions: None

NDA 21-047

Teleconference minutes 5/14/99

Page2

Action Items:

- the sponsor will submit requested information to the FDA within 2 weeks
- minutes will be exchanged with the sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

cc:

Original NDA 21047

HFD-580/DivFile

HFD-580/DMoore/TRumble/

HFD-580/LRarick/SSlaughter/SAllan/Jordan/Parekh/JLau

drafted: dsl, 6.2.99

concurrence: Rumble,6.3.99/Lau,6.9.99/Parekh,6.11.99/

final: 6.14.99

TELECONFERENCE MINUTES

Meeting Minutes

Date: April 27, 1999 **Time:** 10:00 - 10:30 AM **Place:** Parklawn; Rm. 17B-43

NDA: 21-047 **Drug Name:** Repronex (menotropins)

Indications: 1) induction of ovulation and pregnancy and
2) stimulation of the development of multiple follicles for *in vitro* fertilization in women who are ovulating

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: 6-month Status

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Susan Allen, M.D. – Acting Team Leader DRUDP (HFD-580)

Ridgely Bennett, M.D. - Medical Officer, DRUDP (HFD-580)

Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)

Terri Rumble - Chief, Project Management Staff, DRUDP (HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader ONDC @ DRUDP (HFD-580)

Martin Haber, Ph.D. - Chemist, ONDC @ Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)

Johnny Lau, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Moh-Jee Ng, Ph.D. – Statistician, Division of Biometrics II (DBII; HFD-715)

Meeting Objective:

To discuss the status of reviews for NDA 21-047.

Background: This NDA is being submitted to obtain a new subcutaneous (SQ) route of administration. It was filed for the female indications only.

Decisions Reached:

- **Clinical**
 - review pending; a major amendment was submitted on March 24, 1999, which contained the safety update and the final results of the ovulation induction study; review completion is targeted for July 15, 1999
- **Chemistry/Regulatory**
 - review pending; review completion targeted for early May, 1999
 - two EER inspection sites have been requested; inspection reports are pending

MINUTES of TELECONFERENCE

Date: April 13, 1999 **Time:** 9:20 – 9:40 AM **Location:** Parklawn; Ms. Moore's Office

NDA: 21-047 **Drug Name:** Repronex (menotropins for injection, USP)

External Participant: Ferring Pharmaceuticals, Inc.

Type of Meeting: Information Request, Clinical Pharmacology and Biopharmaceutics

FDA Lead: Dr. S. W. Johnny Lau **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)

S. W. Johnny Lau, R. Ph., Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Constituents:

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

Mischele Cobham – Manager of Scientific Information

Meeting Objectives: To request information to assist in the review of NDA 20-047 from the Clinical, Biometrics and Clinical Pharmacology and Biopharmaceutics review disciplines.

Discussion Points:

- the preliminary population pharmacokinetics (pop PK) information package (CD-ROM and paper copy) sent in February 1999, was indeed the final pop PK analysis; the information package sent in March 1999, contained the complete PK analysis with only slight changes in pagination from the February submission
- Dr. Ed Purick performed the pop PK analyses for the sponsor
- some patient data should not have been included in the PK analysis because the samples were hemolyzed; this caused aberrant values which were included in the preliminary reports; these results give a confusing picture of the PK analysis; the sponsor proposes to reanalyze the data once agreement is reached with the FDA as to which data is reasonable to exclude
- no blood samples were taken after the fifth day on Repronex or Pergonal for FSH and LH determinations
- FPI REP 97-01 study provides single-dose and multiple-dose FSH and LH PK data for 150 IU qd Repronex IM and SC for 5 days; study Meno 96/02 provides single-dose FSH PK data for 300IU qd Repronex IM and SC; however, FPI REP 97-01 study has patients receiving 450 IU qd Repronex IM and SC; any FSH and LH PK data for 450 IU qd Repronex IM and SC should be provided, otherwise, provide all available published literature data to support FSH and LH PK for 450 IU qd Repronex IM and SC

- five patients in study FPI REP 97-01 received 450 IU on the first day of dosing; this dose was found to be unacceptable because it was too stimulatory to the patients; two patients had to be discontinued; the dose for the first day was reduced to a level consistent for the first five days
- a few patients were dosed as high as 450 IU after the fifth day of Repronex administration; the sponsor will send a copy of the clinical report and flag the patient numbers and PK information
- **Decisions reached:** The following volumes were requested from the sponsor:

Clinical

- Volume 1.1
- individual study reports for the pivotal studies
- statistical appendix for the pivotal studies

Biometrics

- Volumes 1.1, 1A, 2.1, 2A, 4.1, 4A, 8A, 8H, 8H1, 9.1, 9A, 10C, 10D, 10E, 10F, 10G, 10H, 10I

Clinical Pharmacology and Biopharmaceutics

- full bioanalytical report for FSH, LH, and E₂ including assay validation reports
- the dose of drug administered and the route of administration
- the brand name and lot (number) of leuprolide injection
- lot (number) of Repronex used for IM and SC injections
- the dose, brand name, and lot (number) of hCG injection
- Final protocol of the study and a list of protocol deviations in the study
- Name and sites of investigators
- final copy of the clinical report flagging patients who received 450 IU of menotropins at Day 1 and Day 5

Action Items:

- | Item: | Responsible Person: | Due Date: |
|----------------------------|----------------------------|------------------|
| • submit requested volumes | Ferring Pharmaceuticals | 1-2 weeks |

JSI
Signature, minutes preparer

4/27/99

JSI 4/27/99
Concurrence, Chair

drafted: dm/April 19, 1999/NDA 21-047TC41399.doc

cc:

NDA Arch:

HFD-580.

HFD-580/LRarick/MMann/SSlaughter/SAllen/DMoore/TRumble/JLau/AParekh/MNg/LKammerman

Concurrences:

TRumble 04.21.99/JLau 04.22.99

Moore

Meeting Minutes

Date: December 10, 1998 **Time:** 10:00 - 10:30 AM **Place:** Parklawn; Rm. 17B-43

NDA: 21-047 **Drug Name:** Repronex (menotropins)

Indication: induction of ovulation for *in vitro* fertilization

External Participant: Ferring Pharmaceuticals, Inc.

Type of Meeting: Advice

FDA Lead: Dr. Lisa Rarick

External Participant Lead: Dr. Nardi

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

External Participant:

Ronald Nardi, Ph.D. - President, Scientific and Regulatory Affairs

Meeting Objective:

To discuss the submitted indications and request additional information before filing NDA 21-047.

Discussion Items:

- **Clinical**
 - a list of the investigators and the clinical sites was requested; a copy has been sent to the Project Manager
 - the indication in males should be justified; otherwise, reference to the male indication should be deleted from the labeling
- **Biometrics**
 - a desk copy of the study protocol for the IVF indication was sent to the Project Manager
- **Clinical Pharmacology and Biopharmaceutics**
 - pharmacodynamic (PD) endpoints should be made for all patient populations

Decisions Reached:

- **Clinical:**
 - because the necessary studies are not included for the male indication, only the female indication will be included in the filing for this NDA
- **Chemistry & Manufacturing and Quality Control**
 - a list of the Manufacturing sites should be provided
- **Biometrics**
 - a summary of results by center should be submitted
 - a subgroup analyses by ethnicity should be provided
 - SAS diskettes should be provided

Meeting Minutes

Date: December 7, 1998 **Time:** 10:00 - 10:30 AM **Place:** Parklawn; Rm. 17B-43

NDA: 21-047 **Drug Name:** Repronex (menotropins)

Indications:

In females:

induction of ovulation and pregnancy
stimulation of the development of multiple follicles for *in vitro* fertilization in women who are ovulating

In males:

stimulation of spermatogenesis in men with primary or secondary hypogonadotropic hypogonadism

Sponsor: Ferring Pharmaceuticals, Inc.

Type of Meeting: Filing

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Mrs. Diane Moore

FDA Participants:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)

Shelley Slaughter, M.D., Ph.D. - Acting Team Leader DRUDP (HFD-580)

Ridgley Bennett, M.D. - Medical Officer, DRUDP (HFD-580)

Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)

Terri Rumble - Project Manager, DRUDP (HFD-580)

Diane Moore - Project Manager, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader ONDC @ DRUDP (HFD-580)

Martin Haber, Ph.D. - Chemist, ONDC @ Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Johnny Lau, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-40)

Meeting Objective:

To discuss the fileability of NDA 21-047 for induction of ovulation and pregnancy and *in vitro* fertilization in women and stimulation of spermatogenesis in men with hypogonadotropic hypogonadism (HH).

Background: Repronex has an approved ANDA with an intramuscular (IM) injection route of administration for the same indication; this NDA is being submitted to obtain a new subcutaneous (SQ) route of administration.

Discussion Items:

- **Clinical**
 - Ferring has an ongoing clinical study in women for induction of ovulation which is expected to be completed in February 1999; all patients have been enrolled
- **Clinical Pharmacology and Biopharmaceutics**
 - a single dose bioavailability study was performed comparing SC Menogen® to IM Menogen® in healthy female subjects
 - in a multiple dose study comparing the single dose and steady-state pharmacokinetics of SC Repronex™ to IM Repronex™ and IM Pergonal® in oligoovulatory infertile patients
 - the sponsor plans to submit results from the ongoing pharmacokinetic study in females by the first of next year (49 of 54 patients have been enrolled); interim results on 20 subjects have been presented
 - assay validation for the PK study and analytical methods for the partial data from the PK study should be provided
 - a pharmacodynamic (PD) study is being conducted
 - PK/PD studies in males are required to support the male indication
 - absorption differences are expected between the IM and SQ routes of administration
- **Chemistry/Regulatory**
 - the NDA references an approved ANDA from Ferring which reference Pergonal by Serono; an injunction was placed on the ANDA through the District Court; the decision was appealed to the Appellate court which ruled in favor of the FDA and Ferring; the injunction has been remanded to District Court; at this time, the ANDA is clear; therefore, the ANDA can be referenced for the chemistry information
 - new EER will be forwarded to the Office of Compliance
 - the trademark "Repronex" will be sent to the LNC
- **Biometrics**
 - the statistical section does not contain a study protocol for either the IVF or the spermatogenesis indication
 - for the ART indication, the sponsor has submitted a single study while noting that another controlled study is ongoing; it should be determined whether the single study is sufficient for approval or if the results from the other study are needed
 - the statistical section does not contain a summary of results by center; the number of centers included in the study is not stated
 - a subgroup analysis by race was not performed
 - SAS diskettes should be provided

Decisions Reached:

- **Clinical:**
 - Fileable
 - because the necessary studies are not included for the male indication, only the female indication will be fileable
- **Chemistry & Manufacturing and Quality Control**
 - Fileable; the NDA references Ferring's approved ANDA

MEETING MINUTES

Date: March 10, 1998

Time: 1:30 - 3:00 PM

Location: C/R "N"

IND:

Drug Name: Repronex

External Participant: Ferring Pharmaceuticals

Type of Meeting: Pre-NDA

Meeting Chair: Lisa Rarick, M.D.

External Participant Lead: Ronald V. Nardi, Ph.D.

Meeting Recorder: Alvis Dunson

FDA Attendees:

Lisa Rarick, M.D., Director, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Shelley Slaughter, M.D., Ph.D. - Medical Officer, DRUDP (HFD-580)

Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP
(HFD-580)

Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II
(DNDC II) @ DRUDP (HFD-580)

Martin Haber, Ph.D. - Chemist, (DNDC II) @ Division of Metabolism and Endocrine Drug Products,
DMEDP (HFD-510)

Alex Jordan, Ph.D. - Pharmacologist, DRUDP (HFD-580)

K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation II
(DPE II) @ DRUDP (HFD-580)

Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituents:

Joseph T. Curti, M.D. - President and CEO

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

Seymour Fein, M.D. - Executive Medical Director

Michael Zudiker, Ph.D. - Executive Director, Manufacturing Operations

Jules Mitchel, Ph.D. - President, Target Health

Ralph D'Agostino, Jr., Ph.D. - Assistant Professor, Biostatistics, Wake Forest - Bowman Gray School of
Medicine

Meeting Objectives:

To discuss a planned NDA submission for the use of Repronex administered subcutaneously.

Background:

Repronex is a purified preparation of gonadotropins extracted from the urine of postmenopausal women containing equal amounts of FSH and LH. The name for this product was originally Repronal. On July 3, 1996, Lederle Laboratories transferred ownership of ANDA 73-598 (menotropins) to Ferring Pharmaceuticals, Inc. Upon approval of the ANDA, Ferring began commercial production of menotropins at the Lederle plant in Puerto Rico.

Repronex is approved for induction of ovulation and for I.V.F. when administered by the I.M. route. The purpose of this IND is to use the standard dose regimens for the clinical indications already approved, but by the S.C. route. I.M. injections of menotropins can be painful and inconvenient and S.C. administration may provide a more convenient and better tolerated treatment than I.M. administration with comparable efficacy.

Discussion Points:

The following sponsor issues were addressed:

- Q1. We believe that the protocols represent two adequate and well-controlled trials to evaluate the efficacy and safety of the subcutaneous route of administration.
- A1. A protocol amendment should be submitted clarifying the primary endpoint which should include a discussion of the clinical meaningful difference and a discussion of sample size calculations. The primary endpoint for the induction of ovulation study should be the ovulation rate. The primary endpoints for IVF study should be the number of oocytes recovered and number of mature oocytes.
- Q2. We believe that the planned analysis of the efficacy and safety variables identified in the protocols will permit a determination of the efficacy and safety of this additional route of administration.
- A2. An intent-to-treat analysis (ITT) should be done on all patients including those patients that did not receive therapy. The ITT analysis should include all patients randomized.
- Q3. We believe that the planned pharmacokinetic assessments will provide an adequate description of the pharmacokinetics of this new route of administration.
- A3. The pharmacokinetics plan appears adequate since the study is not intended to show bioequivalence between the I.M. and S.C. routes of administration
- Q4. We believe that CMC and preclinical studies will not be needed for this submission except to reference the approved ANDA.

A4. CMC and preclinical information can be referenced from the approved ANDA as long as the ANDA is with the Agency. All changes made in the ANDA should also be submitted to the NDA through annual reporting, if approved.

- the NDA is planned for submission in July/Aug 1998

Additional discussions centered around the sponsor's plan to submit two new IND's for the urofollitropin product:

- the first IND will be to develop a urinary FSH product for stimulation of follicular development and induction of ovulation
- the drug is expected to be obtained from
- it is acceptable for preclinical data to be referenced from the planned subcutaneous Repronex NDA submission
- the second IND will be to develop a highly purified FSH product; the sponsor believes this product could be filed as a chemistry, manufacturing, and controls (CMC) supplement since they regard this as a purer, improved version of the urinary FSH
- an NDA should be submitted for the highly purified FSH product since this does not appear to be a simple CMC change and clinical studies will be required

Unresolved Issues: None

Action Items:

Item:	Responsible Person:	Due Date:
• submission of a protocol amendment clarifying the primary endpoint to include a discussion of the clinical meaningful difference and a discussion of power calculations	Ferring	?

1. 3. Debarment Statement

Debarment Certification

Ferring Pharmaceuticals Inc. Hereby certifies that it 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 this application.



Ronald V. Nardi, PhD.

Vice President, Regulatory and Scientific Affairs

**14. A PATENT CERTIFICATION WITH RESPECT TO ANY
PATENT WHICH CLAIMS THE DRUG (21 U.S.C. 355 (B) (2) OR (J)
(2) (A))**

In the opinion and to the best knowledge of Ferring Pharmaceuticals, Inc. there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Specifically, other menotropin products approved in the United States are not protected by any patents per the Orange Book. Consequently, Repronex does not infringe on any patents.

*Wayne C. Anderson for
Ron Nardi*

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