CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 4/25/01	**DUE DATE:** 5/25/01	**OPDRA CONSULT:** 01-0092

TO:

Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Dornette Spell-LeSane
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

PRODUCT NAME:	**MANUFACTURER:** Ferring Pharmaceutical Inc.
Bravelle (Purified Urofollitropin for Injection, USP) 75 International Units (IU) **NDA #:** 21-289	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name "Bravelle" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:
OPDRA has no objection to the use of the proprietary name, "Bravelle". See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☒ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approval of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3242
Fax: 301-480-8173

/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 23, 2001

NDA NUMBER: 21-289

NAME OF DRUG: Bravelle (Purified Urofollitropin for Injection), 75 International Units (IU)

NDA HOLDER: 21-289

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the tradename "Bravelle". "Bravelle" is the second name the sponsor submitted to the Agency since the sponsor's prior submitted tradename, ' ——— was unacceptable to OPDRA (see OPDRA consult #00-0326).

PRODUCT INFORMATION

"Bravelle" is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. In conjunction with human chorionic ganadotropin (hCG), "Bravelle" is indicated for multiple follicular development (controlled ovarian stimulation) and ovulation induction in patients who have previously received pituitary suppression. In order to stimulate the development of ovarian follicles, the dose of "Bravelle" must be individualized for each patient. The recommended initial dose for infertile patients with oligo-anovulation is 150 IU daily for the first 5 days of treatment. The recommended dose for patients who are undergoing assisted reproductive technologies is 225 IU. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of "Bravelle" should not exceed 450 IU, and, in most cases, dosing beyond 12 days is not recommended. "Bravelle" will be available in packages containing 5 and 100 vials each of purified urofollitropin for injection in addition to sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "Bravelle" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Bravelle". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with "Bravelle". These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1

Product Name	Dosing (or active ingredient)		Other
Bravelle	[redacted]	[redacted]	[redacted]
Vivelle	Estradiol (Hormone – Rx) Transdermal: 0.025 mg/24 hr, 0.0375 mg /24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr, 0.1 mg/24 hr.	Apply patch (0.025 mg – 0.05 mg/24 hr) to skin twice a week.	S/A, L/A per OPDRA
Provol	*Pygeum africanum* (Dietary Supplement – OTC) Capsule: 50 mg	One capsule twice a day.	S/A per OPDRA
Brevital Sodium	Methohexital Sodium (Barbiturate, General Anesthetic – Rx) Powder for Injection: 500 mg, 2.5 g, 5 g	*Induction:* 1-1.5 mg/kg (1% solution at 1 mL/5 seconds).	S/A, L/A per OPDRA
Brevoxyl	Benzoyl Peroxide (Anti-Infective – Rx) Gel and Cleansing Lotion: 4% and 8%	Apply once or twice a day.	S/A per OPDRA
		*Frequently used, not all-inclusive	**S/A(Sound-alike), L/A (Look-alike

B. PRESCRIPTION ANALYSIS STUDIES

[5] WWW location http://www.uspto.gov/tmdb/index.html.

1. Methodology:

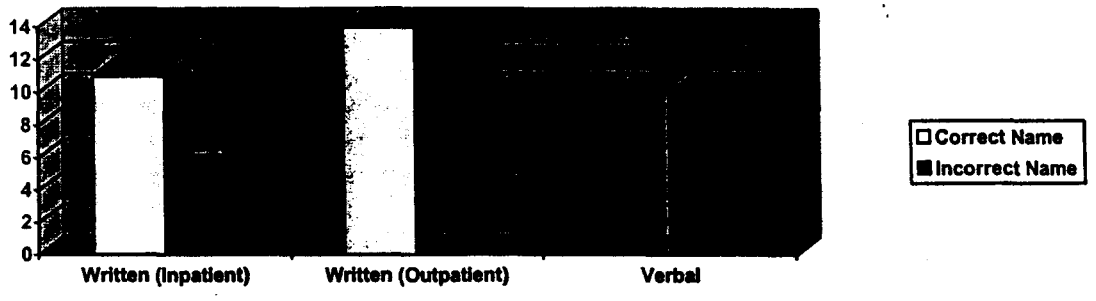
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Bravelle" and with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 85 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient prescription and one outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for "Bravelle" (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
"Bravelle"	
Inpatient: Bravelle 150 IU SQ daily x 5 days #10	*Outpatient:* Bravelle, 150 IU sub-Q, once a day for 5 days, #10.
Outpatient: Bravelle 150 IU SQ QD x 5 days #10	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Bravelle"	Incorrectly Interpreted
Written: Inpatient	28	16 (57%)	11 (69%)	5 (31%)
Outpatient	27	14 (52%)	14 (100%)	0 (0%)
Verbal: Outpatient	30	10 (33%)	0 (0%)	10 (100%)
Total	85	40 (47%)	25 (62%)	15 (38%)



Among the written inpatient prescriptions, 5 (31%) out of 16 respondents interpreted "Bravelle" incorrectly. Interpretations included *Bramile, Bavelle, Branlle,* and *Branke.*

Among the written outpatient prescriptions, all of the 14 respondents (100%) interpreted "Bravelle" correctly. However, one respondent commented that the proprietary name "Bravelle" sounds like an oral contraceptive medication.

Among the verbal outpatient prescriptions, all of the 10 respondents (100%) interpreted "Bravelle" incorrectly. Interpretations included *Bervel, Brevel, Brevelle, Burvel, Broval, Brovel,* and *Brovell.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Bravelle", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names that sound and look similar to "Bravelle" include *Brevoxyl, Brevital, Provol,* and *Vivelle.*

Brevoxyl is a topical anti-infective indicated for mild to moderate acne vulgaris. *Brevoxyl* and "Bravelle" sound similar to each other since "brev" and "brav" sound alike and both proprietary names end with an "l" sound. However, *Brevoxyl* contains three syllables while "Bravelle" only has two, and *Brevoxyl* can be distinguished from "Bravelle" by the sound of its "x". The dosage forms between "Bravelle" and *Brevoxyl* are different (injection vs. gel and lotion) as well as the strengths (75 IU vs. 4% and 8%) and the directions of use (SQ or IM daily vs. Apply to skin once or twice a day). These differences would lower the potential risk of a medication error between these two products.

Brevital Sodium is a barbiturate, which is used as a general anesthetic. *Brevital* may slightly resemble "Bravelle" in writing depending on how the proprietary name is scripted. *Brevital* and "Bravelle" also sound similar since the sounds "brev" and "brav" sound alike and both appear at the beginning of the two proprietary names. In the verbal portion of the OPDRA study, some respondents interpreted the "brav" in "Bravelle" as "brev" (*Brevelle, Brevel*). Also, the "elle" in "Bravelle" can be interpreted as "al", which can be seen in the verbal portion of the OPDRA study (*Broval*). However, *Brevital* may be distinguished from "Bravelle" by the sound of the "t" in *Brevital*. Both drug products are available as powder for injection; however, *Brevital* is available in three strengths (500 mg, 2.5 g, and 5 g) while "Bravelle" is only available in one strength with a different type of measuring units (75 International Units) though 75 IU may be interpreted as *Brevital* 75 mg IV. The settings where the two drug products are dispensed may be different. "Bravelle" may mainly be dispensed by a community pharmacy since the patient can self-administer the drug. *Brevital* is usually dispensed by a hospital pharmacy since general anesthesia is generally used in a hospital setting. Due to the slight differences in the two proprietary names when scripted and pronounced verbally and the different settings where the products are available, the potential risk of medication errors occurring is decreased.

Provol is considered a nutraceutical dietary supplement that claims to help maintain a healthy prostate. *Provol* does sound similar to "Bravelle". Some respondents in verbal portion of the OPDRA study interpreted "Bravelle" as *Broval, Brovel, and Brovell,* which are very similar to *Provol.* However, there are many differences between the two products that may decrease the potential risk of a medication error from occurring. *Provol* is available in a 50-mg capsule while "Bravelle" is available as a 75 International Units injectable. The dosage forms, route of administration, and the strengths are different. Also, *Provol* is recommended to be taken twice a day while "Bravelle" is given once a day. "Bravelle" is available by prescription only while *Provol* is available over-the-counter.

Vivelle is a transdermal estrogen patch indicated for moderate-to-severe vasomotor symptoms associated with menopause, female hypogonadism, female castration, primary ovarian failure, atrophic conditions caused by deficient endogenous estrogen production, atrophic urethritis, prevention of osteoporosis, abnormal uterine bleeding due to hormonal imbalance in the absence

of organic pathology and only when associated with a hypoplastic or atrophic endometrium. *Vivelle* and "Bravelle" look and sound similar mainly due to the "velle" ending on both proprietary names. Both proprietary names also contain two syllables. However, if "Bravelle" was mistaken for *Vivelle*, a strength or rate of release would have to be indicated on the prescription since *Vivelle* is available in multiple strengths or rates of release. "Bravelle" and *Vivelle's* dosage forms are different (injection vs. transdermal patch) as well as the route of administration (parenteral vs. topical) and directions of use (once a day vs. twice a week). Due to these differences, the potential risk of medication errors occurring between these two products is low.

OPDRA has no objections to the use of the proprietary name "Bravelle".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

General Comment

The proprietary name is stated as "Bravelle 75 IU". Please revise it to state "[illegible]" since the IU can be misinterpreted as IV (intravenous).

A. CONTAINER LABEL

1. See General Comment above.

2. The print on the NDC number is too small to read. Please use a larger font size for the NDC number.

B. CARTON LABELING (5 and 100 vials)

1. See General Comment above.

2. As per OPDRA consult #00-0326, the reconstitution instructions "Reconstitute with *1 to 2 mL* of 0.9% Sodium Chloride Injection, USP" is too vague since the exact amount of sodium chloride is not provided. The instructions should state the exact amount of Sodium Chloride that needs to be added to the drug for subcutaneous and intramuscular administration:

   For subcutaneous injection, reconstitute with ... mL of 0.9% Sodium Chloride Injection, USP.

   For intramuscular injection, reconstitute with ... mL of 0.9% Sodium Chloride Injection, USP.

C. PACKAGE INSERT

1. See General Comment above.

2. As per OPDRA consult #00-0326, the Administration section under DOSAGE AND ADMINISTRATION states to dissolve one or more vials of Bravelle in *one-half to one mL* of

sterile saline for injection (concentration should not exceed 225 IU/0.5 mL). This statement is inconsistent to the reconstitution instructions on the carton labeling (see CARTON LABELING comment #2). The reconstitution instructions should be clear and consistent.

3. In the same statement above (PACKAGE INSERT comment #2), it would be difficult to get a total concentration of 225 IU/0.5 mL. Since one vial contains 75 IU, does the sponsor recommend in adding 0.5 mL of sterile saline for injection to one vial, withdraw the total contents of that vial and add it to another vial containing 75 IU of Bravelle, and then add the total of those contents to another vial of Bravelle? Is it possible to dissolve 225 IU of Bravelle in 0.5 mL of sterile saline?

4. The statement "Administer subcutaneously or intramuscularly immediately after reconstitution" should be stated in the beginning of the DOSAGE AND ADMINISTRATION section.

5. As per OPDRA consult #00-0326, the first sentence under the Assisted Reproductive Technologies section (DOSAGE AND ADMINISTRATION) should be revised to include a dose frequency:

   ... is 225 International Units daily. Based ...

IV. RECOMMENDATIONS:

A. OPDRA has no objections to the use of the proprietary name "Bravelle".

B. OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

/S/

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur: /S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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

/s/

Jennifer Fan
5/25/01 11:47:52 AM
PHARMACIST

Jerry Phillips
5/25/01 11:55:14 AM
DIRECTOR

Martin Himmel
5/30/01 01:00:06 PM
MEDICAL OFFICER

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

Application Integrity Policy Information

This new drug application is not on the AIP list.

AR 12/08/02

19.0 FINANCIAL DISCLOSURE

Ferring Pharmaceuticals Inc. hereby certifies that Financial Disclosures for all Clinical Investigators have been received and are filed as appropriate. A list of the principal investigators for this study, FPI FSH 2001-01 are listed on the following pages. An FDA Form 3454 has also been included to cover the investigators in this study.

Ronald V. Nardi, Ph. D
Executive Vice President, Research & Development

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	SEE LIST ATTACHED	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Ronald V. Nardi, Ph.D.	Exec. Vice President, Research & Developme
FIRM/ORGANIZATION	
Ferring Pharmaceuticals Inc. , 120 White Plains Rd., Ste, 400, Tarrytown, NY 10591	
SIGNATURE	**DATE**
Ronald V. Nardi	2/4/02

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts (301) 443-2454 EF

FPI FSH 2001-01

PRINCIPAL INVESTIGATORS
CRAIN, JACK
DICKEY, RICHARD
GOCIAL, BENJAMIN
KATAYAMA, PAUL
KETTEL, MICHAEL
MAGARELLI, PAUL
NAJMABADI, SAM
NICHOLS, JOHN, JR.
PATTON, GRANT
SOMKUTI, STEPHEN
STEINKAMPF, MICHAEL
WEBSTER, BOBBY
YEKO, TIMOTHY

8.0 CLINICAL DATA SECTION (21 CFR 314.50 (D) (5))

I LIST OF INVESTIGATORS

FPI FSH 2001-01

Investigator	Address
CRAIN, Jack	Site #1 Reproductive Endocrinology Associates of Charlotte 1918 Randolph Road, 5th Floor Charlotte, NC 28207
DICKEY, Richard P.	Site #2 Fertility Institute of New Orleans 6020 Bullard Avenue New Orleans, LA 70128-2813
GOCIAL, Benjamin	Site #3 Pennsylvania Reproductive Associates 5217 Militia Hill Road Plymouth Meeting, PA 19462
KATAYAMA, PAUL	Site #4 Advanced Institute of Fertility 2801 West Kinnickinnic River Parkway Suite 535 Milwaukee, WI 53215
KETTEL, MICHAEL L.	Site #5 San Diego Fertility Center 11515 El Camino Real, Suite 100 San Diego, CA 92130-6363
MAGARELLI, PAUL	Site #6 Paul C. Magarelli, MD Reproductive Medicine and Fertility Center 175 South Union Boulevard, Suite 315 Colorado Springs, CO 80910
NAJMABADI, SAM	Site #7 Center for Reproductive Health & Gynecology 23861 McBean Parkway, Suite C-6 Valencia, CA 91355
NICHOLS, John	Site #8 Greenville Memorial Hospital Division of Reproductive Endocrinology & Infertility 890 West Faris Road, Suite 470 Greenville, SC 29605
PATTON, GRANT	Site #9 Southeastern Fertility Center, PA 1375 Hospital Drive Mt. Pleasant, SC 29464-325475

Investigator	Address
SOMKUTI, STEPHEN	Site #10 Abington Reproductive Medicine, PC 1245 Highland Ave, Suite 404 Abington, PA 19001
STEINKAMPF, Michael P.	Site #11 University of Alabama at Birmingham Kirklin Clinic Laboratory Dept of OB/GYN 2000 6th Avenue South Birmingham, Alabama 35233
WEBSTER, BOBBY	Site #12 Woman's Center for Fertility 9000 Airline Highway Suite 670 Baton Rouge, LA 70815
YEKO, TIMOTHY	Site #13 Verkauf, Bernhisel, Tarantino, Goodman & Yeko, M.D.'s, PA 2919 Swann Avenue Suite 305 Tampa, FL 33609

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.

ava 12/08/02

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

Class Labeling

There is no class labeling for this new drug application.

CWR 12/08/02

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

Adverstising Information

Advertisting will be requested for this new drug application upon approval.

OK 12/6/02

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

DDMAC Label Review

There is no DDMAC labeling review. This will be requested upon approval.

OMA 12/08/02

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

Phase 4 Commitments

There are no Phase 4 commitments.

OK 12/08/02

136 pages redacted from this section of the approval package consisted of draft labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: December 13, 2002

To: Mike Bernhard Senior Director, Regulatory Affairs	**From:** Archana Reddy, M.P.H., M.S. Regulatory Project Manager
Company: Ferring Pharmaceuticals, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: (914) 631 - 5120	**Fax number:** (301) 827 - 4267
Phone number: (914) 333 - 8932	**Phone number:** (301) 827 - 4260

Subject: Labeling comments for Bravelle (NDA 21-484).

Total no. of pages including cover: 25

Comments:

Mike,

Please find attached labeling comments in response to your November 26, 2002 labeling submission for pending NDA 21-484. Please provide a response to these comments by Monday.

Thanks,

Archana Reddy, M.P.H.

Document to be mailed: ☐ YES ☑ NO

45 Day Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	✓		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	✓		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	✓		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	✓		
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	✓		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	✓		
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	✓		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓		

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data. Has the applicant submitted line listings in the format agreed to previously by the Division?	✓		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	No foreign data		
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division?	✓		
12) Has the applicant presented the safety data in a manner consistent with center guidelines and/or in a manner previously agreed to by the Division?	✓		
13) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	✓		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?		✓	Draft labeling does not contain revisions requested in letter faxed to sponsor 6/5/01 regarding NDA 21-289
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	✓		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	✓		

ITEM	YES	NO	COMMENT
17) Reasons for refusal to file:			

/S/

Reviewing Medical Officer

Supervisory Medical Officer

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

/s/

Archana Reddy
4/23/02 08:38:22 AM
CSO

Ridgely C. Bennett
4/24/02 02:04:52 PM
MEDICAL OFFICER

NDA FILEABILITY CHECKLIST

NDA Number: 21-484 **Applicant: Ferring Pharmaceuticals** **Stamp Date: 19-FEB-2002**
Drug Name: Bravelle for Injection

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

All CMC information has been cross-referenced to NDA # 21-289, Bravelle for Injection (different indication).

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?			NA
2	Is the section indexed and paginated adequately?			NA
3	On its face, is the section legible?			NA
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?			NA
5	Is a statement provided that all facilities are ready for GMP inspection?			NA (is this correct?)
6	Has an environmental assessment report or categorical exclusion been provided?			NA
7	Does the section contain controls for the drug substance?			NA
8	Does the section contain controls for the drug product?			NA
9	Has stability data and analysis been provided to support the requested expiration date?			NA
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N/A
11	Have draft container labels been provided?			NA
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?			NA
14	Is there a Methods Validation package?			NA
15	Is a separate microbiological section included?			NA

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.
Review Chemist: Martin Haber Date: April 9, 2002

Team Leader: Duu-Gong Wu Date:
cc:
Original NDA 21-484
HFD-580/Division File
HFD-510/Chem/MHaber
HFD-580/PM/AReddy

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

/s/

Martin Haber
4/15/02 02:49:51 PM
CHEMIST

fileable, no cmc to review

Duu-gong Wu
4/22/02 03:20:31 PM
CHEMIST

4/1/02

NDA 21-484
Bravelle (Purified Urofollitropin) 75 IU

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this action of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		Reference is made to NDA 21-289. No new studies were submitted
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were submitted form the NDA.	X		

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie. Adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item #10 below why it is not.	X		
10) Reasons for refusal to file:			

/S/ 4/1/02

Reviewing Pharmacologist

/S/

Supervisory Pharmacologist

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

/s/

Laurie McLeod
4/1/02 02:50:42 PM
PHARMACOLOGIST

Alexander W. Jordan
4/2/02 08:35:56 AM
PHARMACOLOGIST

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

Advisory Committee Meeting

This new drug application was not the subject of an advisory committee meeting.

12/08/10

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

Federal Register Notice

This new drug application was not the subject of any Federal Register notice.

AR 12/08/02

LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

JAMES R. PHELPS
PAUL M. HYMAN
ROBERT A. DORMER
STEPHEN H. McNAMARA
ROGER C. THIES
THOMAS SCARLETT
JEFFREY N. GIBBS
BRIAN J. DONATO
FRANK J. SASINOWSKI
DIANE B. McCOLL
A. WES SIEGNER, JR.
ALAN M. KIRSCHENBAUM
DOUGLAS B. FARQUHAR
JOHN A. GILBERT, JR.
JOHN R. FLEDER
MARC H. SHAPIRO
ROBERT T. ANGAROLA
(1945-1996)

DIRECT DIAL (202) 737-4287

700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

MARY KATE WHALEN
OF COUNSEL

JENNIFER B. DAVIS
FRANCES K. WU
DAVID B. CLISSOLD
CASSANDRA A. SOLTIS
JOSEPHINE M. TORRENTE
MICHELLE L. BUTLER
PATRICIA A.A. VANSTORY
ANNE MARIE MURPHY
PAUL L. FERRARI
JEFFREY N. WASSERSTEIN
MICHAEL D. BERNSTEIN
LARRY K. HOUCK
DARA S. KATCHER*
KURT R. KARST*

*NOT ADMITTED IN DC

August 19, 2002

BY HAND DELIVERY

Formal Dispute Resolution Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Mail Code HFD-002
5600 Fishers Lane
Rockville, Maryland 20857

Re: **FORMAL DISPUTE RESOLUTION REQUEST**
Applicant: Ferring Pharmaceuticals, Inc.
Applications: NDA 21-289 and NDA 21-484
Product: Bravelle™ (urofollitropin injection, purified)
Reviewing Division: Division of Reproductive and Urologic Drug Products (HFD-580)
Proposed Indication: Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program

Dear Sir or Madam:

On behalf of Ferring Pharmaceuticals Inc. (Ferring), we submitted, on April 26, 2002, a request to the Food and Drug Administration's (FDA's or the Agency's) Division of Reproductive and Urologic Drug Products (the Division) for reconsideration of issues concerning the approval of Ferring's New Drug Applications (NDAs) #21-289 and 21-484

2603 MAIN STREET
SUITE 760
IRVINE, CALIFORNIA 92614
(949) 553-7400
FAX: (949) 553-7433

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX: (919) 313-4751

for Bravelle™ (urofollitropin injection, purified) for use in *in vitro* fertilization (IVF).[1] See Attachment A.

Because over three months have passed without a written response to the April 26, 2002 letter, and because several of the issues raised are time sensitive, we are, on Ferring's behalf, and in accordance with FDA's February 2000 guidance entitled, "Formal Dispute Resolution Appeals above the Division Level" (FDR Guidance), submitting this request for formal dispute resolution regarding four specific scientific or procedural issues affecting NDAs #21-289 and 21-484 for Bravelle™ for the IVF indication. This formal dispute resolution request is being submitted in order to initiate the 30-day response clock noted in the FDR Guidance. As required by the FDR Guidance, we note that the Division has previously received and had an opportunity to review all of the material relied upon in this dispute resolution request.

We understand that NDA 21-484 for Bravelle™ in IVF is under active review by the Division. We believe the four issues presented here are ripe for resolution in parallel with the NDA review. As such, we do not anticipate that this formal dispute resolution request will delay or otherwise adversely affect the Division's review of NDA #21-484.

PROCEDURAL BACKGROUND

Ferring submitted NDA #21-289 for Bravelle™ to the FDA on September 29, 2000. The NDA contained reports of two active control Phase III clinical investigations to support the use of Bravelle™ in ovulation induction (OI) (FPI FSH 99-03) and *in vitro* fertilization (FPI FSH 99-04).

On July 27, 2001, Ferring received a not approvable letter from the Division concerning the IVF indication (the Not Approvable Letter). The Not Approvable Letter sets forth facilities, chemistry, and clinical deficiencies, and the information required to address these deficiencies. Ferring responded to the facilities and chemistry issues raised, and Bravelle™ was approved for OI on May 6, 2002. Ferring has attempted, unsuccessfully, to resolve the clinical issues concerning the IVF indication through a Type A meeting, our April 26, 2002 letter and other discussions with the Division.

---

[1] This indication is described in the NDAs as development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Throughout this letter, we refer to this as the IVF indication.

The Not Approvable Letter listed a single clinical deficiency.[2] Specifically, FDA's review concluded that FPI FSH 99-04 failed to meet its prospectively stated statistical efficacy criterion to show non-inferiority to Follistim® (follitropin beta for injection), which FDA interpreted as a lower limit of the 95% confidence interval (CI) of 1.2 oocytes retrieved (10 to 8.8). Ferring's interpretation of the FPI FSH 99-04 protocol is that a 30% difference of the mean oocytes retrieved in the reference group, not 1.2 oocytes, was the prespecified lower CI limit. To remedy the deficiency noted in the Not Approvable Letter, the Division recommended that Ferring conduct a new trial to demonstrate non-inferiority to an active control. On July 30, 2001, Ferring requested a Type A meeting with the Division to discuss the disagreement regarding FPI FSH 99-04, while also planning to conduct the additional study in IVF.[3]

On September 24, 2001, Ferring submitted study protocol FPI FSH 2001-01 to the Division as an IND amendment. FPI FSH 2001-01, a randomized, open label, parallel group, multi-center efficacy study, was intended to respond to the Division's request for an additional Bravelle™ IVF study. The Division responded with written comments dated October 12, 2001. Ferring amended the protocol in accordance with FDA's comments and initiated the study in October 2001.

Ferring reports that it completed the study on January 20, 2002. About that time, Ferring contacted the Division to ask how it should submit these new data. On January 23, 2002, in response to an inquiry from Ferring, Diane Moore, Project Manager in the Division, contacted Ronald Nardi, Ph.D., Vice President of Scientific and Regulatory Affairs at Ferring, and directed Ferring to submit the results of FPI FSH 2001-01 as an "Administrative" NDA. Ferring finalized the final study report on February 1, 2002. On February 5, 2002, approximately five months after the FPI FSH 2001-01 protocol was first submitted to the Division and two weeks after the discussion of the regulatory vehicle for submission of the final report, Ferring received a letter from the Division requesting substantive changes in the design of the completed study. In light of the study's status as

---

2 "Based on the original statistical plan [of FPI FSH 99-04], neither the subcutaneously administered Bravelle™ nor the intramuscularly administered Bravelle™ demonstrated non-inferiority to subcutaneously administered Follistim® for the proposed indication of multiple follicular development for use in [ART]."

3 The Type A meeting was held on August 22, 2001, but did not resolve the substantive issue.

Ferring and Ms. Moore of the Division, during which Ferring informed the Division that the FPI FSH 2001-01 study was completed and would be filed in February 2002. Thus, the Division was aware that the study was completed when it sent Ferring the additional, unanticipated comments to the protocol.

On behalf of Ferring, I discussed this issue with Daniel Shames, M.D., Acting Division Director and Marjorie Kobor, Project Manager, by telephone on June 6, 2002. Dr. Shames explained that FDA did not send its statistical comments in a more timely fashion (as it did with the clinical comments) because the Division had expected to receive a separate statistical analysis plan (SAP) for this protocol and intended to provide comments after receiving the SAP. While we understand that applicants sometimes submit separate SAPs after protocol initiation, this has never been Ferring's practice and Ferring gave no signal that a separate SAP would be submitted. The original protocol contains a four page statistical section similar (or identical) to that in other Ferring studies submitted to the Division under other INDs. Ferring should not be penalized for the Division's erroneous assumption regarding the existence of a separate SAP. While Dr. Nardi's call regarding study completion may have been the first time that the Division realized no SAP was forthcoming, this does not justify issuing protocol comments at such a late date. Because both FDA's and Ferring's statistical approaches are appropriate for analysis of Study 2001-01, and because Ferring's statistical analysis plan was prespecified while the Division's would, given the facts, represent a post-hoc analysis not consistent with the trial's design, we believe the study should be analyzed in accordance with the original protocol. This analysis was submitted in the final study report for Study 2001-01.

In sum, Ferring justifiably and reasonably concluded that it had received all of FDA's comments by October 12, 2001. The Division's request in February 2002 (after the Division had been notified that the trial was already completed) to change the statistical criterion, is inconsistent with Ferring's previous interaction with the Division, and should, as a post-hoc comment incompatible with the basic trial design, be excluded from consideration of the study results. Ferring believes that the supplementary efficacy data provided to the Division in NDA #21-484 from the FPI FSH 2001-01 study confirms that provided in the NDA #21-289 and therefore supports the approval of Bravelle™ for the IVF indication.

Protocol FPI FSH 94-01

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

During its review of the original NDA #21-289, and based on its reading of the protocol that a difference of 1.2 oocytes retrieved was intended as the lower limit of the 95% CI, the Division concluded that Ferring's FPI FSH 99-04 study for Bravelle™ failed to meet its prospectively stated statistical efficacy criterion to demonstrate non-inferiority to Follistim®. Notwithstanding some confusion in the FPI FSH 99-04 protocol and the final statistical report, an analysis of Ferring's actions necessarily leads to the conclusion that the sponsor's intended and prespecified lower limit of the CI in FPI FSH 99-04 was a 30% difference of the mean oocytes retrieved in the reference group. Most notably, FDA's August 1999 approval of Ferring's Repronex® (menotropins for injection, USP) for IVF, was based on Repronex® study FPI Rep 97-02 using a 30% difference of the mean oocytes retrieved in the reference group as the intended lower limit of the CI to demonstrate non-inferiority. That Ferring utilized the identical[5] statistical plan for Bravelle™ is indicative of Ferring's intent to prespecify a 30% difference of the mean oocytes retrieved in the reference group as the lower limit of the CI. Since Repronex®'s approval was based on the same statistical plan, Ferring had a precedent-based reasonable basis for thinking that the Division would interpret the Bravelle™ plan the same way.

The confusion surrounding the intended lower limit of the CI stems from the FPI FSH 99-04 study protocol and final statistical report, in which the lower CI limits were not clearly identified for determining the non-inferiority of Bravelle™ to Follistim®. The power calculation in the statistical consideration section of the FPI FSH 99-04 study protocol states that the sample size "should have ample power to detect a change in the number of oocytes of 1.2 (10 to 8.8)." Only a few lines after this statement, the study protocol states that "[b]ased on these calculations there is an 80% power to detect a relative difference of 30% if the oocyte retrieval rate is 80%" (emphasis added).[6]

---

5 "Identical" to the point of including a typographical error from the earlier successful trial analysis.

6 The final statistical report of the FPI FSH 99-04 protocol proposed to examine whether the differences in the Bravelle™ and Follistim® study groups were "within

The relevant portions of the statistical considerations section of the original FPI FSH 99-04 IVF study protocol are identical to the same sections in the Repronex® FPI Rep 97-02 IVF study protocol. The FPI Rep 97-02 IVF study protocol and the FPI FSH 99-04 IVF study both contain the following language:

> It is assumed that the expected mean of oocytes retrieved per cycle is 10 with a standard deviation of two in the reference group. Power calculations were performed based on $\alpha = 0.05$ (assuming a two-tailed test) and the power = 80%. Based on this calculation, there should have [sic] ample power to detect a change in the number of oocytes of 1.2 (10 vs. 8.8) with a sample size of 44. . . . Based on these calculations there is an 80% power to detect a relative difference of 30% if the oocyte retrieval rate is 80% with 50 evaluable patients in each group.[7]

FDA's approval of the Repronex® IVF study on the basis of a 30% difference of the mean oocytes retrieved in the reference group as the lower limit of the CI formed the basis upon which Ferring chose to design FPI FSH 99-04.

After receiving the Not Approvable Letter, and during an August 22, 2001 Type A meeting, we understand from Ferring that the Division acknowledged that the FPI FSH 99-04 study protocol could be reasonably interpreted to mean that a 30% difference of the mean oocytes retrieved in the reference group, not 1.2 oocytes retrieved, was the intended lower limit of the CI. The Division nonetheless maintains that use of 1.2 oocytes retrieved as the lower limit of the CI is appropriate because it is consistent with the Agency's approval of Follistim®, in which the applicant submitted the results of two pivotal IVF studies comparing Follistim® to Metrodin® (urofollitropin for injection).

20% of each other" (emphasis added). As stated in its correspondence of August 3, 2001 to the Division, Ferring maintains that the 20% difference noted in the final statistical study report submitted with NDA #21-289 was an error, and should be disregarded.

[7] Later changes to the FPI FSH 99-04 protocol modified the analysis, but did not change either of the prespecified criteria.

Drawing a comparison between the approval of Follistim® and Bravelle™ is unwarranted. The intent of the applicant in using 1.2 oocytes as the lower limit of the CI in the Follistim®-Metrodin® IVF studies was to demonstrate the statistical superiority of Follistim® to Metrodin®. The Bravelle™-Follistim® study only attempted to demonstrate non-inferiority. Drawing a comparison between these studies with regard to the lower limit of the CI used is inappropriate. A more accurate indication of Ferring's intended lower limit of the CI is the Agency's approval of Repronex®, in which the applicant demonstrated the non-inferiority of Repronex® to Pergonal® (menotropins).

In sum, Ferring believes that the data submitted to FDA provide substantial evidence of efficacy for the use of Bravelle™ in IVF, and that immediate FDA approval for this indication is warranted. Notwithstanding some confusion in the FPI FSH 99-04 study protocol and final statistical report, it is evident that Ferring intended a 30% difference of the mean oocytes retrieved in the reference group, and not 1.2 oocytes retrieved, as the lower limit of the CI. Ferring's position is supported by FDA's acceptance of this statistical efficacy criterion in the approval of Repronex®. Based on these facts, the FPI FSH 99-04 study demonstrated non-inferiority to Follistim®.

Ferring and the Division last sought, unsuccessfully, to resolve this issue at an August 9, 2001 Type A meeting. Ferring has since conducted an additional study requested by the Division for approval (FPI FSH 2001-01). As such, Ferring believes Bravelle can be approved for the IVF indication based on the results of that study. If the Agency disagrees that Bravelle can be approved for this new use on the basis of FPI FSH 2001-01, then Ferring would like FDA to revisit the history of FPI FSH 99-04. We believe that that history would lead to the conclusion that Ferring intended a 30% difference as the lower limit of the CI.

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

The Division's comments on both FPI FSH 99-04 and FPI FSH 2001-01 raise the question of what constitutes a clinically meaningful lower limit of the 95% CI based on these studies. Ferring believes that the appropriateness of the 30% measure is best evidenced by FDA's acceptance of it in pivotal studies for similar products. Both Repronex® and Gonal-F® (follitropin alpha) were approved for IVF based on non-inferiority studies. In both instances, the lower limit of the CI for those studies was consistent with a 30% difference of the mean oocytes retrieved in the reference group.

FDA's Summary Basis of Approval (SBA) for Repronex® SC includes a review of FPI Rep 97-02, a pivotal, non-inferiority IVF study comparing Repronex® IM, Repronex® SC and Pergonal® I.M. There, FDA computes 95% CIs "to help assess whether clinically important differences [between the investigational products and active control] have been excluded."[8]

In the Gonal-F® SBA, FDA determined that a 1.4 follicle difference in number of oocytes was not clinically significant and was not sufficient to render two products non-equivalent.[9] The SBA goes on to note that even a difference of 3 oocytes "is not expected to have a meaningful consequence on treatment outcome since the mean difference tends to be reduced in subsequent steps of the IVF-ET treatment and in the therapeutic procedures, to reduce the incidence of multiple pregnancies, it is usually not recommended to replace more than three embryos."[10] Thus, even though Gonal-F® was determined to be statistically inferior to the comparator product, Metrodin®, FDA granted approval on the basis that such a difference was not clinically meaningful to treatment outcome.

Further supporting the view that a 30% difference of the mean oocytes retrieved in the reference group of the lower limit of the CI is an appropriate choice of clinically meaningful bound is a recent letter FDA sent to Ferring regarding IND — for Repronex®. In response to Ferring's proposal to test for non-inferiority of Purified Repronex® to Repronex®, FDA states that "we have accepted the stated delta of 3.9 oocytes as your clinically meaningful difference in the test for non-inferiority of Purified Repronex® to Repronex®."[11] The FPI FSH 99-04 IVF study demonstrated numerical superiority for Bravelle™ versus Follistim® —13.3 versus 13.1 oocytes retrieved. Using the 13.1 figure as the reference standard, and 30% as the non-inferiority criterion, a lower limit of the CI of 3.93 oocytes retrieved (30% x 13.1) can be calculated. As FDA has

---

8 Repronex® SC SBA Vol. 2 at 27.

9 Gonal-F® SBA Vol. 2 at 39.

10 Id.

11 Letter from Daniel Shames, M.D., Acting Director, DRUDP, FDA, to Ferring, (Oct. 12, 2001) at 1 (Purified Repronex®).

recognized, 3.93 oocytes is a "clinically meaningful difference in the test for non-inferiority."

In sum, the FDA has regarded differences less than 30% as not clinically meaningful. As evidenced by FDA's acceptance of this standard in pivotal studies for similar products, Ferring believes that a lower limit of the 95% CI based on a 30% difference between treatment groups is an appropriate non-inferiority margin in both FPI FSH 99-04 and FPI FSH 2001-01.

Ferring and the Division last sought to resolve this issue at an August 9, 2001 Type A meeting. This issue is critical not only to the review of the Bravelle™ studies, While Ferring is not requesting advisory committee review of this issue at this time, we do believe that it warrants close attention from the Agency. Consistent with previous decisions by the Division on other IVF drug products, we believe the Agency should conclude that a 30% difference in mean number of oocytes retrieved is a clinically relevant lower limit of the CI for non-inferiority studies in IVF.

Timing of Review

4. **(Procedural) 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 review.**

In discussing the resolution of the clinical deficiency in NDA #21-289, the Division noted that data from an additional, active-control efficacy study in IVF could be submitted as a supplemental NDA (sNDA) after Bravelle™ approval for the OI indication, which could occur upon resolution of several chemistry and facility deficiencies.[12] As discussed above, Ferring designed and conducted such a study (FPI FSH 2001-01). Because NDA #21-289 had not been approved for the OI indication before the final study report for FPI FSH 2001-01 was completed, these data could not be submitted as a sNDA. The Division then advised Ferring to withdraw the IVF indication in NDA #21-289 so that OI could be approved under that NDA, and to submit an "Administrative" NDA for IVF.[13] The

---

12 Letter from Daniel Shames, M.D., Acting Director, DRUDP, FDA, to Ferring. (Oct. 12, 2001) (Bravelle™).

13 Id. (comments regarding withdrawal); Jan. 23, 2002 telephone conversation with

"Administrative" NDA would consist, primarily, of the final study report and data from FPI FSH 2001-01 and a cross-reference to the IVF data in NDA #21-289. Ferring complied with FDA's request and submitted this "Administrative" NDA #21-484 on February 15, 2002.

In accordance with the Prescription Drug User Fee Act II (PDUFA) and FDA's 1998 guidance, "Classifying Resubmissions in Response to Action Letters," a NDA submission that responds to all deficiencies noted in an action letter is either a Class 1 or Class 2 resubmission. The inclusion of efficacy data from a clinical study not part of the original NDA classifies the submission as a Class 2 resubmission with a performance review goal of six months.[14] Because Ferring had already responded to all chemistry issues by October 30, 2001, and because all manufacturing compliance issues were resolved in a December 18-20, 2001 inspection, the February 15, 2002 submission by Ferring of its report from FPI FSH 2001-01 constituted a complete response to all issues raised in the Not Approvable Letter, and, if not for the Division's request that Ferring withdraw the IVF indication and submit an "Administrative" NDA, this complete response would have been a Class 2 resubmission to the IVF portion of NDA #21-289. The PDUFA response date for this submission would be August 15, 2002. Ferring should not incur a review-time penalty for having submitted the FPI FSH 2001-01 report as an "Administrative" NDA in accordance with the Division's specific instructions. Instead, the PDUFA date should be consistent with that of a Class 2 resubmission.

I discussed this issue by telephone with Dr. Shames and Ms. Kobor on June 6, 2002. Dr. Shames noted that, according to the Division's records, Ferring voluntarily withdrew the IVF portion of NDA 21-289 and resubmitted it as a new NDA. In contrast, Ferring's records indicate that the Division, not Ferring, first suggested withdrawal of the IVF portion of NDA 21-289 in its October 12, 2001 letter to Ferring. Based on this letter and on Ferring's report of verbal comments from the Division noting that review of the OI indication would not proceed absent withdrawal of the IVF indication, Ferring had a reasonable basis for believing that Bravelle™ would not be approved for OI until the IVF indication was withdrawn. In this situation, a commercial applicant has little choice but to

---

Diane Moore (comments regarding "Administrative" NDA).

[14] See Federal Food, Drug, and Cosmetic Act § 735(1); Letter from Donna Shalala, Secretary, Health and Human Services to Senator Jim Jeffords, Chairman, Committee on Labor and Human Resources, United States Senate (Nov. 12, 1997).

comply with FDA's request. Any other action would unduly delay the availability of the subject drug for patients. The Division's records, indicating that Ferring volunteered to withdraw the IVF indication and thereby accepted a longer review clock, appear inconsistent with the normal motivations of NDA applicants to seek the speediest path to approval.

While this issue was relevant in our April 26, 2002 letter to the Division, the 6-month review date is upon us with no response. As such, Ferring is prepared to accept a 10-month review clock.

LIST OF DOCUMENTS PREVIOUSLY SUBMITTED TO THE AGENCY

All documents necessary for resolution of these issues should be part of FDA's files for Bravelle (IND —— NDA 21-289, and NDA 21-484) and Repronex (IND —— and NDA 21-047). These documents include:

IND ——	Protocol 94-04	11-04-99
	FDA comments on 94-04	03-00
	Pre-NDA meeting package	03-24-00
	Pre-NDA meeting minutes	04-24-00
	Statistical analysis plan submission for 99-04	09-00
	Protocol 2001-01	09-24-01
	FDA comments to 2001-01	10-12-01
	2001-01 amendment	10-01
	Telephone contact reports	01/02-02
	Additional FDA comments to 2001-01	02-05-02
NDA 21-289	Original NDA	09-29-00
	Not approvable letter	07-27-01
	Type A meeting package	08-09-01

	Minutes of Type A meeting	08-22-01
	NDA correspondence	10-12-01
NDA 21-484	Original NDA	02-15-02
IND [redacted]	Protocol comments	10-12-01
NDA 21-047	Protocol 97-02	10-22-98
	Summary Basis of Approval	08-99

CONCLUSION

Ferring believes that the supplementary efficacy data provided to FDA in NDA #21-484 from the FPI FSH 2001-01 study confirm the efficacy and support the approval of Bravelle™ in IVF. The study, when analyzed in accordance with its prespecified statistical plan, demonstrates the efficacy of Bravelle™ in IVF. Therefore, Ferring believes that the trial it conducted in response to the Division's Not Approvable Letter provides the additional evidence of Bravelle™ treatment effect in IVF, and that approval for this use is now warranted.

Furthermore, notwithstanding some confusion in the FPI FSH 99-04 study protocol and final statistical report, it is evident that Ferring intended a 30% difference of the mean oocytes retrieved in the reference group, and not 1.2 oocytes retrieved, as the lower limit of the CI. Ferring's position is supported by FDA's acceptance of this statistical efficacy criterion in the approval of Repronex®. Based on these facts, the FPI FSH 99-04 study demonstrated non-inferiority to Follistim®. As such, FPI FSH 99-04 is a sufficient demonstration of Bravelle's™ treatment effect of IVF, independent of the results of FPI FSH 2001-01.

For all of these reasons, Ferring also believes that the data submitted to FDA provide substantial evidence of efficacy for the use of Bravelle™ in IVF, and that timely FDA approval for this indication is warranted.

###

Ferring and I are eager to resolve all issues outstanding on this use of Bravelle™. We look forward to your response.

Sincerely,

Frank J. Sasinowski for

cc: R. Nardi, Ph.D.
M. Kobor

JMT dag
2791.001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-289, 21-484

Ferring Pharmaceuticals, Inc.
c/o Hyman, Phelps & McNamara, P.C.
Attention: Frank J. Sasinowski
700 Thirteenth Street, N.W.
Washington, D.C. 20005-5929

Dear Mr. Sasinowski:

We refer to your New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bravelle™ (urofollitropin injection, purified).

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.

Your August 19, 2002, request for dispute resolution, received on August 20, 2002, asked that we consider issues concerning the approval of NDAs 21-289 and 21-484. Four issues were presented in your request: 1) whether the Division's proposed, post-hoc analysis of FPI FSH 2001-01 should be considered for the primary analysis, 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, 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, and 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.

Dispute issues

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

On September 10, 2001, Ferring submitted a letter with two proposals concerning what data would be needed to approve the IVF indication and the logistics of submitting the information after NDA 21-289 would be approved for OI. The protocol for study FPI FSH 2001-01 was submitted to IND — as an amendment dated September 24, 2001. DRUDP forwarded comments to Ferring's September 10, 2001, proposal in a letter dated October 12, 2001. The proposals and DRUDP's comments addressed the information needed to support the IVF indication rather than a specific protocol (e.g., FPI FSH 2001-01). On October 24, 2001, DRUDP received modifications to the protocol dated October 15, 2001. Ferring

initiated the study and completed it on January 20, 2002. DRUDP, unaware that study FPI FSH 2001-01 had began, drafted comments about the protocol in December 2001 and finalized those comments in January 2002. FDA was informed the study had already been completed on or about January 20, 2002. FDA sent its comments on the statistical plan for the study in a letter dated February 5, 2001. You reported that, in a June 6, 2002, telephone conversation with Dr. Daniel Shames, then Acting Director of the Division, and Ms. Margaret Kober, Chief, Project Management Staff, Dr. Shames explained that the statistical comments were sent separately from other comments on the protocol because DRUDP had expected submission of a separate statistical analysis plan even though the submitted protocol included a statistical section. You assert that Ferring reasonably concluded that it had received all of FDA's comments on protocol 2001-01 by October 12, 2001. Ferring disputes DRUDP's letter of February 5, 2001 that states non-inferiority should be considered as not less than 2.2 oocytes for the lower margin of the 95% CI. The rationale for Ferring's position is that although "both FDA's and Ferring's statistical approaches are appropriate for analysis of Study 2001-01...Ferring's statistical analysis plan was prespecified while the Division's would, given the facts, represent a post-hoc analysis not consistent with the trial's design." You desire that the Division's recommended efficacy criteria not be considered for the primary analysis of Study 2001-01.

NDA 21-484 contains Study 2001-01 as the primary efficacy study and was received by FDA on February 19, 2002, following withdrawal of the IVF indication from NDA 21-289 and in response to the non-approval letter of NDA 21-289 dated July 27, 2001. Review of NDA 21-484 is ongoing and has a goal date of December 19, 2002. You submitted Ferring's request for formal dispute resolution on August 19, 2002 stating that you understand that NDA 21-484 for Bravelle for use in IVF is under active review by the Division and that you believe issue #1 is ripe for resolution in parallel with the NDA review.

At this time, this issue is not ripe for dispute resolution because no Agency action has been taken related to Study 2001-01. The appeal process is not meant to circumvent or supplant the Division's role during the review process to perform the primary review of the data and to make a determination of efficacy and safety. Procedurally, your request for dispute resolution to resolve the lack of agreement over the efficacy criteria could have been presented to the Agency prior to Ferring submitting the NDA, when your client became aware on February 5, 2002, of FDA's recommendations. However, once the NDA was submitted by Ferring to respond to the deficiencies of the non-approval letter of July 27, 2001, the Division must be given opportunity to review the data and come to a conclusion about the matter. In fact, should NDA 21-484 be approved, the question about what criterion should be used to evaluate study 2001-01 may be irrelevant to your client at that point.

Finally, I agree with you that the advice letter concerning protocol 2001-01 sent to Ferring by the division on February 5, 2002, was sent late.

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.**

Your client's protocol for FPI FSH 99-04 dated October 4, 1999, on pages 18 and 19 under the section entitled Statistical Methods and Sample Size Justification states two power calculations:

> "Estimates of power to detect differences between the two groups are based on methods described in Dupont and Plummer (1990). It is assumed that the expected mean of oocytes retrieved per cycle is 10 with a standard deviation of 2 in the reference group. Power calculations were performed based on " = 0.05 [appears this way in the document] (assuming a two-tailed test) and the power = 80%. Based on this calculation, there should have ample power to detect a change in the number of oocytes of 1.2 (10 vs. 8.8) with a sample size of 44. The sample size of 60 patients was selected."

> On page 19, the protocol states, "When data analysis is performed, multiple logistic regression techniques will be used, in addition to chi-squared tests. The power is estimated based on the 1 df chi-squared test which should be conservative since the additional information that baseline covariates will add in logistic regression models should add precision to our estimate of the true treatment effect. Based on these calculations there is an 80% power to detect a relative difference of 30% if the oocyte retrieval rate is 80% with 50 evaluable patients in each group. A sample of 60 patients per group was selected."

From the April 24, 2000 Pre-NDA meeting, the FDA meeting minutes state on page 4 under 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 proposed methodology for testing those hypotheses that are consistent with the way they are forumlated...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...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."

Ferring modified the statistical plan and this modification is dated June 6, 2000. This modified plan was sent to FDA on September 14, 2000, after the data lock of August 7, 2000. It was received on September 21, 2000. NDA 21-289, which contained the completed, analyzed study FPI FSH 99-04, was dated September 28, 2000, and was received by FDA on September 29, 2000. The timing of the protocol submission and NDA did not permit FDA review and comment or agreement to the protocol. Regarding the quoted sections of the original plan, page 17 of the modified plan's Power Calculation section still contains two power calculations. The changes are noted below in italics.

> "Estimates of power to detect differences between the two groups are based on methods described in Dupont and Plummer (1990). It is assumed that the expected mean of oocytes retrieved per cycle is 10 with a standard deviation of 2 in the reference group. Power calculations were performed based on □= 0.05 [appears this way in the document] (assuming a two-tailed test) and the power = 80%. Based on this calculation, there should have ample power to detect a change in the number of oocytes of 1.2 (10 vs. 8.8) with a sample size of 44. The sample size of 60 patients was selected. *Dunnett's procedure will be used to determine whether these comparisons are statistically significant.*
>
> When data analysis is performed, *ANCOVA techniques* will be used, in addition to *t*- tests which should be conservative since the additional information that baseline covariates *(age and BMI)* will add in the *ANCOVA* models should add precision to our estimate of the true treatment effect. [appears this way in the document]
>
> Based on these calculations there is an 80% power to detect a relative difference of *less than* 30% if the *number of oocytes retrieved in the reference group is 10* with 50 evaluable patients in each group. A sample of 60 patients per group was selected."

Ferring's NDA clinical summary upon submission of NDA 21-289 stated "for each of these intervals, the one-tailed lower limit of the confidence interval of the difference was compared with the value that corresponded to 20% of the observed Follistim SC mean to determine whether the Purified FSH IM and Purified FSH SC were non-inferior to the Follistim SC." You, your client, ——— ——— acknowledged that the NDA clinical summary was erroneous and confusing. This

summary introduced a one-tailed test and a 20% absolute difference in mean number of oocytes as the criterion used to evaluate efficacy.

The Division issued a non-approval for the IVF indication citing lack of evidence of efficacy from Study 99-04 based on the inability to meet the lower confidence limits of the mean being no worse than 1.2 oocytes. Ferring disagreed that this criterion of no worse than a 1.2 oocyte difference to be ruled out by confidence intervals was prespecified in the protocol, rather a 30% figure was pre-specified. FDA is on record stating at the pre-NDA meeting on April 24, 2000, that the 1.2 oocyte criterion would be used to judge non-inferiority.

The question remains, which of the two power calculations' prespecified deltas is the clinically meaningful difference to exclude to demonstrate non-inferiority. I am not able to find written agreement between FDA and Ferring on the criteria to be used for non-inferiority for Study 99-04 prior to submission of the NDA. There is e-mail confirmation by the FDA statistician to —— —— inquiry of May 19, 2000, asking specifically about specifying the null hypothesis at 35% for ovulation induction (Study 99-03). The E-mail communications did not include copies of the protocols for Studies 99-03 and 99-04. Dr. —— received agreement on Study 99-03's hypothesis. This indication was ultimately approved without further clinical data.

Instead of disputing the non-approval action, Ferring has since conducted an additional study requested by FDA for approval of the IVF indication (Study 2001-01). This study was completed and submitted on February 19, 2002 (NDA 21-484) for review.

At this time no decision has been made regarding NDA 21-484 and Study 2001-01. Should a decision to approve the NDA be made, this would make resolution of whether prespecification of a 30% criterion occurred academic. Should a decision to not approve NDA 21-484 be made, your client should seek an end of review meeting to discuss the application deficiencies.

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.**

You assert that the FDA accepted 30% difference in mean number of oocytes retrieved as the lower limit of the 95% CI for non-inferiority studies supporting approval of Repronex® and Gonal-F® for IVF.

The Division has used a numeric lower bound of the CI to exclude a clinically meaningful difference, not a percentage. For the record, for the IVF indication, Gonal-F (a recombinant human FSH) was compared to Metrodin (a urinary human FSH) in Study GF 5503 but the endpoint was follicles, not total oocytes retrieved. The presence of follicles was determined by interpretation of an ultrasound image. Oocyte retrieval during IVF involves the direct visualization (under magnification) of the female gamete and actual surgical procurement before incubation with male gamete to effect fertilization. The endpoint of mean number of follicles is not comparable to mean number to total oocytes retrieved. In addition, Follistim was studied for the IVF indication in three active-controlled trials. These trials were not designed as superiority trials as stated on page 8 of your letter, but were non-inferiority trials.

In your letter you ask that I conclude that a 30% difference in mean numbers of oocytes retrieved is a clinically relevant lower limit of the CI for non-inferiority studies for IVF. I acknowledge that the standards for demonstration of non-inferiority have not been promulgated to date in written guidance. The process for which a clinically relevant lower limit is established for an indication or for a class of products should involve public input from stakeholders, including the patient community. I agree with your suggestion of an advisory committee to discuss such a scientific issue and am recommending that the Division develop a guidance document on standards for developing effective products for IVF. Ultimately, women experiencing infertility, the population for whom these drugs are intended, desire to

achieve pregnancy and take home a healthy baby. I would be interested in discussing the elimination of use of a surrogate endpoint such as retrieval of oocytes, in future forums.

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.**

You stated in your letter that review of NDA 21-484 has already passed six months and that Ferring has accepted the ten-month review clock applied to this application. Ferring's acceptance makes the question as to what is the appropriate review time frame for NDA 21-484 moot. However, the following explains how the ten-month clock was applied.

In their September 10, 2001 letter, Ferring proposed to amend NDA 21-289 to address CMC deficiencies and submit a supplemental application for the IVF indication to the NDA after it had been approved for the OI indication. DRUDP responded to Ferring's proposal in a letter dated October 12, 2001, notifying Ferring that their proposal was acceptable. The letter included clarification that the IVF indication would have to be withdrawn, an action that was implied in Ferring's proposal, from NDA 21-289 to allow Ferring's submission of only CMC information and correction of cGMP issues at the manufacturing facilities to be a complete response to the July 27, 2001, non-approval action for NDA 21-289. Ferring chose not to wait to submit the additional study report to demonstrate efficacy of the IVF indication as a supplement to an approved NDA (21-289), but rather, submitted the IVF indication with the new study report under a separate NDA (21-484). Subsequently, review of both indications was re-initiated and the applications were under review concurrently, although on separate review clocks.

Withdrawal of the IVF indication from NDA 21-289 removed it from consideration for review and approvability under that NDA. It could only be re-introduced for review prior to approval of NDA 21-289 under an original new application. As an original new application, the ten-month review clock was appropriate.

Conclusions

I am finding that, at this time, issue #1 is not ripe for dispute resolution because no Agency action has been taken on Study 2001-01. I am denying your request for dispute resolution at this time for issue #2 because Agency action on NDA 21-484 may make this issue moot. I am agreeing with your suggestion that issue #3 needs Agency attention and I am recommending to the Division that this be discussed at a public meeting as part of the Good Guidance Process. I am deciding that because your client accepts the ten-month review clock, issue #4 is not a disputed issue but rather your client was in need of an explanation for how the NDA was classified.

If you wish to appeal these decisions to the next level, your appeal should be directed to John Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent through the Center's Dispute Resolution Project Manager, Ms. Kim Colangelo at (301) 594-5479.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H.
Office of Drug Evaluation III
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

Florence Houn
9/18/02 02:19:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-289
NDA 21-484

Hyman, Phelps & McNamara, P.C.
Attention: Frank J. Sasinowski
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Dear Mr. Sasinowski:

We acknowledge receipt on August 20, 2002, of your August 19, 2002, request for formal dispute resolution concerning the New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bravelle™ (urofollitropin injection, purified). This request concerns procedural and scientific disputes regarding NDA 21-289 for Bravelle™ (approved for ovulation induction) and NDA 21-484 for Bravelle™ (under review for *in vitro* fertilization). You are requesting the timely approval of Bravelle™ for use in *in vitro* fertilization based on the results of Study FPI FSH 99-04 (submitted to NDA 21-289) and Study FPI FSH 2001-01 (submitted to NDA 21-484).

Pursuant to the CDER/CBER Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have thirty (30) calendar days from the receipt date of the formal request to respond to the appeal. Therefore, our response to this request is due on or before September 19, 2002.

This request for formal dispute resolution has been forwarded for review to Dr. Florence Houn, Director, Office of Drug Evaluation III. We will contact you should we have any questions or require additional information.

If you have any questions, please contact me at (301) 594-5479.

Sincerely,

/S/

(See appended electronic signature page)

Kim M. Colangelo
Formal Dispute Resolution Project Manager
Center for Drug Evaluation and Research

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

/s/

Kim Colangelo
9/9/22 11:24:27 AM