CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-289

CHEMISTRY REVIEW(S)

Final 4/25/02

CDER CHEMISTRY REVIEW CDER

NDA 21-289

Bravelle (urofollitropin for injection, purified)

Ferring Pharmaceuticals, Inc.

Martin Haber, Ph.D.
Division of Metabolic and Endocrine Drugs

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-289

2. REVIEW #: 2

3. REVIEW DATE: April 26, 2002

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	9/28/00
Amendment	2/15/01
Amendment	4/5/01
Amendment	4/23/01
CMC Review #1	7/5/01
IR Letter	7/9/01
NA Letter	7/29/01
IR Letter	3/18/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	6/27/01
Amendment	7/11/01
Amendment	7/19/01
Amendment	8/9/01
Amendment	10/31/01
Amendment	4/8/02
Amendment	4/18/02
Amendment	4/25/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Ferring Pharmaceuticals, Inc.
Address:	120 White Plains Road, Suite 400
Representative:	Dr. Ronald V. Nardi
Telephone:	(914) 333-8900

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Bravelle
b) Non-Proprietary Name (USAN): Urofollitropin, purified
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Infertility

11. DOSAGE FORM: Lyophilized powder for Injection

12. STRENGTH/POTENCY: 75 IU

13. ROUTE OF ADMINISTRATION: Subcutaneous and Intramuscular Injection

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

x SPOTS product – Form Completed

_____ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Follicle Stimulating Hormone (FSH), a glycoprotein hormone containing two peptide subunits of about 20 KDa each (including carbohydrate). The alpha subunit contains 92 amino acids and the beta subunit contains 111 amino acids. The hormone is purified from the urine of postmenopausal women. See Chemistry Review #1 for amino acid sequences.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	3/3/94	
	III			3	Adequate	3/14/00	
	III			3	Adequate	10/22/99	
	III			3	Adequate	1/4/01	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Repronex (menotropins) NDA	NDA 21-047	Ferring Pharmaceuticals
Urofollitropin, purified	[redacted]	Ferring Pharmaceuticals

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Satisfactory	3/14/02	
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Pending		
OPDRA	Satisfactory	5/23/01	J. Fan, Pharm. D.
EA	NA		
Microbiology	Satisfactory		

The Chemistry Review for NDA 21-289

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

In their 4/18/02 Amendment, Ferring has agreed to make developing and implementing identification tests for lactose and polysorbate 20 (for drug product release) a Phase IV commitment to be completed within one year of NDA approval.

II. Summary of Chemistry Assessments

NDA History: The original NDA for this product from Ferring was submitted on 9/28/00. Numerous CMC deficiencies were communicated to the sponsor in an information request (IR) letter from the FDA dated 7/9/01. For a detailed list, see Chemistry Review #1 dated 7/5/01. Several amendments and responses were made by the firm at the very end of the last review cycle and were not reviewed before the NDA PDUFA action date, 7/29/01. A Not Approvable (NA) letter from the FDA was issued to the firm on 7/27/01 that also contained several chemistry comments. For drug substance, major deficiencies were in description /characterization, methods of manufacturing, reference standards, and specifications. For drug product, major deficiencies were in manufacturing, specifications, and stability. The final complete response by the firm to the IR and NA letters was submitted in an Amendment dated 10/31/01. Those amendments that were not previously reviewed in the first review cycle are reviewed here also in this review, see cover form. During this review, a second IR letter from the FDA dated 3/18/02 was sent to Ferring to clarify remaining CMC issues. The firm responded with the 4/8/02 Amendment. The 4/18/02 Amendment adds two more minor CMC changes to the drug product specifications and the proposed Phase IV commitment. The 4/25/02 Amendment provides updated stability data.

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is a sterile lyophilized powder containing purified urofollitropin (follicle stimulating hormone or FSH), lactose, polysorbate 20 and sodium phosphate in a glass vial with rubber stopper. The product contains 82.5 IU of FSH/vial and is labeled to deliver 75 IU FSH/mL after reconstitution with sterile saline. Bravelle is indicated for ovulation induction.

The drug substance, purified urofollitropin (FSH), is a natural glycoprotein hormone isolated from urine obtained from post-menopausal women. FSH contains two different peptide subunits of about ——— (including carbohydrate). The alpha protein subunit contains 92 amino acids and the beta protein subunit contains 111 amino acids. The proposed drug product formulation was used for all clinical studies.

B. Description of How the Drug Product is Intended to be Used

The dose used must be individualized for each patient by a physician experienced in providing fertility treatments. The recommended initial dose is 150 IU daily for the first five days. Bravelle is supplied in a sterile, lyophilized, single dose vial containing 82.5 IU of FSH, to deliver 75 IU FSH after reconstituting with diluent. Each vial is available with an accompanying vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP. The maximum daily dose is 450 IU FSH. The proposed expiration period is 24 months stored at refrigerated or room temperature.

C. Basis for Approvability or Not-Approval Recommendation

This review covers the firm's complete response to the CMC sections of the information request and not approvable letters from the Agency. The firm has adequately responded to chemistry deficiencies. Therefore, from a chemistry viewpoint, the NDA is approvable.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

Martin Haber, Ph.D./Date: Same date as draft review
Duu-Gong Wu, Ph.D./Date
Archana Reddy/Date

C. CC Block

See DFS

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

70 pages

Summary of Chemistry Review of NDA 21-289 (Bravelle)

A. Drug Substances:

Human follicle stimulating hormone is a natural hormone isolated from urine obtained from post-menopausal women. Like other pituitary hormones, it is composed of two subunits, alfa and beta, with 92 and 111 amino acids, respectively, and glycosylated at two sites in each subunit. The glycosylation renders this protein biologically active. This natural product has been previously approved as either crude or purified form, and this NDA describes another purified form.

Since this is a glycoprotein with theoretically 2970 possible isoforms arising from differences in carbohydrate moities, characterization of the protein is not as simple as ordinary organic molecules. Amino acid sequences of the two subunits are in line with the published data and estimation of molecular weight based on size exclusion chromatography and [redacted] appears to be comparable to what is expected. There seem to be some differences in the isoform profiles between this product and the counterpart, though not definitive, showing the majority of isoforms appear to be in the **more basic (pI 4.5-5.8) region** than the counterpart (pI 3.5-5.2). **Mean specific activity** (8960+/-560IU/mg) is also noted to be somewhat **lower than the counterpart** (>10,000 IU/mg) suggesting a possible correlation between the difference in isoform profile and the biological activity.

One of the distinct characterizing techniques for isoforms is isoelectric focusing technique (IEF) and this application **did not demonstrate their capability of producing a well defined IEF profile** in terms of resolution and sufficient range of PI for covering all isoforms. Without a well defined IEF technique, the consistency of isoform profile from a batch to another can not be assured.

The drug substance is manufactured by [redacted] **in compliance to cGMP.**

The manufacturing process was validated for removal of virus up to 10^{11}-10^{16} fold, which is deemed adequate.

The sponsor proposed specifications for controlling the quality of the drug substance such as identification, specific activity, oxidized forms, impurities, aggregates, dimers, LH limit, water content, appearance, endotoxin, hepatitis B, HIV, safety, microbial limit, and isoforms. **However, they are not considered to be adequate for assuring quality of the drug substance.**

The sponsor needs to upgrade the specifications by establishing a specification for [redacted] analysis, revising the specifications for the oxidized forms, including specifications for dissociated subunits and carbohydrate composition, implementing a validated [redacted] assay, and providing validation data for Hepatitis A and Hepatitis C virus detection method.

In order to make the specifications valid, **a reference standard should be established with extensive characterization. However, the information provided is not deemed adequate.** The sponsor **needs to provide** a testing protocol for establishing in-house reference standard, its potency, batch size and stability, certificate of analysis, the identity of international standard being used, and specification for oxidized forms.

Based on the available stability data, the sponsor proposed to store the drug substance up to [redacted] months at -8°C.

B. Drug Product:

The drug product is sterile lyophilized powder containing purified urofollitropin (75 IU), lactose [redacted], polysorbate 20 (0.005mg), sodium phosphate dibasic heptahydrate [redacted]. The sponsor indicates that the product contains [redacted], which is **not acceptable** unless, adequately justified.

It is manufactured by SP Pharmaceuticals, LLC, 4272 Balloon Park, Albuquergue, NM, and packaged by SP Pharmaceuticals LLC, 4401 Alexander Blvd, Albuquergue, NM, and the facility at 4401 Alexander Blvd, Albuquerque is **not in compliance to cGMP.**

The lyophilized powder is to be reconstituted with 0.9% of sodium chloride injection, USP, which is supplied by [redacted] however, **no information** is available on the manufacture of the **diluent.**

The quality of the drug product is controlled by tests such as appearance, constituted solution, reconstitution time, pH, bacterial endotoxins, sterility, particulate matter, assay, moisture, uniformity of dosage unit, oxidants. **The sponsor needs to implement specifications for monomer content and dissociated subunits.** Also needed is the **method validation package** for the drug product to be **validated by FDA laboratories.**

The drug product is packaged into a [redacted], sealed by [redacted] flip-top seal. The container closure systems are considered to be adequate to protect the drug from the environment.

The sponsor provided several different stability protocols, thereby making it difficult to assess stability of the drug product. The sponsor needs a unified single stability protocol to assess the stability of the drug product. The sponsor proposed [redacted] at either 2-8°C or 25°C, but due to the difficulty of evaluation of available data ([redacted] of drug substance, inadequate monitoring for degradation products, no sterility testing during stability studies, etc.), **no meaningful expiration date can be established at this time.**

The tradename, **Bravelle,** was accepted by OPDRA. The established name should be changed from [redacted] to "urofollitropin for injection, purified".

C. Conclusion and Recommendation:

As recommended from Chemistry Review #1, this NDA is ***approvable*** from chemistry, manufacturing, and controls point of view pending resolution of the following issues.

2. The specifications for the drug substance are not deemed adequate to assure consistent quality of the drug substance.

3. The [redacted] in the manufacture of the drug product should be justified with data.

4. The drug product is to be reconstituted with 0.9% sodium chloride solution, however, no manufacturing information is available for this diluent.

5. The specifications for the drug product [redacted]

6. Three copies of complete method validation package should be submitted for validation by Agency's laboratories.

7. The proposed [redacted]

8. Satisfactory inspection results.

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

cc: original NDA 21-289
HFD-580/Div File
HFD-580/MRhee
HFD-510/DWu/MHaber

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

/s/

Moo-Jhong Rhee
7/25/01 03:15:35 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-289 **DATE REVIEWED:** July 5, 2001

CHEMISTRY REVIEW #: 1 **REVIEWER:** Martin Haber, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9/28/00	9/29/00	10/4/00
AMENDMENT	2/15/01	2/16/01	
AMENDMENT	4/5/01	4/6/01	
AMENDMENT	4/23/01	4/24/01	

NAME & ADDRESS OF SPONSOR:

Ferring Pharmaceuticals, Inc.
120 White Plains Road, Suite 400
Tarrytown, NY 10591 (914) 333-8900

DRUG PRODUCT NAME:

Proprietary: **Bravelle** (formerly Ovanex)
Nonproprietary: Urofollitropin, purified (FSH)
Chem.Type/Therapeutic.Class: Type 3/ Class S

PHARMACOL. CATEGORY/INDICATION: Treatment of infertility; induction of ovulation
DOSAGE FORM: Lyophilized powder in vial
STRENGTHS: 75 I.U./vial
ROUTE OF ADMINISTRATION: I.M. and S.C. Injection
Rx/OTC: X **Rx** ___ **OTC**
SPECIAL PRODUCTS: X Yes ___ No
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Follicle Stimulating Hormone (FSH), a glycoprotein hormone containing two peptide subunits of about 20 KDa each (including carbohydrate). The alpha subunit contains 92 amino acids and the beta subunit contains 111 amino acids, see review notes for sequences. The hormone is purified from the urine of postmenopausal women.

REMARKS:

This is a consult review for HFD-580. This NDA provides for Bravelle (urofollitropin for injection) drug product containing highly purified urofollitropin (urinary FSH). It is derived from the same starting material (human urine) used for the sponsor's approved menotropins product, Repronex (NDA 21-047, discontinued ANDA 73-598/599), which contains both FSH and LH. For drug substance, major deficiencies are in description /characterization, manufacturers, methods of manufacturing, reference standards, specification tests and methods, and stability. For drug product, major deficiencies are in manufacturing, tests and acceptance criteria, and stability. The 2/15/01 Amendment provides revised drug substance methods in Spanish. The 4/5/01 Amendment provides for complete amino acid sequences, carbohydrate composition, and updates on impurities, acceptance criteria and stability. The 4/23/01 Amendment provides for additional method validations. The 4/20/01 and 6/8/01 Amendments provide for labeling updates. The 10 month User fee date is 7/29/00. EER is pending. Microbiology review is complete. For specific chemistry comments, see Review notes and Chemistry Review Summary.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint, the application is **Approvable** pending a satisfactory response to chemistry deficiencies. The sponsor should provide additional chemistry information (see draft letter).

Orig. NDA # 21-289
cc: HFD-510/D-G.Wu/M.Haber
HFD-580/Division file/E.DeGuia/D.Spell-LeSane/M-J.Rhee

Martin Haber, Ph.D.
Review Chemist

R/D Init by: Dr. D-G. Wu, Team Leader Chemist

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

81 Pages

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
7/10/01 10:16:35 AM
CHEMIST

Duu-gong Wu
7/10/01 05:06:03 PM
CHEMIST

Moo-Jhong Rhee
7/12/01 01:20:12 PM
CHEMIST
I concur

NDA 21-289

A Statistical review of stability was not needed.

NDA 21-289

No new DMF reviews or amendments this review cycle. See Chemistry review page 2.

NDA 21-289

The Environmental Assessment review is located on page 72 of Chemistry Review #1.

NDA 21-289

A Microbiology (Efficacy) review was not needed.

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21289/000
Stamp: 29-SEP-2000
Regulatory Due: 29-JUL-2001
Applicant: FERRING PHARMS
120 WHITE PLAINS RD STE 400
TARRYTOWN, NY 10591
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 30-MAY-2001
Brand Name: OVANEX (PUFIFIED UROFOLLITROPIN) 75IU
Estab. Name:
Generic Name: PURIFIED UROFOLLITROPIN

Dosage Form: (FOR INJECTION)
Strength: 75 IU

Application Comment: NDA PROVIDES FOR A PURIFIED PREPARATION OF UROFOLLITROPIN, A GLYCOPROTEIN HORMONE ISOLATED FROM THE URINE OF POSTMENOPAUSAL WOMEN. UROFOLLITROPIN IS ALSO KNOWN AS FOLLICLE STIMULATING HORMONE OR FSH. (on 16-NOV-2000 by M. HABER (HFD-510) 301-827-6420)

FDA Contacts:

E. DEGUIA	(HFD-580)	301-827-4260 ,	Project Manager
M. HABER	(HFD-510)	301-827-6420 ,	Review Chemist
D. WU	(HFD-510)	301-827-6375 ,	Team Leader

Overall Recommendation: WITHHOLD on 23-JUL-2001 by R. WOODS (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No:
Responsibilities:
Profile: CTL
Estab. Comment:

AADA:
OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-NOV-2000				HABERM
OC RECOMMENDATION	17-NOV-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: [redacted]

DMF No:
Responsibilities:
Profile: CEX
Estab. Comment:

AADA:
OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-NOV-2000				HABERM
OC RECOMMENDATION	20-NOV-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Profile: CTL
Estab. Comment:

OAI Status: NONE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	16-NOV-2000			HABERM
SUBMITTED TO DO	20-NOV-2000	GMP		DAMBROGIOJ
DO RECOMMENDATION	24-NOV-2000		ACCEPTABLE	EGASM
			BASED ON FILE REVIEW	
BASED ON EI OF 4/29/99				
OC RECOMMENDATION	24-NOV-2000		ACCEPTABLE	EGASM
			DISTRICT RECOMMENDATION	

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Estab. Comment: [redacted]

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-NOV-2000				HABERM
OC RECOMMENDATION	17-NOV-2000			ACCEPTABLE	FERGUSONS
				BASED ON PROFILE	

Establishment: 1643045
SP PHARMACEUTICALS LLC
4272 BALLOON PARK RD NORTHEAST
ALBUQUERQUE, NM 87109

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-NOV-2000				HABERM
SUBMITTED TO DO	17-NOV-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	27-MAR-2001	PS			WSHERER
INSPECTION SCHEDULED	09-APR-2001				WSHERER
DO RECOMMENDATION	21-JUN-2001			WITHHOLD	WSHERER
				EQUIPMENT QUALIFICATION INADEQUATE QA FUNCTIONS TRAINING	
RECOMMEND WITHHOLD BASED ON 5-8/17-2001 PRE-APPROVAL INSPECTION. COULD NOT ENTER INSPECTION MILESTONE BECAUSE CSO PATRICIA CORTEZ NOT RECOGNIZED BY SYSTEM.					
EIR RECEIVED BY OC	27-JUN-2001				WOODSR
OC RECOMMENDATION	23-JUL-2001			WITHHOLD	WOODSR
				EIR REVIEW-CONCUR W/DISTRICT	

Profile: SVL OAI Status: NONE

Estab. Comment: DRUG PRODUCT MANUFACTURER. DRUG PRODUCT IS TESTED FOR APPEARANCE, CONSTITUTED SOLUTION, CONSTITUTION TIME, PH, MOISTURE, UNIFORMITY OF DOSAGE, ENDOTOXIN, PARTICULATES AND STERILITY. SOME TESTING IS

ALSO DONE BY SP PHARMA AT 4200 BALLOON PARK ROAD. (on 16-NOV-2000 by M. HABER (HFD-510) 301-827-6420)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-NOV-2000				HABERM
SUBMITTED TO DO	17-NOV-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	27-MAR-2001	PS			WSHERER
INSPECTION SCHEDULED	09-APR-2001				WSHERER
DO RECOMMENDATION	21-JUN-2001			WITHHOLD EQUIPMENT QUALIFICATION INADEQUATE QA FUNCTIONS TRAINING	WSHERER
RECOMMEND WITHHOLD BASED ON 5-8/17-2001 PRE-APPROVAL INSPECTION. COULD NOT ENTER INSPECTION MILESTONE BECAUSE SYSTEM WOULD NOT RECOGNIZE CSO PATRICIA CORTEZ.					
EIR RECEIVED BY OC	27-JUN-2001				WOODSR
OC RECOMMENDATION	23-JUL-2001			WITHHOLD EIR REVIEW-CONCUR W/DISTRICT	WOODSR

Establishment: 1722034
SP PHARMACEUTICALS LLC
4401 ALEXANDER BLVD NE
ALBUQUERQUE, NM 87107

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: SVL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-NOV-2000				HABERM
SUBMITTED TO DO	17-NOV-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	27-MAR-2001	PS			WSHERER
INSPECTION SCHEDULED	09-APR-2001				WSHERER
DO RECOMMENDATION	21-JUN-2001			ACCEPTABLE INSPECTION	WSHERER
RECOMMEND APPROVAL BASED ON 5-8/17-2001 PRE-APPROVAL INSPECTION. NO INSPECTION MILESTONE CREATED BECAUSE SYSTEM WOULD NOT RECOGNIZE CSO PATRICIA CORTEZ. THIS LOCATION IS PRIMARILY WAREHOUSING AND PACKAGING.					
OC RECOMMENDATION	25-JUN-2001			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment:

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: OAI ALERT

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	16-NOV-2000				HABERM
SUBMITTED TO DO	20-NOV-2000	10D			DAMBROGIOJ
DO RECOMMENDATION	21-NOV-2000			WITHHOLD	DPAGANO
				PEND REG ACTION - WARNING LTR	
ASSIGNED INSPECTION	06-FEB-2001	PS			DPAGANO
INSPECTION SCHEDULED	24-MAY-2001				DPAGANO
INSPECTION PERFORMED	19-JUN-2001		14-JUN-2001		DPAGANO
DO RECOMMENDATION	19-JUN-2001			WITHHOLD	DPAGANO
				INADEQUATE LAB CONTROLS PREVIOUS DEVIATIONS PERSIST	
METHOD VALIDATION ISSUES.					
EIR RECEIVED BY OC	22-JUN-2001				HARTMANB
OC RECOMMENDATION	26-JUN-2001			WITHHOLD	HARTMANB
				EIR REVIEW-CONCUR W/DISTRICT	
FD 483 ONLY					

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21289/000**
Stamp: **29-SEP-2000** Regulatory Due: **29-JUL-2001**
Applicant: **FERRING PHARMS**
120 WHITE PLAINS RD STE 400
TARRYTOWN, NY 10591

Priority: **3S** Org Code: **580**
Action Goal: District Goal: **30-MAY-2001**
Brand Name: **OVANEX(PUFIFIED UROFOLLITROPIN)75IU**
Established Name:
Generic Name: **PURIFIED UROFOLLITROPIN**
Dosage Form: **FIJ (FOR INJECTION)**
Strength: **75 IU**

FDA Contacts:			
E. DEGUIA	**(HFD-580)**	**301-827-4260**	**, Project Manager**
M. HABER	**(HFD-510)**	**301-827-6420**	**, Review Chemist**
D. WU	**(HFD-510)**	**301-827-6375**	**, Team Leader**

Overall Recommendation:

WITHHOLD on 23-JUL-2001 by R. WOODS (HFD-324) 301-827-0062

Establishment: —
—

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: —

Establishment: —
—

DMF No:
AADA No:

Profile: **CEX** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **20-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **24-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: —
—

Establishment: —
—

DMF No:
AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-NOV-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **1643045**
SP PHARMACEUTICALS LLC
4272 BALLOON PARK RD NORTHEAS
ALBUQUERQUE, NM 87109

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-2001**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRICT**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE RELEASE TESTER

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JUL-2001**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRICT**

Establishment: **1722034**
SP PHARMACEUTICALS LLC
4401 ALEXANDER BLVD NE
ALBUQUERQUE, NM 87107

DMF No:
AADA No:

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **25-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **OAI ALERT**
Last Milestone: **OC RECOMMENDATION**

Responsibilities:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: **26-JUN-2001**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRICT**

APPEARS THIS WAY
ON ORIGINAL

NDA 21-289

Methods validation will be completed upon approval.