CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DF

Food and Drug Administration
Rockville MD 20857

NDA 20-582

AUG 15 1997

Organon, Inc.
Attention: Mr. Albert Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your pending January 11, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **Follistim** (follitropin beta for injection).

We have completed our review of the physician package insert dated May 14, 1997, in conjunction with your letter dated July 11, 1997, for your submission and have several comments. Revisions have been incorporated directly into the enclosed package insert. Additions have been noted in redline, deletions have been noted as ~~strikeouts~~, rearranged sentences are in *italics*.

In addition, we have reviewed the carton and container labels from your submission dated June 12, 1997, and find the picture to be unacceptable.

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

If you have any questions, please contact Lana L. Pauls, M.P.H., Chief, Project Management Staff, at (301) 827-4260.

Sincerely,

Marcum 8/14/97

Lisa D. Rarick, M.D.
Director
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
revised physician insert

cc:
Original NDA 20-582
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-580/RBennett/HJolson/DWu/MJRhee/KRaheja/KGBarnette
HFD-820/ONDC Division Director

Drafted by: LPauls/August 11, 1997
Concurrences:
HJolson 08.11.97/RBennett 08.12.97/DWu 08.12.97/JHELE 08.13.97
INFORMATION REQUEST (IR)

LLP 8/14/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rumble

Food and Drug Administration
Rockville MD 20857

NDA 20-582

MAR 25 1997

Organon, Inc.
Attention: Mr. Albert Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your pending January 11, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **TRADENAME** [follitropin (rDNA origin) for injection].

We have completed our review of the physician package insert for your submission and have several comments. Revisions have been incorporated directly into the enclosed package insert. Additions have been noted in double underline, deletions have been noted as ~~strikeouts~~.

Please note, the issue regarding the established name is still under discussion and any outcome will be communicated seperately.

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

If you have any questions, please contact Lana L. Pauls, M.P.H., Chief, Project Management Staff, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
revised physician insert

LLP 3/19/97

cc:
Original NDA 20-582
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-580/RBennett/HJolson/DWu/MJRhee/KRaheja/KGBarnette
HFD-820/ONDC Division Director

Drafted by: /March 17, 1997/
Concurrences:
RBennett 03.17.97/HJolson, KRaheja, KMeaker, MJRhee 03.18.97/DWu, JMele 03.19.97

INFORMATION REQUEST (IR)

NDA 20-582

DEC 19 1996

Organon, Inc.
Attention: Mr. Albert P. Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your pending January 11, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **TRADENAME** [follitropin (rDNA origin) for injection].

We have completed our review of the Biopharmaceutics section of your submission and have identified the following deficiencies:

General

An *in vivo* bioequivalence study comparing the 75 IU/vial and the 150 IU/vial formulation strengths should be performed. The proposed protocol should be submitted to the Agency for review prior to initiation. The 150 IU vial cannot be approved without the results from this trial.

Labeling

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Lana L. Pauls, M.P.H., Chief, Project Management Staff, at (301) 827-4260.

Sincerely yours,

Heidi Jolson M.D. for LR 12/19/96

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-582
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-580/ADunson/KGBarnette

Drafted by: LPauls/December 16, 1996/N20582IR.BPH

Concurrences:
KGBarnette 12.16.96/ADorantes 12.18.96/HJolson 12.19.96

INFORMATION REQUEST (IR)

DEC 5 1996

NDA 20-582

Organon, Inc.
Attention: Mr. Albert P. Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your pending January 11, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim [follitropin (rDNA origin) for injection].

We also refer to your amendment dated May 14 and 16, and October 8 and 10, 1996.

We have completed our review of the Manufacturing and Quality Controls section of your submission and have identified the following deficiencies:

General

1. The information provided in various parts of the Drug Substance section is fragmented and often without clear references to what was performed by the referenced DMF holder and what was performed by the NDA applicant. Therefore, it was very difficult to verify and review the content of your submission. For future submissions, please follow the current format specified in the FDA guideline and guidance documents.

2. If the referenced DMF holder, is owned by the same parent company as your company, then the entire content of the DMF including stability data should be submitted to the Drug Substance section of your NDA.

Drug substance

1. The facilities used for testing of your in-house reference standard and for characterization of the cell banks should be identified. Specifically, the name and address for the facility used for testing the adventitious agents (virus, bacteria, and mycoplasma) in the cell banks, if it is not one of the facilities listed in the DNA submission, should be included.

2. The inconsistency in the testing facilities listed in Vol.1.3, pages 112 and 133 for the drug substance should be clarified.

3. A detailed description for preparation of the Master and Working Cell Bank, including conditions, media, volume, and qualification tests, should be provided.

4. A qualification protocol is needed for the preparation of future cell banks.

5. The conclusion that no reduction in gene copy numbers during production based on a visual comparison of band intensity on autoradiographs (Vol. 1.3, pages 74 and 78) is not acceptable. The method used to estimate gene copy number in the CHO.FSH.30 and the production cells must be validated for accuracy.

6. Tests and specifications for the drug substance should be revised to include tests for oxidized recFSH and dissociated subunits. In addition, the acceptable limits for the carbohydrate composition should be provided.

7. The chromatograms for peptide mapping and (oligomer contamination) and the photographs of IEF gels (pI distribution) for the three representative lots of drug substance described in Vol. 1.3, pages 270-276 should be provided.

8. Information provided for your in-house reference standard is inadequate. Results of additional physical/chemical/biological characterizations, including full amino sequence, correct arrangement of the disulfide bonds, gylcosylation sites, and oligosaccharide map should be provided.

9. For the batch analysis of Reference Standard ORG 32489 Batch E and Batch J (Vol. 1.4, pages 228-229), the chromatograms for (Oligomer contamination) and (peptide mapping) as well as the photographs for SDS-PAGE and gels (subunit contamination and pI distribution) should be provided.

10. Information on the storage conditions and its stability during storage for your in-house reference standards (Batch E and J) should be provided.

11. A qualification protocol for your future in-house reference standard should be provided.

Drug product

1. The Tests and Specifications section for the drug product should be revised to include tests for dissociated subunits and protein content. The limit for oxidation, which has not been defined in the current submission, should be provided. In addition, representative certificates of analysis for the drug product should be provided for lots tested according to the revised tests and specifications.

2. The method used for determining the oxidized form of recFSH is not acceptable. This method can only detect the oxidized a-subunit. A different method capable of detecting the real content of oxidized form, preferably the whole rhFSH molecule, should be developed.

3. Chromatograms for the results of (oligomer contamination) and (Oxidation) for the three representative lots of drug products (Vol. 1.8, pages 157-173) should be provided.

4. Based on the six-month data compiled from the results of inadequate stability testing (Vol. 1.10, pages 98-110), the proposed expiration dating of 24 months can not be granted. Tests for monitoring degradation product such as oxidized recFSH, dissociated subunits, as well as changes in the carbohydrate composition should be included. Additional stability data derived from the revised stability protocol is needed in order to establish a valid expiration dating. The analytical results to be submitted should contain the representative chromatograms for

5. Stability data for the drug product reconstituted with actual diluent should be provided.

6. Stability protocol and data should also be provided for the diluent.

Environmental Assessment

The maximum expected environmental concentration (MEEC) of the estimated amount of annual use of Follitropin in the United States five years after approval should be provided. Please see "*Guidance for Industry - For the Submission of an Environmental Assessment in Human Drug Applications and Supplements, November 1995*" for further information.

Labeling

Please note, deficiencies have been found in the DMF cited in support of your NDA. These deficiencies will be sent under separate cover to the DMF holder.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Lana L. Pauls, M.P.H., Chief, Project Management Staff, at (301) 827-4260.

Sincerely,

Hardi Dolan MD L LR 12/5/96

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-582
HFD-580/Div. Files
HFD-580/ADunson/L.L.Pauls
HFD-510/DWu
HFD-580/MJRhee
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: LPauls/November 26, 1996/N20582IR.CHM

Concurrences:
DWu, MJRhee 12.05.96

INFORMATION REQUEST (IR)

LLP 12/5/96

NDA 20-582

OCT 28 1996

Organon, Inc.
Attention: Mr. Patrick J. Osinski
Vice President, Product Development and
Government Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Osinski:

Please refer to your pending January 11, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follitropin [follitropin beta (rDNA origin) for injection].

We have completed our review of the Microbiology section of your submission and have identified the following deficiencies:

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
(301) 827-4260

Sincerely yours,

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

LLP 10/29/96

cc:
Original NDA 20-582
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-580/MJRhee
HFD-160/BUratani
HFD-820/Yuan Yuan Chiu (only for CMC related issues)

drafted: LPauls/October 25, 1996/N20582IR.MIC

Concurrence:
MJRhee 10.25.96

INFORMATION REQUEST (IR)

SEP 24 1996

NDA 20-582

Organon, Inc.
Attention: Mr. Patrick J. Osinski
Vice President, Product Development and
Government Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Osinski

Please refer to your pending January 11, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim [follitropin beta (rDNA origin) for injection].

We also refer to your letter dated May 14, 1996.

Your proposed tradename, Follistim, has been determined to be acceptable for use.

Please note that all reviews are ongoing. Upon completion of reviews, comments if any will be forwarded if time allows prior to an action being taken on your application.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
(301) 827-4260

Sincerely yours,

9-24-96

Lisa Rarick, M.D.
Acting Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-582
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-510/DWu/SMoore
HFD-820/Yuan Yuan Chiu (only for CMC related issues)

drafted: LPauls/September 23, 1996/N20582NA.ME

NDA 20-582

Organon, Inc.
Attention: Ms. Edwina Muir
Manager, Regulatory Affairs
375 Mount Pleasant Ave.
West Orange, NJ 07052

MAR - 4 1996

Dear Ms. Muir:

Please refer to your pending January 11, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for follitropin beta (rDNA origin) for injection.

We have completed a preliminary review of the Biopharmaceutics section of your submission and have identified the following deficiencies:

We would appreciate your prompt written response along with a revised package insert so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Project Manager
(301) 443-3510

Sincerely yours,

3/4/96

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-582
HFD-510/Div. Files
HFD-510/SMalozowski
HFD-870/GBarnette/ADorantes
DISTRICT OFFICE

drafted: LPauls/November 20, 1995/N20582IR.BPH

Concurrences:
KGBarnette 02.16.96/ADorantes, RBennett 02.27.96

INFORMATION REQUEST (IR)

LLP 3/4/96

Pauls

NDA 20-582

JAN 18 1996

Organon, Inc.
Attention: Ms. Edwina Muir
Manager, Regulatory Affairs
375 Mount Pleasant Ave.
West Orange, NJ 07052

Dear Ms. Muir:

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

Name of Drug Product:	Follistim [follitropin beta (rDNA origin) for injection]
Therapeutic Classification:	Standard
Date of Application:	January 10, 1996
Date of Receipt:	January 11, 1996
Our Reference Number:	20-582

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 11, 1996, in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact Lana Pauls, M.P.H. at (301) 443-3510.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

EMGalliers 1/18/96

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-582
HFD-510/Div. Files
HFD-80
HFD-510/CSO/L.L.Pauls

drafted: LPauls/January 18, 1996/N20582.ack

ACKNOWLEDGEMENT (AC)

LLP 1/18/96

FEB 27 1996

NDA 20-582
follitropin beta (rDNA origin) for injection
Organon, Inc.

February 12, 1996

Memorandum of 21-day (filing) Meeting

Attendees:
Dr. Sobel
Dr. Rarick
Dr. Bennett
Dr. Moore
Dr. Wu
Dr. Raheja
Ms. Pauls
Mr. Marticello (HFD-713)
Dr. Barnette (HFD-870)

Not Present:
Dr. Jordan
Dr. Cooney (HFD-
Dr. Dorantes (HFD-870)

Purpose:

To determine whether the follitropin beta application is acceptable for filing. follitropin is indicated for:

a. induction of ovulation; and
b. use in assisted reproductive technology

Discussion:

The various disciplines discussed their portions of the application as follows:

Clinical:	Acceptable for filing. The pivotal trials have already been identified and sent to Dr. Turner in DSI.
Chemistry:	Acceptable for filing.
Pharmacology:	Acceptable for filing.
Statistics:	Acceptable for filing.
Biopharmaceutics:	Acceptable for filing. However, there is insufficient data to review the high dose (150 IU). The firm will be requested to perform an additional study should they wish to pursue approval for the highr dose.
Microbiology:	Acceptable for filing.
Environmental Assessment:	Acceptable for filing. To be completed with the chemistry review.

DSI: Dr. Bennett has already conveyed the studies to be audited directly to Dr. Turner.

Conclusions:

The application is acceptable for filing. The UF Goal date is January 11, 1997. The review team agreed that virtual (e-mail) status meetings would be sufficient.

Lana L. Pauls, M.P.H.
Consumer Safety Officer
2/27/96

cc:
NDA Arch
HFD-510
HFD-344/GTurner
HFD-870/GBarnette/ADorantes/JHunt
HFD-510/Attendees (present or absent listed above)
HFD-713/DMarticello/ENevius
HFD-805/DHussong/PCooney
HFD-510/LPauls/02.07.96/N20582fl.mtg

Concurrences:
RBennett 02.13.96/LRarick, 02.14.96/DWu 02.17.96/SMoore, KRaheja, SSobel 02.20.96