

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-273

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53(c)(1)

- (i) U.S. Patent No. 4,589,402
Expiration Date - July 26, 2004
- (ii) Type of Patent : Method of Use
- (iii) Name of Patent Owner of Record:

Serono Laboratories, Inc.
Randolph, Massachusetts

ORIGINAL DECLARATION

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 4,589,402 covers the formulation, composition and/or method of use of Follistim[®]-AQ (follitropin beta injection). This product is the subject of this application for which approval is being sought.



Patrick J. Osinski
Vice President
Organon Inc.

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53(c)(1)

- (i) U.S. Patent No. 5,767,251
Expiration Date - June 16, 2015

- (ii) Type of Patent : Drug Product

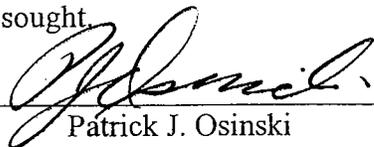
- (iii) Name of Patent Owner of Record:

Genzyme Corporation
Cambridge, Massachusetts

ORIGINAL DECLARATION

21 CFR §314.53(c)(2)

The undersigned declares that Patent No. 5,767,251 covers the formulation, composition and/or method of use of Follistim[®]-AQ (follitropin beta injection). This product is the subject of this application for which approval is being sought.



Patrick J. Osinski
Vice President
Organon Inc.

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53 (c) (1)

(i) U.S. Patent No. 5,929,028

Expiration Date - April 14, 2018

(ii) Type of patent: Drug Product (formulation)

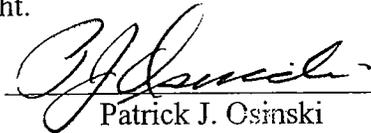
(iii) Name of Patent Owner of Record: Akzo Nobel N.V.
Arnhem, Netherlands

(iv) Name of Agent: William Blackstone, Esq.
Akzo Nobel Patent Dept.
1300 Piccard Drive, Suite 206
Rockville, MD 20850-4373

ORIGINAL DECLARATION

21 CFR §314.53 (c) (2)

The undersigned declares that Patent No. 5,929,028 covers the formulation, composition and/or method of use of Follistim[®]-AQ (follitropin beta injection). This product is the subject of this application for which approval is being sought.



Patrick J. Osinski
Vice President
Organon Inc.

0015

EXCLUSIVITY SUMMARY

NDA # 21-273

SUPPL # 000

HFD # 580

Trade Name Follistim® AQ

Generic Name (follitropin beta for injection)

Applicant Name Organon, Inc.

Approval Date, If Known August 26, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES NO

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

Sponsor submitted bioequivalence data comparing this product with Follistim (NDA 20-582) and supportive safety and efficacy data of pharmacokinetics studies between intramuscular administration and subcutaneous administration.

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2: Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 20-582

Follistim® (follitropin beta for injection)

NDA# 21-211

Follistim® AQ (follitropin beta for injection) Cartridge

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is

"yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

Investigation #1

!

YES

! NO

Explain:

! Explain:

Investigation #2

!

YES

! NO

Explain:

! Explain:

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

YES

NO

If yes, explain:

Name of person completing form: John Kim, R.Ph., J.D.

Title: Regulatory Health Project Manager

Date: August 2, 2005

Name of Office/Division Director signing form: Daniel Shames, M.D.

Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

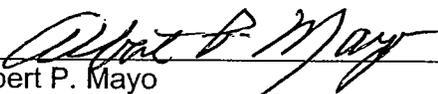
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
8/26/2005 10:23:50 AM

DEBARMENT CERTIFICATION

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc. did not and will not use in any capacity the services of any person debarred under subscriptions (a) or (b) [Section 306 (a) or (b)], in connection with the New Drug Application for Follistim®- AQ (follitropin beta injection), NDA No. 21-273



Albert P. Mayo
Executive Director
Regulatory Affairs



Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-273 Supplement Type (e.g. SE5): N/A Supplement Number: 000

Stamp Date: 24-Jul-2000 Action Date: 26-Aug-2005

HFD- 580 Trade and generic names/dosage form: Follistim[®] AQ (follitropin beta for injection)

Applicant: Organon, Inc. Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 2

Indication #1: The development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

Attachment A

Indication #2: The induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

This page was completed by:

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.
Regulatory Project Manager

cc: NDA 21-273
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Nenita Crisostomo
8/25/2005 04:20:36 PM



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

FACSIMILE TRANSMITTAL SHEET

DATE: August 23, 2005

To: Lawrence C. Starke, Ph.D. Director, Regulatory Affairs	From: Nenita Crisostomo, RN Project Manager
Company: Organon, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-325-4769	Fax number: 301-827-4267
Phone number: 973-325-4500	Phone number: 301-827-4260
Subject: Discipline Review Completed for NDA 21-273 NDA 21-273 Follistim AQ: FDA-proposed PPI	

Total no. of pages including cover: 16

Comments:

Dear Dr. Starke,

Attached are the FDA-proposed Patient Package Insert draft copies for your review. Please submit your response on/before close of business on August 24, 2005, and call me if you have any questions at Ph. 301-827-7260.

Thank you,
nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-4260. Thank you.

15 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-1



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

FACSIMILE TRANSMITTAL SHEET

DATE: August 23, 2005

To: Lawrence C. Starke, Ph.D. Director, Regulatory Affairs	From: Nenita Crisostomo, RN Project Manager
Company: Organon, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-325-4769	Fax number: 301-827-4267
Phone number: 973-325-4500	Phone number: 301-827-4260
Subject: Discipline Review Completed for NDA 21-273 NDA 21-273 Follistim AQ: FDA-proposed PI	

Total no. of pages including cover: 31

Comments:

Dear Dr. Starke,

Attached are the FDA-proposed Physician Insert draft copies for your review. Please submit your response on/before close of business on August 24, 2005, and call me if you have any questions at Ph. 301-827-7260.

Thank you,
nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-4260. Thank you.

30 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-2



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

FACSIMILE TRANSMITTAL SHEET

DATE: August 22, 2005

To: Lawrence C. Starke, Ph.D. Director, Regulatory Affairs	From: Nenita Crisostomo, RN Project Manager
Company: Organon, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-325-4769	Fax number: 301-827-4267
Phone number: 973-325-4500	Phone number: 301-827-4260
Subject: Discipline Review Completed for NDA 21-273 NDA 21-273 Follistim AQ: FDA-proposed PI & PPI	

Total no. of pages including cover: 50

Comments:

Dear Dr. Starke,

Attached are the FDA-proposed Physician Insert and the Patient Package Insert draft copies for your review. Please submit your response on/before August 23, 2005, and call me if you have any questions at Ph. 301-827-7260.

Thank you,
nita

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-4260. Thank you.

49 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-3

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

/s/

Nenita Crisostomo
8/22/2005 05:44:04 PM
CSO

Nenita Crisostomo
8/22/2005 05:45:27 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-273

INFORMATION REQUEST LETTER

Organon USA Inc.
Attention: Victor Paulus
Director, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Mr. Paulus:

Please refer to your July 21, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®] AQ (follitropin beta injection).

We also refer to your resubmission dated June 24, 2005.

We are reviewing the clinical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.



If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
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/

Margaret Kober
7/14/05 09:23:42 AM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-273

Organon USA Inc.
Attention: Lawrence C. Starke, Ph.D.
Senior Director, Regulatory Affairs
56 Livingston Avenue
Roseland, NJ 07068

Dear Dr. Starke:

We acknowledge receipt on June 27, 2005 of your June 24, 2005 resubmission to your new drug application for Follistim[®] AQ (follitropin beta injection).

We consider this a complete, class 1 response to our third approvable action letter dated May 17, 2005. Therefore, the user fee goal date is August 26, 2005.

If you have any questions, call John Kim, R.Ph., J.D., Regulatory Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
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/

Margaret Kober
7/12/05 11:10:37 AM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-273

Organon, Inc.
Attention: Albert P. Mayo
Vice President, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated July 21, 2000, received July 24, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®] AQ (follitropin beta injection).

We acknowledge receipt of your submissions dated: November 19, December 6, 2004; February 8, March 10, 21(2), and 25, 2005.

The November 19, 2004 submission constituted a complete response to our July 17, 2003 action letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiency:

Following the inspection (April 25, 2005 through May 3, 2005) of the Swords, County Dublin, Ireland manufacturing facility for this application, our field investigator conveyed deficiencies to the facility's representative. Satisfactory resolution of these deficiencies is required before this application may be approved.

Labeling discussions for this product will be deferred until all manufacturing facility deficiencies have been satisfactorily resolved. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call John Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
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/

Margaret Kober
5/17/05 03:07:08 PM
signed for Dr. Shames



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-273

INFORMATION REQUEST LETTER

Organon, Inc.
Attention: Albert P. Mayo
Vice President, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your July 21, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®] AQ (follitropin beta injection).

We also refer to your November 19, 2004 submission, containing a complete response to our approvable letter dated July 17, 2003.

We are reviewing the Clinical and Chemistry, Manufacturing and Controls sections of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical

1. Submit summaries of the two studies (E1616 and E1713) that were performed for local tolerance using the follitropin beta.
2. Submit a summary of Study 058007, a follow-up of Protocol 058004 that was previously submitted and reviewed for this NDA. The summary should include pregnancy data including multiple pregnancy, birth, and miscarriage, preferably in a table format.

Chemistry, Manufacturing and Controls

1. Revise the Description section of the package insert and all carton labels to include the compendial grades of the inactive ingredients.
2. Revise the dosage strengths on the container and carton labels as follows:
"75 IU /
"150 IU:
3. Include "Discard Unused Portion" and "Single Use Vial" on the principal display panel of carton labels.

If you have any questions, call John Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
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/

Margaret Kober
3/1/05 05:17:29 PM
Chief, Project Management Staff

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 12/10/04	DESIRED COMPLETION DATE: 2/10/05 PDUFA: 5/20/05	ODS CONSULT#: 00-0134-5
--------------------------------	--	--------------------------------

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Archana Reddy, MPH
Project Manager
HFD-580

PRODUCT NAME:

Follistim AQ (Follitropin Beta Injection)
75 International Units/0.5 mL
150 International Units/0.5 mL

NDA: 21-273

NDA SPONSOR:

Organon, Inc.

SAFETY EVALUATOR: Nora Roselle, PharmD

DMETS RECOMMENDATION:

DMETS recommends implementation of the container label, carton and insert labeling revisions outlined in the Section II of this review.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: January 21, 2005

NDA # 21-273

NAME OF DRUG: **Follistim AQ** (Follitropin Beta Injection)
75 International Units/0.5 mL
150 International Units/0.5 mL

NDA HOLDER: Organon, Inc

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580), to review the container labels, carton and insert labeling of Follistim AQ.

On September 29, 1997, the Agency approved "Follistim (Follitropin beta for injection)" under NDA 20-582, which was also manufactured by Organon. As per the online version of Drugs@FDA and verbal communication with Organon (1/25/05), Follistim is no longer marketed and was discontinued by the sponsor in March 2004. Follistim was supplied as a lyophilized powder for injection and could be administered either subcutaneously or intramuscularly.

On March 23, 2004, the Agency approved "Follistim-AQ Cartridge (Follitropin Beta Injection), 437.5 International Units/0.525 mL (delivering 300 International Units) and 737.5 International Units/0.885 mL (delivering 600 International Units)" under NDA 21-211. Follistim-AQ contains the same active ingredient, recombinant follicle-stimulating hormone, as Follistim; however, it is supplied as an aqueous solution. Follistim-AQ Cartridge (NDA 21-211) is supplied in a ready-for-use disposable cartridge containing either 300 or 600 International Units per 1.5 mL. The cartridge fits into a pen injector device and features an adjustable dosing system for administering the drug. The pen injector device with cartridge is intended for subcutaneous use only.

The sponsor is also submitting for the approval of "Follistim AQ (Follitropin Beta Injection), 75 International Units/0.5 mL and 150 International Units/0.5 mL" under NDA 21-273. DMETS conducted proprietary name reviews for NDA 21-273 in October 2000 and March 2003 (ODS Consult - 00-0263 and 00-0134-1) and found the name acceptable. This NDA is the same active ingredient as Follistim-AQ Cartridge, however the product will be supplied in vials for either subcutaneous or intramuscular injection.

PRODUCT INFORMATION

Follistim AQ (follitropin beta injection) is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Follistim AQ is also indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. Follistim AQ will be supplied as a sterile aqueous solution in two different concentrations: 75 International Units/0.5 mL and 150 International Units/0.5 mL. Follistim AQ should be refrigerated until dispensed.

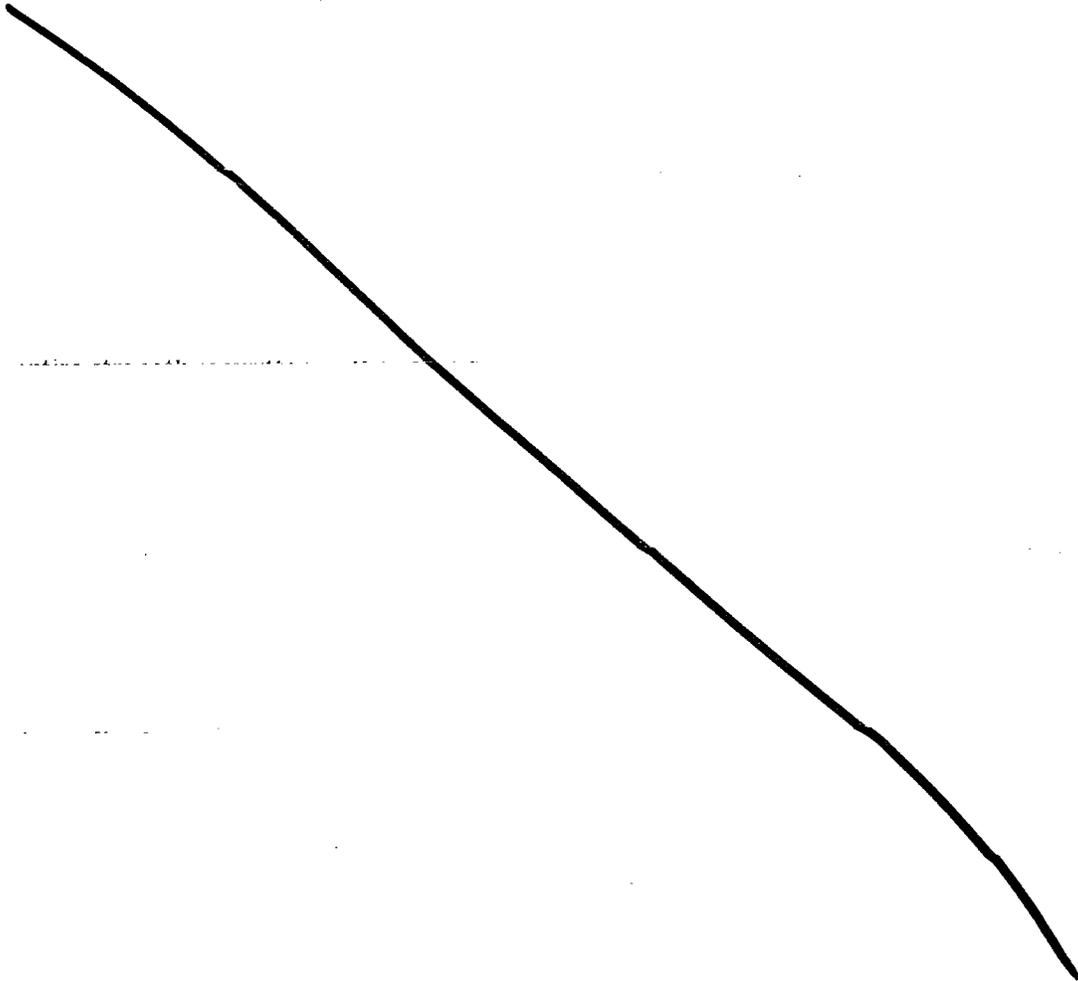
The usual dosage of the product differs with each indication:

For Assisted Reproductive Technologies (ART), a starting dose of 150 to 225 International Units is recommended for at least the first four days of treatment. After this, the dose may be adjusted for the individual patient based upon their ovarian response. Daily maintenance dosages ranging from 75 to 300 International Units for six to twelve days were sufficient, although longer treatment may be necessary. Patients who were low or poor responders maintenance doses of 375 to 600 International Units were administered. The maximum daily dose is 600 International Units.

For ovulation induction the recommended starting dose of Follistim AQ is 75 International Units for up to 14 days. The dose is then increased by 37.5 International Units at weekly intervals until follicular growth and/or serum estradiol levels indicate an adequate response. The maximum daily dose for ovulation induction is 300 International Units.

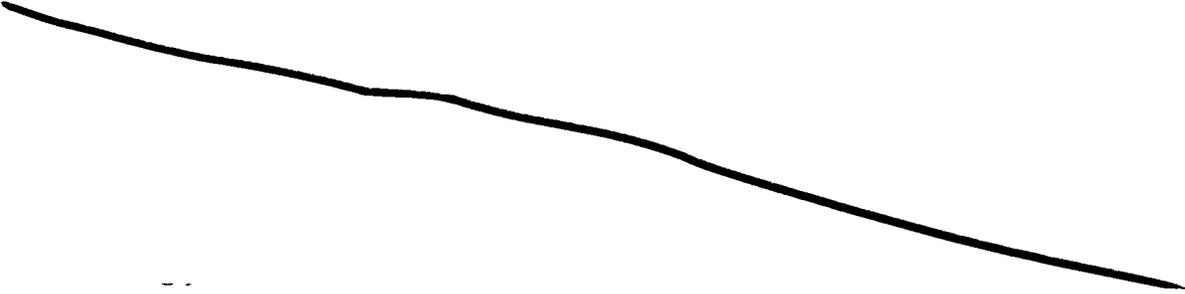
II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the "Follistim AQ" container labels, carton, and insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.



mg
i

¹ http://www.jcaho.org/accredited+organizations/patient+safety/05+npsg/05_npsg_hap.htm



III. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the container label, carton and insert labeling revisions outlined in Section II of this review.

DMETS 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, project manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh, MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Nora L. Roselle
2/11/05 02:22:20 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
2/11/05 02:52:07 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/11/05 02:58:22 PM
DRUG SAFETY OFFICE REVIEWER

Teleconference Minutes

Date: June 28, 2004 **Time:** 11:05 – 11:25 A.M. **Location:** PKLN 17B-43

NDA: 21-273

Drug Name: Follistim[®] AQ (follitropin beta injection)

Sponsor: Organon, Inc.

Indications: (1) Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program.
(2) The induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

Type of Meeting: Type A (Stalled Programs)

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

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

External Participant Lead: Lawrence Starke, Ph.D.

FDA Attendees:

Shelley R. Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Suong Tran, Ph.D., Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Karen Hoover, M.D., M.P.H., Medical Intern, DRUDP (HFD-580)

External Participants:

Organon USA Inc.:

Lawrence C. Starke, Ph.D. Director, Regulatory Affairs
Thomas Delters, R.Ph. Senior Manager, Regulatory Affairs
Mary Mahony, Ph.D. Associate Director (Reproductive Medicine), Medical Affairs
Nancy Alexander, Ph.D., Director, Medical Affairs

N.V. Organon (Netherlands):

Dr. J.P.W.M. Lamers-Lemmers, Ph.D., Global Regulatory Affairs Team Leader

Organon Ireland LTD:

Una Hearty, Ph.D., Qualified Person
Brian Masterson, Manager, Parenterals, Production
Eilish Kelly, Validation Manager
Dara Clarke, Ph.D., Manager, Regulatory Affairs
Lavelle Fitzsimons, Group Leader, Analytical Laboratories

Background:

Follistim[®] AQ (follitropin beta injection) is a new pharmaceutical presentation of the approved product, Follistim[®] (follitropin beta for injection) NDA 20-582. Follistim[®] AQ is an injectable aqueous solution of 75, 150, 225 and 300 IU follitropin beta in a vial. Because of chemistry and microbiology deficiencies, this new drug application received an approvable action on May 24, 2001. A complete response addressing all chemistry and microbiology deficiencies was received on October 18, 2002. Subsequently, the sponsor received an approvable action letter on July 16, 2003 because of deficiencies at the West Orange, NJ manufacturing site. This site has since been closed down by the sponsor. The sponsor plans to transfer the manufacturing and testing operations for this drug product to the Organon Ireland, LTD facility located in Swords, County Dublin, Ireland.

Meeting Objective:

To come to agreement on the sponsor's transfer plans for Follistim[®] AQ to Organon Ireland LTD, including a discussion on validation, manufacturing, and stability information from Organon Ireland LTD required for approval of the 75 IU, and 150 IU strengths.

Discussion:

Regulatory Comments:

Sponsor Questions and Responses:

CMC Question 1:

Organon wishes to seek concurrence from the Agency that stability information from Organon Ireland, LTD to be provided in the response letter is adequate to support approval of the 75, and 150 IU/vial strengths with the proposed shelf life and storage conditions.

DRUDP Response:

[Redacted]

CMC Question 2:

Provided that our response to the approvable letter of July 17, 2003, which will contain updated information on the Organon Ireland facility, is deemed to be a complete response to the action letter, will review of this submission be on a 6-month clock?

DRUDP Response:

[Redacted]

1 Page(s) Withheld

 ✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Action Item:

- 1) The Project Manager will fax the minutes of this meeting to the sponsor within 30 days.

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

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Cc:

Archival NDA 21-273

HFD-580/Division Files

HFD-580/Reddy/Rhee/Slaughter/Tran/Gassman/

Created by: Archana Reddy, July 13, 2004

Concurrence: mjr/July 14, 2004, ag/July 14, 2004, st/July 15, 2004, srs/July 22, 2004

Finalized: ar/July 26, 2004

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

/s/

Shelley Slaughter
7/26/04 01:38:18 PM
I concur.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-273

Organon, Inc.
Attention: Lawrence Starke, Ph.D.
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Dr. Starke:

Please refer to your New Drug Application (NDA) for Follistim[®] AQ (follitropin beta injection).

We also refer to your May 27, 2004, correspondence, received May 28, 2004, requesting a Type A meeting to come to agreement with the Agency regarding your transfer plans for Follistim[®] AQ. You are proposing to move the manufacturing and testing of Follistim[®] AQ to the Organon Ireland Ltd. site, located in Swords, County Dublin, Ireland, as well as provide additional documentation to the NDA, which may be required to support this transfer.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The teleconference is scheduled for:

Date: June 28, 2004

Time: 11:00 A.M. – 12:00 P.M.

CDER participants:

Daniel Shames, M.D., Division Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

Donna Griebel, M.D., Deputy Director, DRUDP (HFD-580)

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

Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)

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

Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP (HFD-580)

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

Suong Tran, Ph.D., Chemistry Reviewer, DNDC III @ DRUDP (HFD-580)

Bryan Riley, Ph.D., Microbiology Reviewer, Office of Pharmaceutical Science (HFD- 805)

Provide the background information for this meeting (three copies to the IND and 10 desk copies to me) two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by June 14, 2004, we may cancel or reschedule the meeting.

NDA 21-273

Page 2

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
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/

Jennifer L. Mercier
6/10/04 01:17:19 PM
for Margaret Kober



NDA 21-273
NDA 20-582

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

Dear Mr. Mayo:

We received your December 23, 2003 correspondence on December 24, 2003, requesting a meeting to discuss your plans for an alternate manufacturing site for Follistim[®] and Follistim[®] AQ. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fml.htm>.

You requested a type A meeting. The Type A teleconference is scheduled for:

Date: January 21, 2004
Time: 2:00 - 3:00 P.M.
CDER participants: Moo-Jhong Rhee, Ph.D. (Chemistry Team Leader), Daniel Shames, M.D. (Division Director), Margaret Kober, R.Ph. (Chief, Project Management Staff), Suong Tran, Ph.D. (Chemistry Reviewer), Swapan De, Ph.D. (Chemistry Reviewer), Duu-Gong Wu, Ph.D., (Deputy Director, Division of New Drug Chemistry II), David Lin, Ph.D. (Chemistry Team Leader)

Provide the background information for this meeting at least two weeks prior to the meeting. If we do not receive it by January 7, 2004, we may need to reschedule the meeting.

NDA 21-273
NDA 20-582
Page 2

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Archana Reddy, M.P.H.
Regulatory Project Manager
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
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/

Archana Reddy
1/7/04 01:26:52 PM

6 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-

5

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

/s/

Suong Tran
6/23/04 09:56:20 AM
CHEMIST

signed-off email

Moo-Jhong Rhee
6/23/04 12:46:18 PM
CHEMIST
I concur

6 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-

6



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-273

Organon, Inc.
Attention: John Leach
Associate Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Leach:

Please refer to your October 17, 2002, resubmission submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act to your new drug application for Follistim[®] AQ (follitropin beta injection).

On April 14, 2003, we received the executed batch records on the two additional validation batches as agreed upon at the teleconference held on March 19, 2003 between David Lin, Ph.D. (Chemistry Team Leader, DRUDP) and Lawrence Starke, of Organon, Inc. This submission is a major amendment to this application and the receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 18, 2003.

If you have any question, please call Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
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/

Margaret Kober
4/22/03 03:24:32 PM
Chief, Project Management Staff

Other:

- DMETS review is complete and the tradename is acceptable.
- DDMAC review is complete and signed off in DFS.
- Labeling review is pending.

Action Item:

The Project Manager will e-mail Bronwyn Collier (ADRA, ODE III) to confirm that the regulatory clock can be extended by three months, since the sponsor is planning to submit new data for review 4 days before the PDUFA goal date of April 18, 2003.

Cc:

Archival NDA 21-273
HFD-580/Division Files
HFD-580/Reddy/Lin/Slaughter/Willett/Gassman/

Created by: Archana Reddy, 4.10.03
Concurrence: dtl/5.12.03, ss/5.12.03
Finalized: ar/5.12.03

Meeting Minutes

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

/s/

Shelley Slaughter
5/13/03 01:37:04 PM
I concur.

MEMORANDUM

Date: March 20, 2003

To: Dr. Daniel Shames
Director
Division of Reproductive and Urologic Drug Products
HFD-580

From: Lisa Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications
HFD-42

Re: NDA 21-273
Follistim AQ (follitropin beta) Injection

Material Reviewed: October 18, 2002, proposal of Prescribing Information (PI)

Recommendations

In the Adverse Reactions section, it would be helpful to preface all of the incidence tables with a list of common adverse events because these incidences vary greatly among the different protocols. For example, it is not clear why there would be such a discrepancy between the incidences of adverse events for Protocol 142001 (Follistim AQ Cartridge) and Follistim AQ injection. Promotional materials for Follistim AQ will capitalize on the lowest incidences found in the PI. A summary statement about the experience with Follistim AQ, in the beginning of the Adverse Reactions section, can avert this problem.

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

/s/

Lisa Stockbridge
3/20/03 01:46:25 PM
DDMAC REVIEWER

Fulvicin P/G and Follistim AQ sound similar. Fulvicin P/G contains griseofulvin and is used as a systemic antifungal medication. Fulvicin P/G and Follistim AQ sound similar because both names share a similar sounding prefix "Ful" vs. "Fol" and suffix "in". Additionally, the middle syllable in each name ends with an "s" sound. Fulvicin P/G and Follistim AQ, however, differ with respect to many other characteristics such as dosage form (tablets vs. injection), route of administration (oral vs. subcutaneous and intramuscular), and strength (125 mg, 165 mg, 250 mg, 330mg vs. 75 IU/0.5 mL, 150 IU/0.5 mL, 225 IU/0.5 mL, 300 IU/0.5 mL). Although the dosing range (375 mg vs. 375 IU) and daily dosing regimen (once daily) may overlap, the likelihood for confusion is minimal given that the modifiers "AQ" and "P/G" will be present to distinguish one name from the other. Additionally, a search in the *FDA Adverse Event Reporting System (AERS)* database did not reveal confusion between the currently marketed products Follistim and Fulvicin.

As for the potential for confusion between Follistim and Follistim AQ, especially since the products share an overlapping strength of 75 IU, the potential for harm is minimal. Follistim and Follistim AQ share an identical active ingredient, indications for use, dosing regimen, and routes of administration. Therefore, DMETS has no objections to the use of the proprietary name Follistim AQ. DMETS recommends that the labels and labeling for Follistim and Follistim AQ be clearly distinguishable.

In review of the container labels, carton and insert labeling of Follistim AQ, DMETS has identified areas of possible improvement, which might minimize potential user error.

CONTAINER LABEL AND CARTON LABELING



nt
t

If you have any questions or need clarification, please contact the Division Project Manager, Sammie Beam, at 301-827-3242.

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

/s/

Alina Mahmud
3/25/03 07:39:08 AM
PHARMACIST

Carol Holquist
3/25/03 07:45:52 AM
PHARMACIST

TELECON MINUTES

Date: March 19, 2003 **Time:** 3:00 – 3:20 P.M. **Location:** PKLN 17B-43

NDA: 21-273 **Drug Name:** Follistim AQ[®] (follitropin beta injection)

Sponsor: Organon, Inc.

Indication: Assisted Reproductive Technology (ART)

Type of Meeting: CMC Guidance

Meeting Chair: David Lin, Ph.D.

External Participant Lead: Lawrence Starke, Ph.D.

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

FDA Attendees:

Archana Reddy, M.P.H., Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (HFD-580)

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

External Participants:

Lawrence Starke, Ph.D., Associate Director

Background:

Follistim AQ[®] (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. Follistim AQ[®] is an injectable aqueous solution of 75, 150, IU follitropin beta in a vial. This new drug application received an approvable action on May 24, 2001 due to chemistry and microbiology issues. A complete response addressing all chemistry and microbiology deficiencies was received on October 18, 2002. The user fee goal date for this new drug application is April 18, 2003.

Discussion:

- although the overall GMP was found to be acceptable, DRUDP's concern with the West Orange, NJ manufacturing facility as it relates to the manufacturing of Follistim[®] AQ was discussed with the sponsor
- sponsor indicated that no new batches have been made since manufacture of the clinical batches
- DRUDP recommended to sponsor that they manufacture at least two additional validation batches of any of the strengths; sponsor stated that 1 month would be required for batches to be released; if the manufacture of these batches cannot be completed by the goal date this would be considered an approvability issue

Decision Reached:

The sponsor agreed to produce two additional validation batches of the drug product and will coordinate with the District office concerning the timing of the inspections.

Action Item:

1. The Project Manager will fax the meeting minutes to the sponsor within 30 days.

Meeting Chair
David Lin, Ph.D.

Meeting Recorder
Archana Reddy, M.P.H.

Note to sponsor: Please note that these minutes are considered the official meeting minutes. Any discrepancies or differences should be reported to the Division as soon as possible.

Meeting Minutes
NDA 21-273
Page 3 of 3

Cc:
Archival NDA 21-273
HFD-580/Division Files
HFD-580/Reddy/Lin/Slaugther/Willett/Gassman/

Created by: Archana Reddy, 3.18.03
Concurrence: dtl/4.0303
Finalized: ar/3.04.03

Meeting Minutes

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

/s/

David T. Lin
4/4/03 03:59:53 PM
I concur.

MEETING MINUTES

Date: March 18, 2003 **Time:** 2:00 – 2:30 P.M. **Location:** PKLN 17B-43

NDA: 21-273 **Drug Name:** Follistim AQ[®] (follitropin beta injection)

Sponsor: Organon, Inc.

Indication: Assisted Reproductive Technology (ART)

Type of Meeting: 5-Month Status Meeting

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

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

FDA Attendees:

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

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

Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)

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

Allen Fenselau, Ph.D., Chemistry Reviewer, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Background:

Follistim AQ[®] (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. Follistim AQ[®] is an injectable aqueous solution of 75, 150, follitropin beta in a vial. This new drug application received an approvable action on May 24, 2001 due to chemistry and microbiology issues. A complete response addressing all chemistry and microbiology deficiencies was received on October 18, 2002. The user fee goal date for this new drug application is April 18, 2003.

Clinical

- labeling review is ongoing; overall it looks acceptable and is identical to other labels
- draft review is complete

Chemistry

- recommend approvable action based upon manufacturing issue

Microbiology

- sponsor has addressed all the issues

Decision Reached:

The reviews should go to the Medical Team Leader by March 18, 2003.

NDA 21-273
Page 2

Cc:
Archival NDA 21-273
HFD-580/Division Files
HFD-580/Reddy/Lin/Slaugther/Willett/Gassman/

Created by: Archana Reddy, 3.18.03
Concurrence: jw/3.20.02, ag/3.19.03, ss/5.1203
Finalized: ar/5.12.03

Meeting Minutes

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

/s/

Shelley Slaughter
5/13/03 03:48:55 PM
I concur.

MEETING MINUTES

Date: February 20, 2003 **Time:** 2:00 – 2:30 P.M. **Location:** PKLN 17B-43

NDA: 21-273 **Drug Name:** Follistim AQ[®] (follitropin beta injection)

Sponsor: Organon, Inc.

Indication: Assisted Reproductive Technology (ART)

Type of Meeting: 4-Month Status Meeting

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

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

FDA Attendees:

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

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

Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)

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

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

Background:

Follistim AQ[®] (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. Follistim AQ[®] is an injectable aqueous solution of 75, 150, ██████████ follitropin beta in a vial. This new drug application received an approvable action on May 24, 2001 due to chemistry and microbiology issues. A complete response addressing all chemistry and microbiology deficiencies was received on October 18, 2002. The user fee goal date for this new drug application is April 18, 2003.

Clinical

- sponsor has sent a letter stating that the cause of death in Australia (case report 199800041) was unknown, although suicide was suspected; an autopsy was not conclusive, but there is no evidence that this death was related to Follistim use
- sponsor indicated that no further information on the second death that occurred in Vietnam could be obtained; a letter to the sponsor will be sent to see if any additional information is available

Chemistry

- major issue is Organon's drug product manufacturing site in West Orange, NJ; the Division has not been notified of any other problems

- a teleconference to discuss remaining chemistry issues is needed; will recommend to sponsor that they manufacture three additional batches, but two additional batches with no GMP problems is also acceptable

Microbiology

- sponsor has addressed all the issues

Regulatory Issues:

- Tradename review and DDMAC review of the package insert is pending.

Decision Reached:

The reviews should go to the Medical Team Leader by March 18, 2003.

NDA 21-273
Page 3

Cc:
Archival NDA 21-273
HFD-580/Division Files
HFD-580/Reddy/Lin/Slaugther/Willett/Gassman/

Created by: Archana Reddy, 3.18.03
Concurrence: dtl/4.05.03, ag/3.19.03, ss/5.12.03
Finalized: ar/5.12.03

Meeting Minutes

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

/s/

Shelley Slaughter
5/14/03 01:03:10 PM
I concur.

MEETING MINUTES

Date: December 5, 2002 **Time:** 9:45 – 10: 15 A.M. **Location:** PKLN 17B-43

NDA: 21-273 **Drug Name:** Follistim AQ® (follitropin beta injection)

Sponsor: Organon, Inc.

Indication: Assisted Reproductive Technology (ART)

Type of Meeting: Filing Meeting

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

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

FDA Attendees:

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

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

Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)

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

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

Background:

Follistim AQ® (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. Follistim AQ® is an injectable aqueous solution of 75, 150, ██████████ follitropin beta in a vial. This new drug application received an approvable action on May 24, 2001 due to chemistry and microbiology issues. A complete response addressing all chemistry and microbiology deficiencies was received on October 18, 2002. The user fee goal date for this new drug application is April 18, 2003.

Clinical

- Safety update is current to May 2002
- NDA is fileable

Chemistry

- the sponsor has addressed all chemistry issues
- major issue is Organon's drug product manufacturing site in West Orange, NJ; the Division has not been notified of any other problems
- there is a sterility assurance problem according to the Office of Compliance; Division has the authority to override this recommendation from the District (no information has been provided to override the decision)
- general GMP is probably acceptable

NDA 21-273

Page 2

- NDA is fileable

Clinical Pharmacology

- NDA is fileable
- NDA was reviewed in the first cycle and there were no deficiencies identified

Microbiology

- sponsor has addressed all the issues

Decision Reached:

- NDA is fileable

Action Items:

- The Project Manager will request a DMETS consult for tradename review and a DDMAC consult of the package insert.

Cc:

Archival NDA 21-273

HFD-580/Division Files

HFD-580/Reddy/Lin/Slaughter/Willett/Gassman/

Created by: Archana Reddy, 2.06.03

Concurrence: dtl/2.06.03, ag/2.20.03, ss/2/24/03

Finalized: ar/2.24.03

Meeting Minutes

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

/s/

Shelley Slaughter
2/27/03 10:55:52 AM
I concur.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-273

Organon, Inc.
Attention: John Leach
Associate Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Leach:

We acknowledge receipt on October 18, 2002, of your October 17, 2002, resubmission to your new drug application for Follistim[®] AQ (follitropin beta injection).

We consider this a complete, class 2 response to our May 24, 2001 action letter. Therefore, the user fee goal date is April 18, 2003.

If you have any question, call Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
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/

Margaret Kober
10/31/02 04:35:50 PM
Chief, Project Management Staff



NDA 21-273

DISCIPLINE REVIEW LETTER

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

Dear Mr. Mayo:

Please refer to your July 24, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim AQ (follitropin beta for injection).

We also refer to your submissions dated October 31, 2000, March 13, April 20, and May 3, 2001.

We have reviewed the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests.

1. Please revise the Total Oxidation specification to be expressed as the oxidation of the alpha subunit alone.
2. Revise the L-Methionine Content stability specification to _____
3. Based on the stability data provided to the NDA, please revise the Subunit Content stability specification to NMT _____
4. Item #1 in the stability protocol should be revised to the following:

“The first three commercial batches will be tested at the following intervals, which are shown on the table presented below. These testing intervals are based on and intend to support the proposed expiration dating of Follistim... AQ (follitropin injection) _____

In addition, reference made to “removing samples from the 25° C/60% RH condition and placing at the 5° C condition” should be deleted.

5. _____

6. For the Method Validation Package, a "List of Samples to be Provided" with the approximate quantity of each component to be provided to each FDA lab needs to be submitted to the NDA. In addition, the certificates of analysis for the samples and reference standards, and material safety and data sheets (MSDS) of the drug substance and drug product components need to be provided.

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
HFD-580
DNDC 2, Office of New Drug Chemistry
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/

Moo-Jhong Rhee
5/14/01 02:29:20 PM

NDA 21-273
Follistim®AQ (follitropin beta for injection)
Organon, Inc.

OPDRA Review

The primary OPDRA review dated October 11, 2000 stands.
A secondary OPDRA review is not required since Follistim is already a marketed name.

Report received from Sammie Beam May 22, 2001

 5/23/01
Dornette Spell-LeSane, NP-C, Regulatory Project Manager

MEETING MINUTES

Date: May 9, 2001

Time: 2:00 – 2:45 PM

Location: Parklawn; Room 17B-43

NDA 21-273

Drug Name: Follistim-AQ® (follitropin beta injection)

Sponsor: Organon

Indication: Assisted Reproductive Technology (ART)

Type of Meeting: 10-month Status Meeting

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

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

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

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

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

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

Venkat Jarugula, Ph.D., Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics @ DRUDP (HFD-580)

David Lin, Ph.D., Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)

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

David Hussong, Ph.D., Microbiology Reviewer, (HFD-805)

Meeting Objectives: To discuss the on-going review of this NDA.

Background:

Follistim AQ® (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. Follistim- AQ® in an injectable aqueous solution of 75, 150 follitropin beta in a vial. A response to a Microbiology Information Request letter was received from the sponsor on April 20, 2001. The 10-month User Fee goal date is May 24, 2001.

Discussion:

Microbiology:

- initial review of sponsor's response to IR letter is unsatisfactory
- review is pending, will likely recommend **approvable** due to inadequate responses to information request

Biopharmaceutics:

- Clinical Pharmacology and Biopharmaceutics review is complete
- the NDA is **acceptable** from Clinical Pharmacology and Biopharmaceutics perspective

Chemistry:

- Chemistry review is complete
- an Deficiency Request letter has been drafted with chemistry issues to be conveyed to the sponsor
- the Organon facility in West Orange, NJ remains on "withhold" status
- on May 8, 2001, the sponsor submitted 18-month stability data; that data has been reviewed and incorporated into chemistry review
- the ~~stability~~ stability data remains pending, sponsor to submit to the NDA before action date but will not be reviewed this cycle
- Chemistry is recommending **approvable** pending resolution of the following:
 - satisfactory facility inspection
 - satisfactory review from microbiology
 - satisfactory revisions to the label

Clinical:

- Review is complete
- Clinical will recommend **approval** based on acceptability of bioequivalence study

DSI (Division of Scientific Investigations):

- clinical inspection summary is completed
- data submitted to support this NDA is acceptable

Decisions Made:

An approvable action for this NDA will be taken

Action Items:

1. Microbiology review to delineate approvable issues for action letter; to be completed by May 16, 2001.
2. Finalize chemistry Discipline Review letter.
(DR Letter faxed to sponsor May 14, 2001)
3. Include chemistry label comments into draft label.
4. Draft approvable letter, include chemistry, microbiology and labeling issues.

Signature, minutes preparer

Concurrence, Chair

10-Month Status Meeting
May 9, 2001
Page 3

cc:

NDA Arch: 21-273

HFD-580

HFD-580/Shames/Bennett/Rhee/Jarugula/Slaughter/Parekh/Lin/

drafted: Spell-LeSane

concurrences: Rumble, Jarugula, Lin, Hussong, Slaughter, Bennett, 5.15.01,

final: Spell-leSane, 5.23.01

MEETING MINUTES

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

/s/

Shelley Slaughter
5/24/01 10:18:14 AM

DeGuia

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 25, 2001

TO: Freshnie DeGuia, Regulatory Project Manager
Ridgely Bennett, M.D., Clinical Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: John Martin, M.D., Branch Chief
Good Clinical Practice 1, HFD-46
Division of Scientific Investigations

FROM: Susan Molchan, M.D., Medical Officer
Good Clinical Practice 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-273 (Protocol # [redacted] An Open-Label, Randomized, Group-Comparative, Multicenter Study to Assess the Efficacy and Safety of a Follistim Solution Formulation Compared to a Freeze-Dried Cake Formulation, both Administered Subcutaneously for the Induction of Ovulation in Clomiphene-Resistant Subjects with Chronic Anovulation.

APPLICANT: Organon, Inc.

DRUG: Follistim-AQ (follitropin beta injection)

THERAPEUTIC CLASSIFICATION: 3(S)

INDICATION: Induction of ovulation

REVIEW DIVISION GOAL DATE: April 24, 2001

ACTION GOAL DATE (PDUFA Date): May 24, 2001

I. BACKGROUND

The goals of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events.

II. RESULTS

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
James Young, MD	Grand Rapids	MI	Nov 20, 2000	Feb 1, 2001	VAI-R
Kaylen Silverberg, MD	Austin	TX	Nov 20, 2000	Apr 24, 2001	NAI
Michael Kettel, MD	La Jolla	CA	Nov 20, 2000	Feb 20, 2001	VAI

Protocol

1. **Site #1** James Young, MD
221 Michigan N.E., Suite 406
Grand Rapids, MI 49503

- a. Twenty-four subjects were enrolled at this site. The inspector reviewed all records for the presence of informed consent forms and performed selected checks of specific information for other study records.
- b. There were no limitations on the inspection.
- c. A form 483 was issued citing a number of examples of failing to adhere to the protocol, inadequate and inaccurate records, inadequate patient consent forms, and inadequate drug accountability. As noted to the medical reviewer, the primary deviations that may have affected the primary efficacy measure for some subjects were: inclusion of a few patients who should have been excluded as per protocol, dose escalation was not always done as per protocol.

2. **Site #2** Kaylen Silverberg, M.D.
3705 Medical Parkway, Suite 420
Austin, TX 78705

- a. Twenty-six subjects were enrolled at this site. The inspector reviewed all records for the presence of informed consent forms and performed selected checks of specific information for other study records.
- b. There were no limitations on the inspection.
- c. No form 483 was issued at this site.

3. **Site #3** Michael Kettel, MD
San Diego Fertility Center
11515 El Camino Real, Suite 100
San Diego, CA 92130

- a. Twenty-three subjects were enrolled at this site. The inspector reviewed all records for the presence of informed consent forms and performed an in depth review of the records of 14 subjects.
- b. There were no limitations on the inspection.
- c. A form 483 was issued citing a few examples of inadequate and inaccurate records, and inadequate drug accountability. As noted to the review division, the deficiencies noted were relatively minor and adequately addressed by the investigator at the conclusion of the inspection.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this NDA by Drs. Silverberg and Kettel appeared to be adequate and in compliance with U.S. Federal regulations and/or good clinical investigational practices.

For Dr. Young's site, there were a number of examples of failing to adhere to the protocol, inadequate and inaccurate records, inadequate patient consent forms, and inadequate drug accountability. As noted, the primary deviations that may have affected the primary efficacy measure for some subjects were: inclusion of a few patients who should have been excluded as per protocol, dose escalation was not always done as per protocol.

Follow-up action: A written response was requested from Dr. Young, addressing the deficiencies noted and noting actions and a plan to assure that such deficiencies are not repeated.



Susan Molchan, M.D., Clinical Reviewer
DSI/GCPBI

CONCURRENCE:



John Martin, M.D.
Branch Chief
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigation

DISTRIBUTION:

- NDA 21-273
- HFD-45/Division File
- HFD-46/Program Management Staff (electronic copy)
- HFD-580/DeGuia
- HFD-46/Martin
- HFD-46/ Molchan
- HFD-46/Ibarra-Pratt
- HFD-46/ CIB File #10348
- HFD-46/Reading File

MEETING MINUTES

Date: April 16, 2001

Time: 2:00 – 3:00 PM

Location: Parklawn; Room 17B-43

NDA 21-273

Drug Name: Follistim-AQ® (follitropin beta injection)

Sponsor: Organon

Indication: Assisted Reproductive Technology (ART)

Type of Meeting: 9-month Status Meeting

Meeting Chair: Dr. Daniel Shames

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:

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

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

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

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

Venkat Jarugula, Ph.D., Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics

David Lin, Ph.D., Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)

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

Meeting Objectives: To discuss the on-going review of this NDA.

Background:

Follistim – AQ® (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. Follistim- AQ® in an injectable aqueous solution of 75, 150 XXXXXXXXXX follitropin beta in a vial. A Microbiology information request letter was conveyed to the sponsor on April 2, 2001. The 10-month User Fee goal date is May 24, 2001.

Discussion:

Biopharmaceutics:

- sponsor cross-referenced an existing BE study that was conducted for another NDA (21-211) for Follistim-AQ cartridge (solution injected with a pen injector) to support the solution formulation in this NDA and requested a biowaiver for the present NDA
- in this BE study it was shown that the bioavailability of FSH was not affected by varying concentrations in the range of 150-833 IU/ml
- the results of the cited BE study are acceptable to support the solution formulation of the current NDA
- no major labeling issues, sponsor will need to submit a new paragraph to the “**Pharmacokinetics**” section otherwise the labeling is the same as the approved product

- the Clinical Pharmacology Biopharmaceutics briefing will be held April 24, 2001

Decision:

- the NDA is **acceptable** from Clinical Pharmacology and Biopharmaceutics perspective

Chemistry:

- the Organon facility in West Orange, NJ remains on “withhold” status; there is no alternate site for this manufacturing facility
- complete stability data has not been submitted
- an IR letter will need to be sent to the sponsor with chemistry issues cited
- chemistry will meet the 10-month goal date

Decision:

- Chemistry will recommend an **approvable** if the West Orange facility remains on “withhold”

Microbiology:

- review of sponsor’s response to IR letter is pending

Decision:

- **review is pending with recommendation not yet determined**

Clinical:

- the sponsor submitted an ovulation induction study as supportive data for this NDA

Decision:

- Clinical will recommend **approval** based on acceptability of bioequivalence study

Pharmacology Toxicology:

- Review completed February 5, 2001

Decision:

- Pharm-Tox recommends **approval**

Biometrics:

- review is **pending**

DSI (Division of Scientific Investigations):

- clinical inspection summary is pending
- the third inspection is pending

Next Meeting:

- Wednesday May 9, 2001

Action Items:

1. Obtain status of DSI clinical summary
(**Clinical summary received April 25, 2001; Drs. Silverberg (NAI) and Kettle (VAI) appear to be adequate and in compliance, Dr. Young received (VAI-R), a written response from Dr. Young is pending, not an approvable issue**)
2. Obtain status of Microbiology review
3. Obtain from sponsor status of corrective actions listed in WARNING LETTER issued by compliance on September 19, 2000.
4. Prepare chemistry information request letter
(**chemistry review completed May 4, 2001, IR letter prepared May 6, 2001**)
5. Discipline reviews should be available for review by secondary reviewer, Dr. Slaughter by April 27, 2001

Signature, minutes preparer

Concurrence, Chair

cc:

NDA Arch: 21-273

HFD-580

HFD-580/Shames/Bennett/Rhee/Jarugula/Slaughter/Parekh/Lin/

drafted: Spell-LeSane

concurrences:

final:

MEETING MINUTES

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

/s/

Daniel A. Shames
5/15/01 05:14:44 PM



NDA 21-273

INFORMATION REQUEST LETTER

Organon, Inc.
Attention: Peter Stokman
Associate Director, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, NJ 07052

Dear Mr. Stokman:

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

We are reviewing the Microbiology section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

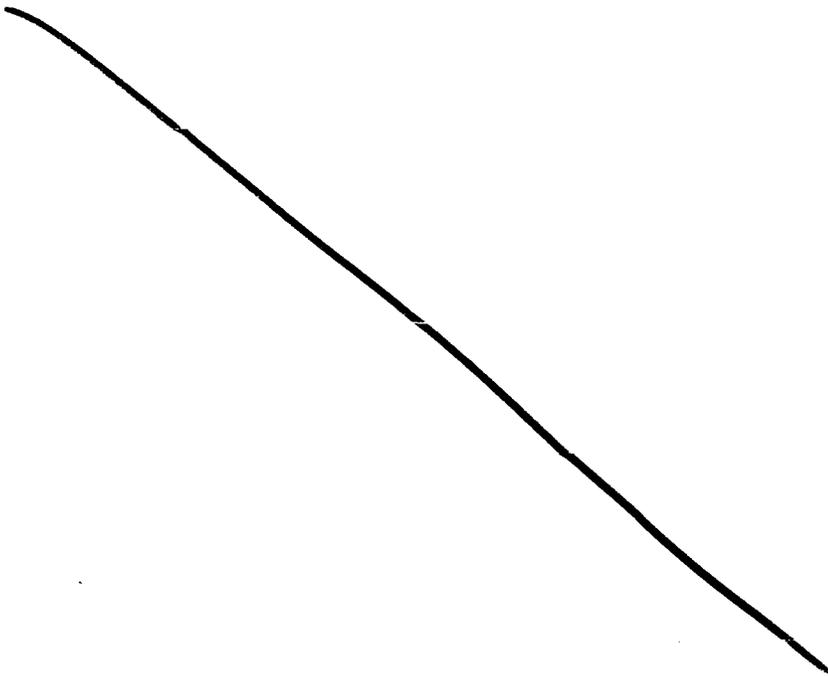
1. Please describe the storage and distribution systems for Water for Injection in the facility.

2.

3.

4.

5.



6.

7.

8.

9. Please describe the frequency of repeating scheduled media fills for this processing line.

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Moo-Jhong Rhee
4/2/01 03:58:00 PM

MEETING MINUTES

Date: March 19, 2001

Time: 2:00 – 3:00 PM

Location: Parklawn; Room 17B-43

NDA 21-273

Indication: Assisted Reproductive Technology (ART)

Drug Name: Follistim®-AQ
(follitropin beta injection)

Type of Meeting: Status Meeting

Meeting Chair: Dr. Daniel Shames

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

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

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

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

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

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

Venkat Jarugula, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics

Ameeta Parekh, Ph.D. - Team Leader, Office of Clinical Pharmacology and Biopharmaceutics

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

David Lin, Ph.D. - Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)

Meeting Objectives: To discuss the on-going review of this NDA.

Background:

Follistim – AQ (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. The currently approved product is available as a freeze-dried cake, to be administered after reconstitution with Water for Injection. Follistim- AQ in an injectable aqueous solution of 75, 150, ██████████ follitropin beta in a vial.

The User Fee goal date is May 24, 2001.

Decisions reached:

Clinical

- review is in progress
- this NDA is based on the bioequivalence study submitted in NDA 21-211; data from an Ovulation Study (Study 058-004) which was submitted as supportive information, appears to demonstrate that the liquid formulation may be better numerically, but not statistically (not adequately powered)

Chemistry

- Chemistry, Manufacturing and Controls (CMC) information and drug product data from the approved NDA 20-582 are incorporated into this NDA by cross-reference
- the Organon facility in West Orange, NJ received a warning letter from the Office of Compliance and still on “withhold” status; there is no alternate site
- additional stability data will be submitted
- action date will depend on the timeline for the completion of the Chemistry review; if additional time is needed then the action date for this NDA may possibly be pushed back to 11 months

Biopharmaceutics

- this application cross-references the BE study submitted for the pending NDA 21-211 Follistim – AQ (follitropin beta for injection) Cartridge
- an *in-vitro* study, comparing the approved lyophilized cake and the liquid formulations, mimicking the worst-case clinical scenario, was conducted to demonstrate amount of drug loss during injection;
- the BE study and the in-vitro study demonstrate that the aqueous solution is bioequivalent to the cake formulation
- draft review has been forwarded to the Team Leader for concurrence

Biometrics

- final review is now in draft form

DSI (Division of Scientific Investigations)

- inspection on two sites has been completed; a third is pending; Inspection Summary should be provided next week
- **Action Items:**
- The UF goal date will be discussed at the next status meeting

Signature, minutes preparer

Concurrence, Chair

cc:

NDA Arch:

HFD-580

HFD-580/Shames/Bennett/Rhee/Jarugula/Slaughter/Parekh/Lin/Kammerman

drafted: DeGuia/

concurrences:Slaughter04.17.01/Jarugula,Parekh04.18.01/Rhee04.23.01/Lin,Bennett,Shames04.24.01

final:DeGuia04.26.01

MEETING MINUTES

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

/s/

Daniel A. Shames
4/26/01 11:29:51 AM

NDA 21-273

D/F

INFORMATION REQUEST LETTER

Organon, Inc.
Attention: Peter Stokman
Associate Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

SEP 21 2000

Dear Mr. Stokman:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim - AQ (follitropin beta injection).

We are reviewing the Clinical Pharmacology/Biopharmaceutics and Chemistry sections of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide information to explain the inconsistency in results reported regarding the loss of FSH dose during reconstitution and injection of the approved Follistim (lyophilized cake) in NDA 21-211 and NDA 21-273 .
2. Please submit the assay validation data for the enzyme immunoassay method used for the determination of FSH in the in vitro study of NDA 21-273.
3. No data are submitted to support labeling for intramuscular administration of Follistim-AQ. Bioequivalence of the Follistim-AQ solution to the approved product following intramuscular administration should be demonstrated to support the approval of Follistim-AQ for intramuscular use (please refer to FDA's letter dated 09/17/99).
4. Please clarify which facility will perform the stability testing of the drug product.
5. Please confirm that the Organon facility in West Orange, NJ is the manufacturing site for the drug product.

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Diane Moore for Terri Rumble

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 12, 2000

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: The file (NDA 21-273)

I have reviewed the financial disclosure information submitted by Organon, Inc. in support of their NDA 21-273. The documents reviewed were dated July 17, 2000 (financial disclosure form) and September 1, 2000 (clarifying information).

One clinical study was conducted to support the safety and efficacy for Follistim Solution formulation. The study number and its respective outcome with regard financial disclosure obligations is summarized below:

Study No.	Study Status	Financial Disclosure Documentation
058-004 Open-label multi-center trial	Ongoing as of February 2, 1999	Appropriate documentation; no financial arrangements/proprietary interest

Conclusion:

Organon Inc. had a 93% compliance rate in regard to obtaining the necessary information from its investigators regarding financial disclosure. There were no financial interests reported by those who complied. Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

3 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

DIF

MEETING MINUTES

Date: September 19, 2000

Time: 3:00 – 4:00 PM

Location: Parklawn; Room 17B-43

NDA 21-273

Indication: Assisted Reproductive Technology (ART)

Drug Name: Follistim®-AQ
(follitropin beta injection)

Type of Meeting: Filing Meeting

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Susan Allen, M.D., M.P.H. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

Daniel Shames, M.D. - Deputy Director, DRUDP (HFD-580)

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

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

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

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

Venkat Jarugula, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics

Ameeta Parekh, Ph.D. - Team Leader, Office of Clinical Pharmacology and Biopharmaceutics

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

Shahla Farr, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objectives: To discuss the fileability of this NDA.

Background:

Follistim – AQ (follitropin beta for injection) is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582. The currently approved product is available as a freeze-dried cake, to be administered after reconstitution with Water for Injection. Follistim- AQ in an injectable aqueous solution of 75, 150, follitropin beta in a vial. It is a ready-to-use presentation and facilitates self-administration by the patients.

Organon, Inc. requested a biowaiver on January 11, 2000 providing information to substantiate that the concentration difference between the approved product and the new liquid formulation does not impact bioavailability. In a teleconference between the Division and Organon on March 31, 2000, a decision was reached that Organon must submit supportive data from an *in-vitro* study to further support the biowaiver.

Decisions reached:

Clinical

- the application is fileable from a clinical perspective
- this NDA is based on a bioequivalence study and a clinical report for Ovulation Induction (OI) study which provided comparative information between this liquid formulation and the approved lyophilized cake formulation
- a quick preview of the OI study appears to demonstrate that the liquid formulation may be better numerically, but not statistically (not adequately powered); a lower dose (less IU) is needed for ovulation induction

Chemistry

- this NDA is fileable from Chemistry perspective
- Chemistry, Manufacturing and Controls (CMC) information and drug product data from the approved NDA 20-582 are incorporated into this NDA by cross-reference
- drug substance and composition are identical with the approved Follistim except that it has no benzyl alcohol and this for single use vial
- DMFs (Drug Master Files) are provided
- the facility that will perform the stability testing should be clarified
- the Organon facility in West Orange, NJ needs to be confirmed as the manufacturing site for the drug product
- storage conditions and expiry dating should be clarified; ~~_____~~
- Tradename consult will be sent to Office of Post-Marketing Drug Risk Assessment (OPDRA)

Biopharmaceutics

- the BE study for this application cross-references the BE study submitted for the pending NDA 21-211 Follistim – AQ (follitropin beta for injection) Cartridge
- an *in-vitro* study, comparing the approved lyophilized cake and the liquid formulations, mimicking the worst-case clinical scenario, was conducted to demonstrate amount of drug loss during injection; this resulted in ~~—~~ drug loss which conflicts with the ~~—~~ loss in the BE study for the NDA 21-211, the supportive NDA; sponsor will be asked to explain the inconsistency
- no data was provided to support labeling for intramuscular (IM) administration; both subcutaneous (SC) and IM administrations are proposed in the label, however, there is no mention of IM administration in the clinical study; the sponsor will be asked to explain this discrepancy
- this application is fileable; has several significant review issues

Statistics

- this application is fileable
- **Action Items:**
- schedule a teleconference with the sponsor to discuss Chemistry and Biopharm issues

Ed de Guiz 10/19/00
Signature, minutes preparer

Susan Adams
Concurrence, Chair

cc:

NDA Arch:

HFD-580

HFD-580/Allen/Rumble/Bennett/Rhee/Jarugula/Slaughter/Parekh/Shames/Lin

drafted: DeGuia/09.27.00

concurrences: TRumble09.28.00/DShames,

VJarugula10.02.00/LKammerman10.04.00/SSlaughter10.05.00/AParekh,RBennett10.18.00

final: EDeGuia

MEETING MINUTES

*Entered in DFS
10/23/00*



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-273

JUL 26 2000

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

Dear Mr. Mayo:

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

Name of Drug Product: Follistim - AQ (follitropin beta injection)
Therapeutic Classification: Standard (S)
Date of Application: July 21, 2000
Date of Receipt: July 24, 2000
Our Reference Number: NDA 21-273

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 September 22, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 24, 2001 and the secondary user fee goal date will be July 24, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at

NDA 21-273

Page 2

www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

A handwritten signature in black ink that reads "Dornette Spell-LeSane". The signature is written in a cursive style and is positioned above the typed name of the signatory.

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-273	Efficacy Supplement Type SE- N/A	Supplement Number 000
Drug: Follistim® AQ (follitropin beta for injection)		Applicant: Organon, Inc.
RPM: John Kim, R.Ph., J.D.		HFD- 580 Phone # 301-827-3003
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3S
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates:		
		26-Aug-2005 4th Cycle
		20-May-2005 3rd Cycle
		18-Jul-2003 2nd Cycle
		24-May-2001 1st Cycle
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None
		Subpart H
		<input type="checkbox"/> 21 CFR 314.510 (accelerated approval)
		<input type="checkbox"/> 21 CFR 314.520 (restricted distribution)
		<input type="checkbox"/> Fast Track
		<input type="checkbox"/> Rolling Review
		<input type="checkbox"/> CMA Pilot 1
		<input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 3961
• User Fee waiver		N/A
		<input type="checkbox"/> Small business
		<input type="checkbox"/> Public health
		<input type="checkbox"/> Barrier-to-Innovation
		<input type="checkbox"/> Other (specify)
• User Fee exception		N/A
		<input type="checkbox"/> Orphan designation
		<input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)
		<input type="checkbox"/> Other (specify)

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="radio"/> Yes <input checked="" type="radio"/> No
• This application is on the AIP	<input type="radio"/> Yes <input checked="" type="radio"/> No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="radio"/> Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="radio"/> Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input type="radio"/> Verified
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	21 CFR 314.50(i)(1) <input type="radio"/> (ii) <input type="radio"/> (iii)
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	N/A
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	<input checked="" type="radio"/> N/A (no paragraph IV certification) <input type="radio"/> Verified
<p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee</p>	<p><input type="radio"/> Yes <input type="radio"/> No</p> <p><input type="radio"/> Yes <input type="radio"/> No</p> <p><input type="radio"/> Yes <input type="radio"/> No</p>

filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

() Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<ul style="list-style-type: none"> • 26-Aug-2005 • No
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<p>() Yes, Application # _____ (X) No</p>
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	28-Sep-2000

General Information	
Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	17-May-2005 AE 17-Jul-2003 AE 24-May-2001 AE
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	23-Aug-05
• Most recent applicant-proposed labeling	24-Aug-05 19-Nov-2004 11-May-2001
• Original applicant-proposed labeling	24-Jul-2000
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	20-Mar-2003 DDMAC 11-Feb-2005 DMETS 25-Mar-2003 DMETS 23-May-2001 DMETS 05-Oct-2000 DMETS
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	25-Mar-2004 Gonal-f 11-Dec-2003 Follistim AQ Cart
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	24-Jun-2005 Approved label 24-Jul-2000
• Reviews	See 11-Feb-2005 and 25-Mar-2003 DMETS labeling reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	14-Jul-2005 4 th Cycle 12-Jul-2005 17-May-2005 3 rd Cycle 01-Mar-2005 23-Dec-2004 29-Nov-2004 28-Jun-2004 10-Jun-2004 07-Jan-2004 17-Jul-2003 2 nd Cycle 31-Oct-2002

	24-May-2001 1 st Cycle 14-May-2001 (2) 02-Apr-2001 21-Sep-2000 26-Jul-2000
❖ Memoranda and Telecons	04-Jun-2004 19-Mar-2003
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	20-Feb-2004 3 rd Cycle 07-Apr-2003 2 nd Cycle 18-Mar-2003 20-Feb-2003 05-Dec-2002 09-May-2001 1 st Cycle 16-Apr-2001 19-Mar-2001 28-Sep-2000 19-Sep-2000 21-Mar-2000
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews	See Clinical & Medical Team Leader's reviews
• Division Director	
• Medical Team Leader	NA 4 th Cycle 17-May-2005 3 rd Cycle 16-Jul-2003 2 nd Cycle 24-May-2001 1 st Cycle
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	25-Aug-2005 4 th Cycle 16-May-2005 3 rd Cycle 16-Jul-2003 2 nd Cycle 13-Dec-2002 16-May-2001 1 st Cycle 12-Oct-2000
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See clinical review#4 See clinical review#3, pages 21-23 See clinical review#2, page 17 30-Jan-2003 22-May-2001 1 st Cycle
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	See clinical review#4 See clinical review#3, page 26 See clinical review#2, page 8 See clinical review#1, page 22
Pediatric Page(separate page for each indication addressing status of all age groups)	25-Aug-2005

❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
Statistical review(s) (<i>indicate date for each review</i>)	14-May-2001 1 st Cycle
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	22-Aug-05 4 th Cycle 26-Apr-2005 3 rd Cycle N/A 2 nd Cycle 16-May-2001 1 st Cycle 06-Oct-2000
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	25-Apr-2001 1 st Cycle
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	22-Jul-2005 4 th Cycle 05-May-2005 3 rd Cycle 16-Jul-2003 2 nd Cycle 22-May-2001 1 st Cycle 07-May-2001
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	07-May-2001 1 st Cycle See CMC review#1, § D, page 29.
• Review & FONSI (<i>indicate date of review</i>)	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	N/A 4 th Cycle 19-Apr-2005 3 rd Cycle 11-Apr-2003 2 nd Cycle 16-May-2001 1 st Cycle 02-Apr-2001
❖ Facilities inspection (provide EER report)	Date completed: 11-Jul-2005 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	25-Jul-2005 4 th Cycle 09-May-2005 3 rd Cycle N/A 2 nd Cycle 14-May-2001 1 st Cycle
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A