

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-211

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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)

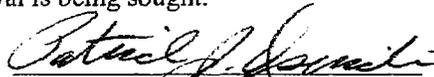
(iii) Name of Patent Owner of Record: Akzo Nobel N.V.
Arnhem, Netherlands

(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 for injection) Cartridge. This product is the subject of this application for which approval is being sought.



Patrick J. Osinski
Vice President
Organon Inc.

0015

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53(c)(1)

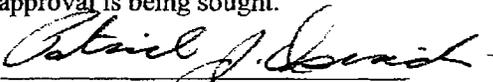
- (i) U.S. Patent No. 4,589,402
Expiration Date - July 26, 2004
- (ii) Type of Patent : Method of Use
- (iii) Name of Patent Owner of Record:

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 for injection) Cartridge. This product is the subject of this application for which approval is being sought.



Patrick J. Osinski
Vice President
Organon Inc.

0016

CONFIDENTIAL

PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR §314.53(c)(1)

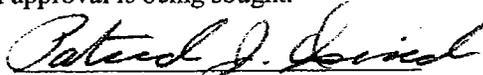
- (i) U.S. Patent No. 5,767,251
Expiration Date - June 16, 2015
- (ii) Type of Patent : Drug Product
- (iii) Name of Patent Owner of Record:

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 for injection) Cartridge. This product is the subject of this application for which approval is being sought.



Patrick J. Osinski
Vice President
Organon Inc.

0017

EXCLUSIVITY SUMMARY for NDA # 21-211 SUPPL # N/A

Trade Name Follistim[®]-AQ Cartridge

Generic Name follitropin beta injection

Applicant Name Organon, Inc.

HFD- 580

Approval Date March 23, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES/ X / NO / /

b) Is it an effectiveness supplement? YES / / NO / X /

If yes, what type (SE1, SE2, etc.)?

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

YES / / NO / X /

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.

This is a new pharmaceutical presentation of the approved Follistim, NDA 20-582. A bioavailability study was performed between this aqueous solution (administered with a pen injector) and the approved Follistim formulated as a freeze-dried lyophilized cake (administered after reconstitution with Water for Injection.

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 /X/

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 /X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /X/ NO /___/

If yes, NDA # 20-582 Drug Name Follistim[®] (follitropin beta for injection)

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 #

NDA #

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 9. IF "YES," GO TO PART III.

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain:
!
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ 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: _____

Archana Reddy, M.P.H.
Signature of Preparer
Title: Regulatory Project Manager

3/23/04
Date

Daniel Shames, M.D.
Signature of Office or Division Director

3/24/04
Date

cc:
Archival NDA 21-211
HFD- 580/Division File
HFD- 580/Reddy
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-211 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: January 23, 2004 Action Date: March 23, 2004

HFD 580 Trade and generic names/dosage form:

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): 1

Indication #1: Assisted Reproductive Technologies

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:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Archana P. Reddy, M.P.H.
Regulatory Project Manager

cc: NDA 21-211
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number: 021211 **Trade Name:** FOLLISTIM AQ(FOLLITROPIN BETA INJ)300IU/
Supplement Number: 000 **Generic Name:** FOLLITROPIN BETA INJECTION
Supplement Type: N **Dosage Form:**
Regulatory Action: OP **COMIS Indication:** DEVELOPMENT OF MULTIPLE FOLLICLES IN OVULATORY PATIENTS PARTICIPATING IN A ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAM/INDUCTION OF OVULATION/PREGNANCY IN ANOVULAT
Action Date: 1/31/00
Indication # 1 Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation in anovulatory infertile patients whom the cause of infertility is functional and is not due to primary ovarian failure.
Label Adequacy: Does Not Apply
Formulation Needed: NO NEW FORMULATION is needed
Comments (if any): 11-15-00

	Lower Range	Upper Range	Status	Date
Adult	Adult	Waived		11/30/00

Comments: This drug will be used in patients of reproductive age so is not likely to be used in a substantial number of pediatric patients. There were no pediatric data submitted to this NDA.

This page was last edited on 11/21/00

E. de Guis
 Signature

11/21/00
 Date

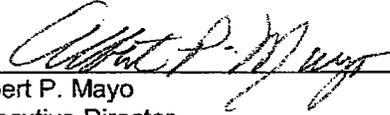
CONFIDENTIAL

Follistim® - AQ (follitropin beta injection) Cartridge
Debarment Certification

1

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) Cartridge, NDA No. 21-211.



Albert P. Mayo
Executive Director
Regulatory Affairs



Date

0018

MEMORANDUM

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

Date: April 20, 2000 *LLP 4/20/00*

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 21-211)

I have reviewed the financial disclosure information submitted by Organon, Inc. in support of NDA 21-211.

One study was conducted to support the safety and efficacy for Follistim AQ (follitropin beta injection), a liquid formulation of the originally-approved lyophilized powder. The study number and its outcome with regard to financial disclosure obligations is summarized below:

Study No.	Study Status	Financial Disclosure Documentation
37626	Study completed	Appropriate documentation; no financial arrangements/proprietary interest

Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

cc:
Orig NDA 21-211
HFD-580/FdeGuia

Freshnie:

I have reviewed the information that you provided for Follistim AQ. The information is sufficient, and the application is acceptable for filing from a Section K perspective.

Lana

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

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

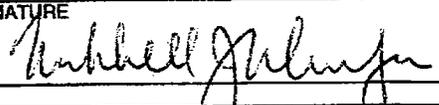
Please mark the applicable checkbox.

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

Clinical Investigators		

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

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

NAME Mitchell J. Weinberger, Ph.D.	TITLE Executive Director, Clinical Development Department
FIRM/ORGANIZATION Organon Inc.	
SIGNATURE 	DATE 1/27/00

Paperwork Reduction Act Statement

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

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

0019

ATTACHMENT

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

CLINICAL INVESTIGATOR AND CO-INVESTIGATORS

Study: An Open-label, Single Center, Single dose, Cross-over Study to Compare Pharmacokinetics of FSH After Administration of Two Pharmaceutical Formulations of Org 32489 in Healthy Female Subjects whose Pituitary Function Has Been Suppressed by Lyndiol® (Protocol no. 37626)

<p>Investigator:</p> <p>Prof. Dr. A.F. Cohen Center Code: NL 066 Centre for Human Drug Research Zernikedreef 10 2333 CL Leiden the Netherlands</p>	<p>Co-investigators:</p> <p>_____</p>
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DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0938 Expiration Date: March 31, 2003 See OMB Statement on page 2.
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE (Title 21, Code of Federal Regulations, 314 & 601)		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Organon USA Inc.		DATE OF SUBMISSION March 17, 2004
TELEPHONE NO. (Include Area Code) (973) 325-4833		FACSIMILE (FAX) Number (Include Area Code) (973) 325-4833
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 375 Mt. Pleasant Avenue West Orange, NJ 07052		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Organon USA Inc. 375 Mt. Pleasant Avenue West Orange, NJ 07052 Tel: (973) 325-4833 FAX: (973) 325-4769
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-211		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) follitropin beta		PROPRIETARY NAME (trade name) IF ANY Follistim® AQ Cartridge (follitropin beta injection)
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) Recombinant Follicle Stimulating Hormone (FSH)		CODE NAME (if any) Org 32489
DOSAGE FORM: aqueous solution for injection	STRENGTHS: 300 IU or 600 IU FSH activity per cartridge	ROUTE OF ADMINISTRATION: subcutaneous
(PROPOSED) INDICATION(S) FOR USE: 1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program. 2. Induction of ovulation in the anovulatory infertile patients for whom the cause of infertility is functional and not due to primary ovarian failure.		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: Holder of Approved Application		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION Response to FDA Information Request Letter of March 15, 2004		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED: 1	THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Cross References (list related License Applications, INDs, NDAs, PWAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)		

This application contains the following items: *(Check all that apply)*

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling <i>(check one)</i> <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50(c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section; (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 300(k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50(k)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER <i>(Specify)</i> Response to FDA Information Request Letter of March 15, 2004

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 806, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Albert P. Meyer</i>	TYPED NAME AND TITLE Albert P. Meyer Vice President, Regulatory Affairs	DATE March 17, 2004
ADDRESS (Street, City, State, and ZIP Code) 375 Mt. Pleasant Avenue West Orange, NJ 07052		TELEPHONE NUMBER (973) 325-4633

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-89
1401 Rockville Pike
Rockville, MD 20852-1448
FORM FDA 356h (4/00)

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Organon USA Inc.



Regulatory Affairs Department

375 Mt. Pleasant Avenue West Orange, NJ 07052

To: Archana Reddy	From: Larry Starke
Fax: 301-827-4267	Pages: 48 50
Date: 03/17/04	Sender's Phone: 973-325-4921
Re: NDA 21-211: Response to labeling comments	CC:

Urgent For Review Please Comment Please Reply

• **Comments:**

Archana,

As discussed attached please find the revised copy of the prescribing information (package insert) and patient information leaflet. As agreed, we are faxing what we have completed. The hard copy of this submission along with the electronic files will be sent by Federal Express today. The Follistim Pen™ Instructions for Use Manual is be changed by an outside agency and will be provided under separate cover once it is completed.

The Agency's comments on the patient information leaflet were extensive and the changes provided reflect our understanding of these comments and the overall theme of improving the readability of the leaflet. Due to the complex nature of these changes we believe it would be in the best interest of both the Agency and Organon if a teleconference could be held sometime today to discuss these changes.

Regards,

Larry Starke

THIS FACSIMILE MESSAGE IS CONFIDENTIAL AND MAY CONTAIN INFORMATION INTENDED ONLY FOR THE USE OF THE INDIVIDUAL OR COMPANY NAMED ABOVE.

If the reader is not the intended recipient, or the employee or agent responsible to deliver it to the intended recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please immediately notify us by telephone, so that we may arrange for the return of the original message to us. Thank you.



**CONFIDENTIAL**

March 17, 2004

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

NDA No: 21-211
Follistim® AQ Cartridge (follitropin beta injection)
Response to Labeling Comments

Dear Sir/Madam:

Reference is made to our NDA for Follistim® AQ Cartridge (No. 21-211) submitted on January 28, 2000; to the Approvable Letter dated December 23, 2003; to our complete response to the Approvable Letter dated January 22, 2004; to your telefax dated March 15, 2004 which provided general clinical labeling comments; and to our teleconference on March 16, 2004 to clarify certain issues.

Accordingly we herewith provide our responses to these clinical labeling comments. The responses are presented in the same order as found in the above-referenced telefax.

A. Prescribing Information:

1. *The new labeling is acceptable with the following changes:*
 - a. *On line 89, pituitary is spelled incorrectly.*
The spelling of pituitary on line 89 has been corrected.
 - b. *On line 184, insert a space between the period and the next sentence.*
The next sentence has been moved to a new line (181)
 - c. *On line 380 (page 19), availability is spelled incorrectly.*
The spelling of bioavailability on line 376 has been corrected.
 - d. *On line 382, syringe is spelled incorrectly.*
The spelling of syringe on line 378 has been corrected.
 - e. *Delete lines 176-181.*
The following text has been deleted:



375 Mt. Pleasant Avenue
West Orange
New Jersey 07062
USA
Tel.: (973) 325-4500
Fax: (973) 325-4589

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Page 2

- f. *Change the injection instructions for the Follistim Pen™ as list in the Patient Information Leaflet (listed in Section B.7 below).*

Please see the revised Instructions for Use Manual in Attachment 3.

- g. *The Ease of Use section (lines 124-134) reads:*

"The ease of use of Follistim® AQ Cartridge with the Follistim Pen™ was demonstrated in both the COH and Ovulation Induction groups. In both groups, all subjects (100%) rated the overall experience of self-injecting as "very good" to "good" on Day 2. On Day 6 in the COH group, more subjects rated the overall experience as "very good" as compared to Day 2, 54 subjects (90%) versus 49 subjects (81.8%), respectively and only one subject (1.7%) had a "neutral" response. In the Ovulation Induction group, the experience rating of "very good" increased from 90.7% on Day 2 to 95.2% on Day 8."

Comments: The following alternative language is recommended, "In an observer questionnaire, designed to assess the "Ease of Use of Follistim® AQ Cartridge with the Follistim Pen™, subjects rated their experience with the pen injector device. Subjects undergoing ART and OI rated their injection experience in two separate studies. On Day 6 in the ART group, more subjects rated the overall experience as "very good" as compared to Day 2, 54 subjects (90%) versus 49 subjects (81.8%), respectively and only one subject (1.7%) had a "neutral" response. In the Ovulation Induction group, the experience rating of "very good" increased from 90.7% on Day 2 to 95.2% on Day 8."

The requested change has been made on lines 126-132.

2. *We recommend you make the changes as shown in bold and/or italics to the injection instructions for Follistim Pen™ in the labeling (see Attachment).*

The revised Instructions for Use Manual will be provided under separate cover.

In addition, the following editorial changes have also been made:

Line 1 and 316: Follistim® AQ (follitropin beta injection) Cartridge has been changed to Follistim® AQ Cartridge (follitropin beta injection) to be consistent with the rest of the labeling.

Lines 107 and 117: (OI) was added after Ovulation Induction.

Table 2: "(" was added before pg/mL and the "r" in pgr was deleted.

Line 387: ® was added after Follistim.

Line 457-458: the 800 number was added.

Line 468: changed date of the PI.

Finally, all annotation footnotes were removed.

B. Patient Informational Leaflet:

1. *The new Patient Information Leaflet is too cumbersome, especially the side effects section (lines 76-122). Refer to the alternative language in the sections below (listed as 2 through 7). The conversion table should be deleted from the Patient Information Leaflet.*

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The conversion table has been deleted from the patient information leaflet.

2. We recommend the following alternative language for introduction of the Patient Information Leaflet (to replace lines 6-19 and 42-53):

**Follistim® AQ (fol-i-stim) Cartridge 300 IU and 600 IU
(follitropin beta injection)**

Read the patient information carefully before you start using Follistim® AQ Cartridge with Follistim Pen™ and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is Follistim® AQ Cartridge?

- Follistim® AQ Cartridge is a medicine that contains the hormone follicle stimulating hormone (FSH). FSH may help (stimulate) the ovaries to make eggs in women who have fertility problems. FSH will not help women who have a condition called primary ovarian failure.

What is Follistim® AQ Cartridge used for?

- Follistim® AQ Cartridge is used:
 - a. To help women who have problems with ovulation. Follistim® AQ Cartridge will not help women whose ovaries do not work at all (primary ovarian failure).
 - b. For women that are in an Assisted Reproductive Technology (ART) program, such as in-vitro fertilization.

The requested changes have been made on lines 5-21. Please note that (fol-i-stim) will not fit as part of the logo, therefore we have left it in line 5.

3. We recommend the following alternative language for the section (lines 55-65):
Who should not use Follistim® AQ Cartridge?

Do not use Follistim® AQ Cartridge if you:

- are allergic to recombinant human FSH products (see the end of this leaflet for a list of all the ingredients in Follistim® AQ Cartridge)
- have primary ovarian failure (your ovaries do not work at all)
- are pregnant, or think you might be pregnant
- have uncontrolled thyroid or adrenal gland problems
- have tumors in your ovaries, breasts, uterus, hypothalamus, or pituitary gland
- have heavy or irregular vaginal bleeding and the cause is not known
- have ovarian cysts or enlarged ovaries, not due to polycystic ovary syndrome (PCOS)

Tell your healthcare provider if you are breast feeding. It is not known if Follistim® AQ passes into your milk.

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The requested changes have been made on lines 36-50. Please note that the list of all ingredients has been added on lines 486-489. In addition, the bullet about allergies to streptomycin or neomycin has been kept (line 46-47) to be consistent with the professional labeling.

4. We recommend the following alternative language for the side effects section (lines 77-98):

Follistim® AQ Cartridge may cause serious side effects. This usually happens if too much Follistim® AQ Cartridge is used or it is not used the right way.

Ovarian Hyperstimulation Syndrome (OHSS). OHSS is a serious medical problem that can happen when the ovaries are overstimulated. In rare cases it has caused death. OHSS causes fluid to build up suddenly in the stomach and chest areas. OHSS may occur after treatment with Follistim® AQ Cartridge.

Call your healthcare provider right away if you get any of the following symptoms:

- severe pelvic pain (lower stomach area)
- nausea
- vomiting
- sudden weight gain
- reduced urine output

Lung and blood vessel problems. Follistim® AQ Cartridge and other FSH products may cause serious lung problems including fluid in the lungs (atelectasis) and acute respiratory distress syndrome (ARDS). Follistim® AQ Cartridge and other FSH products may also cause blood clots in blood vessels. This can lead to blood vessel problems (thrombophlebitis), stroke, loss of a limb, or a blood clot in the lung (pulmonary embolus).

Multiple births. Follistim® AQ Cartridge and other FSH products can cause multiple births. Your healthcare provider will discuss your chances of multiple births.

Other side effects with Follistim® AQ Cartridge include stomach pain, gas, pelvic pain, nausea, breast pain, injection site problems, enlarged stomach area, back pain, constipation, headache and ovarian pain. If you get any side effects that concern you, call your healthcare provider.

These are not all the side effects of Follistim® AQ Cartridge. Contact your doctor without delay if you are experiencing symptoms including significant abdominal pain, or if symptoms develop some days after the last injection has been given (see also, "Who should not take Follistim® AQ Cartridge?," section of this leaflet).

The requested changes have been made on lines 54-86

5. We recommend the following alternative language for the section (lines 125-137):

How should I use Follistim® AQ Cartridge?

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- Your healthcare provider will decide on the dose of Follistim® AQ (follitropin beta injection) Cartridge that is best for you. This dose may be increased or decreased as your treatment goes on. This will depend on your type of treatment. It is very important that you follow your healthcare provider's instructions exactly.
- Follistim® AQ Cartridge is given by an injection just under the skin (subcutaneous injection).

Your healthcare provider's office will teach you how to inject yourself. See the end of this leaflet for "How to inject Follistim® AQ Cartridge." Do not inject Follistim® AQ Cartridge at home until your healthcare provider's office has taught you the right way.

Close care by your healthcare provider is very important. Usually ultrasound scans (special x-rays) of the ovaries are regularly made. Blood or urine samples are regularly taken. The results of these tests allow your healthcare provider to choose the right dose of Follistim® AQ Cartridge for you each day. This is very important. Too high a dose of FSH may lead to rare, but serious problems in which the ovaries become overstimulated (too active). This may be noticed as pain in the abdomen (stomach area). Regular checking of your response to FSH treatment helps your healthcare provider lower your chances of ovarian overstimulation. Call your healthcare provider right away if you get strong abdominal pain. Also, call your healthcare provider right away if this happens some days after the last injection has been given.

The requested changes have been made on lines 89-110

6. We recommend the following changes to the complete instructions and diagrams for the Follistim Pen™ instructions in the Patient Information Leaflet (line 136-458):
 - a. The instructions for use should start at the top of the page.

Line 167 starts a new page in this version of the patient information leaflet. Please note that the final layout for the patient information leaflet will be in a package insert format.

- b. Generate a list, "What you will need for injection," as stated in the video.

This has been added on lines 133-138.

- c. Move lines 194-197 to the first sentence and separate each action with a space.

This change has been made on lines 170-174.

- d. Move line 198 to a box directly under the Instructions for Use.

Changes has been made on line 168.

- e. Use the same language for line 220 as used in lines 194-197. We recommend including a section entitled "Loading the Follistim Pen™."

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Section heading that correspond to the language on lines 194-197 have been added on lines 226, 316 and 340-341.

f. *Left justify the numbered steps and position the pictures so that they match with the steps.*

The numbered steps have been left justified and the pictures have been placed to the right of the corresponding step.

g. *On line 249, move the marks so that they are in parenthesis next to what they refer to.*

This change has been made on line 239-240.

h. *We recommend that you take out the italics in the box and replace them with bold print.*

Box lines have been removed and the text has been changed to bold print without italics.

i. *In the "General information about Follistim® AQ Cartridge," we recommend that you add the toll free number and website information.*

This information was added on lines 541-543.

7. *We recommend you make the changes as shown in bold and/or italics to the injection instructions for Follistim Pen™ in the Patient Information Leaflet (see Attachment).*

The requested changes provided in the attachment have been with the following modifications to what was requested by the Agency.

Washing of the hands directions have been moved from the old step 15 to lines 215-216 to emphasize aseptic technique at the beginning of the instructions for use process.

In order to address the Agency's concern of having an exposed sterile needle while trying to prep the area for injection. The old steps 14 and 15 have been moved to lines 260-272 (steps 8 and 9)

In the attachment provided by the Agency, changes were requested to step 11. Upon reviewing this request, we would like to inform you that these changes are not appropriate because they were not consistent with the instructions in the old step 16 (new step 15, lines 346-356) or with the functional design of the pen. Specifically, in step 11 of your correspondence, the Agency suggested use of a new Follistim® AQ Cartridge for injection if there is not enough medication in the cartridge the patient is currently using. In contrast, in step 16 of your proposed revisions, it is acknowledged that if there is not enough medicine in the cartridge the patient will administer the drug remaining in the current cartridge, record the number of IUs remaining to be administered as shown in the dosage window of the pen, start over with a new cartridge and needle, and then inject the remainder of their prescribed dose. Your proposed step 16 more accurately reflects

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Page 7

the functional design of the pen. Therefore, we have incorporated the information from your steps 11 and 16 in our current proposed step 13 (lines 317-322) and step 15 (lines 346-356) and the important bolded statement (lines 371-372) following step 16.

Please note the following:

Lines 374-378: Step 17: The outer needle shield has a flat top and will sit upside down without moving. The patient will be able to insert the needle into the outer needle shield without holding on to it.

Additional changes (moving of information and deleting duplicate information) have been made to improve the consistency and readability of the leaflet and to make it less cumbersome.

C. Video

1. *The changes to the video are acceptable.*
2. *We recommend that the toll free hotline number be included and clearly visible in the video.*

The toll free hotline number will be included and clearly visible in the video. As agreed to in the teleconference of March 16, the dose conversion table will also be deleted.

D. Survey

We recommend that you submit the proposal for the survey on the conversion table prior to initiation. This will allow us to make comments on the proposed survey.

We agree to submit our proposal for the survey to the Agency for comments.

Accordingly, in order to address the Agency's comments provided in the March 15, 2004 telefax this submission includes the following:

- **Draft Package Insert - Attachment 1** contains the revised draft package insert. Additionally, a Word and pdf file has been provided for the package insert on the enclosed CD-ROM.
- **Draft Patient Information Leaflet - Attachment 2** contains the revised draft patient information leaflet. Additionally, a Word and pdf file has been provided for the patient information leaflet on the enclosed CD-ROM.

The files contained in the CD-ROM have been checked for viruses using McAfee VirusScan [Version 4.5.0.534/Scan Engine: 4.1.60/Virus Def: 4.0.4338].

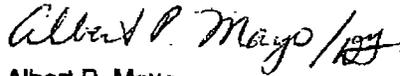
We believe the attached labeling satisfactorily addresses all comments from your March 15 telefax and that approval of Follistim® AQ Cartridge should be forthcoming. However, if further discussion is needed, we respectfully request a teleconference so that any further comments can be addressed quickly.

Central Document Room
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Page 8

If you have any additional comments or questions, please contact Lawrence Starke, Ph.D. at 973-325-4921.

Please note that Organon USA Inc. regards this submission and all correspondence related thereto as confidential, trade secret and proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and 21 CFR.

Sincerely,



Albert P. Mayo
Vice President, Regulatory Affairs

FDA Form 356H
Attachments and CD containing label files
Submitted in duplicate
via Federal Express Airbill No. 812785707225
and via telefax to Archana Reddy

cc: 5 copies to:
Archana Reddy, M.P.H.
Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III, Document Control Room 17B45
5600 Fishers Lane
Rockville, MD 20857
via Federal Express Airbill No.

35 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 1

NDA 21-211
Follistim® - AQ (follitropin beta injection)
Organon, Inc.

FDA revised labeling and reviews

Not Approvable (NA) action: labeling not finalized

Appears This Way
On Original

Appears This Way
On Original



NDA 21-211

INFORMATION REQUEST LETTER

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

Dear Mr. Mayo:

Please refer to your January 28, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®]-AQ Cartridge (follitropin beta injection).

We also refer to your submission dated January 22, 2004, containing a complete response to our approvable letter dated December 23, 2003.

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

A. Draft Prescribing Information

The following sections were noted to contain paragraphs or passages that may need to be altered.

1. Special populations (Page 5: Lines 102 - 108): This section refers to a Japanese study on body weight using the approved product Follistim[®], not Follistim[®]-AQ Cartridge.

Comment: Delete this paragraph.

2. Clinical studies:

- "Local tolerance" (Page 7: Lines 136-147).
- "Ease of Use" (Page 8: Lines 148-162).
- Comparator information from the original studies for the approved Follistim[®] product - Tables 4, 5, 6, 7, 8, 9 and 10 (Studies 37608, 37604, 37609) (Lines 163-222).

Comments:

1. We recommend a minor revision to Table 2. Either put serum estradiol level in pg/mL or provide a footnote for Table 2 with a conversion factor.
2. Delete the Local Tolerance section.
3. Shorten the Ease of Use section to two or three sentences.

4. Remove Tables 4, 5, 6, 7, 8, 9 and 10 containing comparator information from the original Follistim[®] label.
3. Warnings (Page 14):
 - “Follistim[®]-AQ (follitropin beta injection) Cartridge should only be used by physicians who are experienced in infertility treatment. Follistim[®]-AQ Cartridge administered with the Follistim Pen[™] contains a potent gonadotropic substance and delivers on average an 18% higher amount of follitropin beta as compared to lyophilized preparations administered by conventional syringe. Accordingly, a lower starting dose for gonadotropin stimulation and dose adjustments during gonadotropin stimulation should be considered for each woman treated with Follistim[®]-AQ Cartridge” (Lines 257-263).
 - Multiple births use information from the original studies for the approved Follistim[®] product (Lines 345-349).

Comments:

1. Bold lines 257-263.
 2. Delete multiple birth comparator information (Lines 345-349).
4. Precautions (Page 18):
 - General – Statement “Change in brand (manufacturer), type (recombinant, urinary, etc.) and/or method of administration (Follistim Pen[™], conventional syringe) may result in the need to adjust the dose” (Lines 355 – 357).
 - Information for patients: “Patients should read and follow...” (Lines 353-365).

Comments:

1. Move Lines 355-357 to the Warnings section after lines 257-258.
 2. Insert a sentence at line 360 as information for patients to begin with “Physicians need to instruct patients in correct use and dosage of Follistim[®]-AQ Cartridge.”
5. Adverse Reactions (Page 21):
 - Assisted Reproductive Technology (ART): Studies with comparator information from the original studies for the approved Follistim[®] product – Tables 11 and 13 (Lines 417- 421 and 429-437).

Comment:

1. We recommend deleting Tables 11, 13 and the text that accompanies these tables.
6. Dosage and Administration (Page 25):
 - “Follistim[®]-AQ Cartridge is delivered by the Follistim Pen[™] which accurately and precisely delivers the dose to which it is set” (Lines 471-472).

- A detailed description of the 18% higher amount delivered by the Pen Injector (Lines 472-483).
- Conversion Chart - Table 15(Lines 485-490).

Comments:

1. Delete either the word “accurately” or “precisely” (Lines 471-472).
2. Reword Lines 472-483 so that it is easier to follow this section.
3. Move conversion chart (Table 15) to the beginning and add the 375 IU conversion factor (Lines 485-485).

7. Assisted Reproductive Technologies (ART) (Page 26: Lines 500-503):

“A starting dose of 150 to 225 IU or lower of Follistim[®]-AQ Cartridge is recommended for at least the first four days of treatment. If a prescriber generally uses a starting dose of 150-225 IU of lyophilized gonadotropin, then the prescriber should consider using a lower starting dose of Follistim[®]-AQ Cartridge.”

- “However in patients that were low or poor responders, maintenance doses of 375 to 600 IU were administered according to individual response.” (Lines 496-497)
- This latter category comprised approximately 10% of the women evaluated in the clinical study. The maximum individualized dose of lyophilized Follistim[®] requiring reconstitution in clinical studies is 600 IU.” (Lines 498-499)

Comments:

1. The dosing instructions for ART should be identical to Study 142-001. The recommended starting dose should be 150 IU. Therefore, “A starting dose... is recommended for at least the first five days.”
2. Maximum daily dose should be identical to Study 142-001.
3. Delete Lines 496-498 so that it is easier to follow this section.

8. Ovulation Induction (Page 27):

“A starting dose of 75 IU or lower of Follistim[®]-AQ Cartridge is recommended for at least the first 7 days of treatment with dose adjustments at weekly intervals. If a prescriber generally uses a starting dose of 75 IU of lyophilized gonadotropin, then the prescriber should consider using a lower starting dose of Follistim[®]-AQ Cartridge.”

Comments:

1. Instructions for ovulation induction should be identical to Study 142-002. The recommended starting dose should be 75 IU.
2. Maximum daily dose should be identical to Study 142-001.

B. Patient Informational Leaflet (PPI)

1. The information on the 18% higher dose and the conversion table needs to be incorporated at the beginning of the leaflet.

2. Line 15: "What is Follistim[®]-AQ Cartridge? Follistim[®]-AQ Cartridge is for.....":

Comment: Revise to include the following statements:

- a. This is not Follistim[®].
- b. Consult with physician or provider if you have any questions. (**Bold this.**)

3. "OTHER SIDE EFFECTS WITH FOLLISTIM[®]-AQ CARTRIDGE" (Page 2 of Information Leaflet: Lines 167 – 173):

Comment: Revise the side effects in order of serious and life threatening side effects first and separate out to make this section easier to read.

4. "HOW TO INJECT FOLLISTIM[®]-AQ CARTRIDGE" (Page 3 of Information Leaflet):

Comments: Include complete instructions and diagrams for the Pen injector device. You can refer to the Center for Devices and Radiological Health's Guidance on Medical Device Patient Labeling: "Final Guidance for Industry for Writing Device Instructions for Patients."

C. Education Training Program

Incorporate the following information into the video:

1. This is not Follistim[®].
2. The 18 % higher dose delivered by Follistim[®]-AQ Cartridge and the conversion table for dosage.
3. If you have any questions about the dosage of Follistim[®]-AQ Cartridge, please consult your provider.

D. Proposed Educational Program

1. A Toll Free 24-Hour Hotline number should be provided for patients and prescribers.
2. We request you conduct a survey after one year to evaluate the use of the conversion table. The details of the survey should be sent to us in advance so that we may offer comments.

NDA 21-211
Page 5

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

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/s/

Margaret Kober
3/1/04 11:47:35 AM
Chief, Project Management Staff

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

2 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-2



NDA 21-211

INFORMATION REQUEST LETTER

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

Dear Mr. Mayo:

Please refer to your January 28, 2000, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®]-AQ Cartridge (follitropin beta injection).

We also refer to your submissions dated January 22, and February 26, 2004. These submissions contained your complete response to our approvable letter dated December 23, 2003 and your response to our clinical labeling comments dated February 24, 2004.

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

A. Prescribing Information:

- I. The new labeling is acceptable with the following changes.
 - a. On line 89, pituitary is spelled incorrectly.
 - b. On line 184, insert a space in between the period and the next sentence.
 - c. On line 380 (page 19), availability is spelled incorrectly.
 - d. On line 382, syringe is spelled incorrectly.
 - e. Delete lines 176-181.
 - f. Change the injection instructions for the Follistim Pen[™] as listed in the Patient Information Leaflet (listed in Section B.7 below).
 - g. The Ease of Use section (lines 124-131) reads:

"The ease of use of Follistim[®]-AQ Cartridge with the Follistim Pen[™] was demonstrated in both the COH and Ovulation Induction groups. In both groups, all subjects (100 %) rate the overall experience of self injection as "very good" to "good" on Day 2.^{17,18} On Day 6 in the COH group, more subjects rated the overall experience as "very good" as compared to Day 2, 54 subjects (90 %) versus 49 subjects (81.8 %), respectively¹⁹ and only one subject (1.7 %) had a "neutral" response.²⁰ In the Ovulation Induction group, the experience rating of "very good" increased from 90.7 % on Day 2 to 95.2 % on Day 8.²¹

Comments: The following alternative language is recommended, "In an observer questionnaire, designed to assess the 'Ease of Use' of Follistim[®]-AQ Cartridge with the Follistim Pen[™], subjects rated their experience with the pen injector device. Subjects undergoing ART and OI rated their injection experience in two separate studies. On Day 6 in the ART group, more subjects rated the overall experience as "very good" as compared to Day 2, 54 subjects (90 %) versus 49 subjects (81.8 %), respectively¹⁹ and only one subject (1.7 %) had a "neutral" response.²⁰ In the Ovulation Induction group, the experience rating of "very good" increased from 90.7 % on Day 2 to 95.2 % on Day 8."²¹

2. We recommend you make the changes as shown in bold and/or italics to the injection instructions for Follistim Pen[™] in the labeling (see Attachment).

B. Patient Information Leaflet:

1. The new Patient Information Leaflet is too cumbersome, especially the side effects section (lines 76-122). Refer to the alternative language in the sections below (listed as 2 through 7). The conversion table should be deleted from the Patient Information Leaflet.
2. We recommend the following alternative language for introduction of the Patient Information Leaflet (to replace lines 6-19 and 42-53):

**Follistim[®]-AQ (fol-i-stim) Cartridge 300 IU and 600 IU
(follitropin beta injection)**

Read the patient information carefully before you start using Follistim[®]-AQ Cartridge with FollistimPen[™] and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is Follistim[®]-AQ Cartridge?

- Follistim[®]-AQ Cartridge is a medicine that contains the hormone follicle stimulating hormone (FSH). FSH may help (stimulate) the ovaries to make eggs in women who have fertility problems. FSH will not help women who have a condition called primary ovarian failure.

What is Follistim[®]-AQ Cartridge used for?

- Follistim[®]-AQ Cartridge is used:
 - a. To help women who have problems with ovulation. Follistim[®]-AQ Cartridge will not help women whose ovaries do not work at all (primary ovarian failure).
 - b. For women that are in an Assisted Reproductive Technology (ART) program, such as *in-vitro* fertilization.

3. We recommend the following alternative language for the section (lines 55-65):
Who should not use Follistim[®]-AQ Cartridge?

Do not use Follistim[®]-AQ Cartridge if you:

- are allergic to recombinant human FSH products (see the end of this leaflet for a list of all the ingredients in Follistim[®]-AQ Cartridge)
- have primary ovarian failure (your ovaries do not work at all)
- are pregnant, or think you might be pregnant
- have uncontrolled thyroid or adrenal gland problems
- have tumors in your ovaries, breasts, uterus, hypothalamus, or pituitary gland
- have heavy or irregular vaginal bleeding and the cause is not known
- have ovarian cysts or enlarged ovaries, not due to polycystic ovary syndrome (PCOS)

Tell your healthcare provider if you are breast feeding. It is not known if Follistim[®]-AQ passes into your milk.

4. We recommend the following alternative language for the side effects section (lines 77-98):

Follistim[®]-AQ Cartridge may cause serious side effects. This usually happens if too much Follistim[®]-AQ Cartridge is used or it is not used the right way.

Ovarian Hyperstimulation Syndrome (OHSS). OHSS is a serious medical problem that can happen when the ovaries are overstimulated. In rare cases it has caused death. OHSS causes fluid to build up suddenly in the stomach and chest areas. OHSS may occur after treatment with Follistim[®]-AQ Cartridge.

Call your healthcare provider right away if you get any of the following symptoms:

- severe pelvic pain (lower stomach area)
- nausea
- vomiting
- sudden weight gain
- reduced urine output

Lung and blood vessel problems. Follistim[®]-AQ Cartridge and other FSH products may cause serious lung problems including fluid in the lungs (atelectasis) and acute respiratory distress syndrome (ARDS). Follistim[®]-AQ Cartridge and other FSH products may also cause blood clots in blood vessels. This can lead to blood vessel problems (thrombophlebitis), stroke, loss of a limb, or a blood clot in the lung (pulmonary embolus).

Multiple births. Follistim[®]-AQ Cartridge and other FSH products can cause multiple births. Your healthcare provider will discuss your chances of multiple births.

Other side effects with Follistim[®]-AQ Cartridge include stomach pain, gas, pelvic pain, nausea, breast pain, injection site problems, enlarged stomach area, back pain, constipation, headache and ovarian pain. If you get any side effects that concern you, call your healthcare provider.

These are not all the side effects of Follistim[®]-AQ Cartridge. Contact your doctor without delay if you are experiencing symptoms including significant abdominal pain, or if symptoms develop some days after the last injection has been given (see also, "Who should not take Follistim[®]-AQ Cartridge?," section of this leaflet).

5. We recommend the following alternative language for the section (lines 125-137):

How should I use Follistim[®]-AQ Cartridge?

- Your healthcare provider will decide on the dose of Follistim[®]-AQ (follitropin beta injection) Cartridge that is best for you. This dose may be increased or decreased as your treatment goes on. This will depend on your type of treatment. It is very important that you follow your healthcare provider's instructions exactly.
- Follistim[®]-AQ Cartridge is given by an injection just under the skin (subcutaneous injection).

Your healthcare provider's office will teach you how to inject yourself. See the end of this leaflet for "How to inject Follistim[®]-AQ Cartridge." Do not inject Follistim[®]-AQ Cartridge at home until your healthcare provider's office has taught you the right way.

Close care by your healthcare provider is very important. Usually ultrasound scans (special x-rays) of the ovaries are regularly made. Blood or urine samples are regularly taken. The results of these tests allow your healthcare provider to choose the right dose of Follistim[®]-AQ Cartridge for you each day. This is very important. Too high a dose of FSH may lead to rare, but serious problems in which the ovaries become overstimulated (too active). This may be noticed as pain in the abdomen (stomach area). Regular checking of your response to FSH treatment helps your healthcare provider lower your chances of ovarian overstimulation. Call your healthcare provider right away if you get strong abdominal pain. Also, call your healthcare provider right away if this happens some days after the last injection has been given.

6. We recommend the following changes to the complete instructions and diagrams for the Follistim Pen[™] instructions in the Patient Information Leaflet (lines 136-458):
- a. The instructions for use should start at the top of the page.

- b. Generate a list, "What you will need for injection," as stated in the video.
- c. Move lines 194-197 to the first sentence and separate each action with a space.
- d. Move line 198 to a box directly under the Instructions for Use.
- e. Use the same language for line 220 as used in lines 194-197. We recommend including a section entitled "Loading the Follistim Pen™."
- f. Left justify the numbered steps and position the pictures so that they match with the steps.
- g. On line 249, move the marks so that they are in parenthesis next to what they refer to.
- h. We recommend that you take out the italics in the box and replace them with bold print.
- i. In the "General information about Follistim®-AQ Cartridge," we recommend that you add the toll free number and website information.

7. We recommend you make the changes as shown in bold and/or italics to the injection instructions for Follistim Pen™ in the Patient Information Leaflet (see Attachment).

C. Video:

1. The changes to the video are acceptable.
2. We recommend that the toll free hotline number be included and clearly visible in the video.

D. Survey:

We recommend that you submit the proposal for the survey on the conversion table prior to initiation. This will allow us to make comments on the proposed survey.

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

Sincerely,

Margaret M. Kober

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-211

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

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated January 28, 2000, received January 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®]-AQ Cartridge (follitropin beta for injection).

We acknowledge receipt of your submission dated January 22, 2004 received on January 23, 2004.

We consider this a complete, class 1 response to our December 23, 2003 action letter. Therefore, the user fee goal date is March 23, 2004.

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. We note that you have not fulfilled the requirement. We are, however, waiving the requirement for pediatric studies for this application.

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

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/s/

Margaret Kober
2/6/04 11:19:43 AM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-211

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

Dear Mr. Mayo:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®]-AQ Cartridge (follitropin beta for injection).

We also refer to the Agency letter dated December 23, 2003, containing a response to your Dispute Resolution dated October 31, 2003. We are advising you that the correct date of the action of the approvable letter should be December 23, 2003 not June 23, 2003. A Not Approvable action letter was issued by the Agency on June 23, 2003. This letter serves as clarification to the December 23, 2003 letter sent by the Agency.

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

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
1/12/04 10:48:20 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated January 28, 2000, received January 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®]-AQ Cartridge (follitropin beta for injection).

We acknowledge receipt of your submissions dated August 5 (2), August 11, and October 31, 2003.

Your October 31, 2003, request for dispute resolution, received on November 3, 2003, concerned the Division's decision to not approve NDA 21-211 under section 505(d) of the Act and 21 CFR 314.125 (b). This appeal was submitted in response to the June 23, 2003, not approvable letter.

The November 24, 2003, response to your request for dispute resolution from Dr. Julie Beitz, Deputy Director of the Office of Drug Evaluation III, informed you of the decision to issue an approvable letter for this application. Therefore, this letter informs you that the application is considered approvable as of June 23, 2003. Before the application may be approved, the following information must be submitted:

1. Draft professional labeling.
2. Draft patient package insert.
3. Plans for an educational program for patients and prescribers focusing on correct use of the pen injector and the need for careful dose conversion when switching from syringe to pen injector or *vice versa*.

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.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the 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 Archana Reddy, M.P.H, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Division Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
12/23/03 11:13:09 AM
signed for Dr. Shames

MEETING MINUTES

Date: July 24, 2003 **Time:** 3:00 – 4:30 P.M. **Location:** PKLN. Conf. Rm. L

NDA: 21-211

Drug: Follistim[®]-AQ Cartridge (follitropin beta for injection with a pen-injector device)

Sponsor: Organon, Inc.

Indication: 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 Cartridge is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.

Type of Meeting: Type A (Post Action)

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

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

External Participant Lead: Albert Mayo, Vice President, Regulatory Affairs

FDA Participants:

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

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

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

Sonia Castillo, Ph.D., Statistical Reviewer, Division of Biometrics II (DB II)

External Participants:

Andre Broekmans, M.D., Vice President Regulatory Affairs and Pharma Policy

Albert Mayo, Vice President Regulatory Affairs,

Marjo Peters, Ph.D., Senior Director Development Projects

Bernadette Mannaerts, Clinical Group Director, Infertility

Keith Gordon, Ph.D., Senior Director, Medical Services, Fertility

Mary Mahony, Ph.D., Associate Director, Reproductive Medicine, Medical Affairs

John Leach, Director, Regulatory Affairs, Profertility

Consultant

Meeting Objectives (stated in the Sponsor's briefing package):

Type A meeting to discuss the not approvable letter dated June 23, 2003 for Follistim® AQ Cartridge. In particular,

1. To address concerns that the average 18 % difference in the dose delivery between the current lyophilized product and the ready to use solution in the pen could have clinical implications, particularly with regard to safety.
2. To address the clinical issues specifically related to the clinical information found in Study 142-001 and Study 142-002 provided in the December 20, 2002 submission.

Background:

The new drug application for Follistim®-AQ Cartridge was submitted on January 28, 2000. A teleconference between the Agency and the Sponsor was held on March 22, 2000. In this teleconference, the Deputy Division Director reiterated to the Sponsor the discussion points of the March 18, 1999 guidance meeting. The Sponsor was told that the safety and efficacy of the BD Pen™ injector must be linked to Follistim by establishing bioequivalence. The Sponsor was presented with alternatives to conducting another pharmacokinetics trial to establish bioequivalence. A not approvable letter was sent to the sponsor on November 29, 2000 and a letter clarifying these not approvable issues was dated February 14, 2001. Organon's response to the not approvable letter was received on December 23, 2002. The sponsor submitted two clinical studies (142-001 and 142-002) that addressed the issues of use of the Follistim Pen™ by patients. However, the lack of bioequivalence to the approved product Follistim® was not addressed, and this is the main issue for the Not Approvable action dated June 23, 2003. The sponsor has chosen to further support the efficacy and safety of the Follistim®-AQ Cartridge by presenting in the briefing package for this meeting, additional clinical data that has not been previously reviewed by the Division. A Type A meeting request was received on July 7, 2003 and a Type A meeting package was received on July 14, 2003.

DISCUSSION:

1. The sponsor feels that there was inadequate feedback from the Division on the two clinical study protocols 142-001 and 142-002.

DRUDP Response:

- The Division recognizes that communication could have been better. The original reviewer interpreted the protocols for patient comprehension only. The Division will conduct a future internal meeting to discuss this.

2. It has been established that there is a lack of bioequivalence of Follistim[®]-AQ Cartridge as administered by Pen injector and the approved product Follistim[®]. What alternatives would be acceptable to the Division for approving the Follistim[®]-AQ Cartridge?

DRUDP Response:

- At this time, the Division considers that additional clinical data for each indication will be required to determine efficacy and safety of Follistim[®]-AQ Cartridge. The Division will hold an internal meeting to discuss the issues of study size and endpoints.
3. The sponsor wished to respond to the Division's concerns about the increased dose delivered by the Follistim Pen[®] device resulting in an increased risk of OHSS in patients undergoing ART procedures. The sponsor reviewed both previous and new safety data for the approved product Follistim[®]. The sponsor presented a post-hoc analysis using logistic regression for ovarian OHSS. The sponsor concluded that the clinical safety data from the two clinical studies did not demonstrate an excessive OHSS risk based on conclusions from the statistical model presented.

DRUDP Response:

- The Division recognizes that additional clinical studies specifically designed to determine the rate of OHSS for a given gonadotropin product is not currently feasible. However, the additional dose delivered by the Follistim Pen[™] presents unresolved safety concerns.

Other DRUDP Comments:

1. The Division continues to have concerns about the higher bioavailability of the dose delivered by the Follistim Pen[™]. None of the submitted clinical studies address this question.
2. A simple "closest dose" conversion chart has not resolved the lack of bioequivalence between Follistim[®]-AQ Cartridge and the approved product Follistim. The conversion chart is confusing and is not acceptable to the Division.
3. The post-hoc analysis of OHSS is not acceptable given that all the data is from previous clinical studies with the approved Follistim[®] product, not Follistim[®]-AQ Cartridge. In addition, the post-hoc analysis includes studies that the Division has not reviewed.
4. The sponsor may submit the new clinical data presented in the meeting package. However, the Division's position is that this new clinical data from the sponsor will be insufficient to justify approval of Follistim[®]-AQ Cartridge.

Decisions Reached:

1. The sponsor can submit the additional clinical studies for Follistim[®] and Follistim[®]-AQ Cartridge that were discussed in the meeting package, but have not been submitted to the Division.

2. The sponsor can provide an additional submission to justify their position that additional clinical studies are not necessary for the approval of Follistim[®]-AQ Cartridge. The Division will review the submitted information and provide comment.
3. The sponsor can submit additional clinical studies for the two stated indications of Follistim[®]-AQ Cartridge that will demonstrate safety and efficacy of Follistim[®]-AQ Cartridge relative to the currently marketed Follistim[®] formulation as a comparator. In general, these type of studies are usually designed as non-inferiority studies.
4. The sponsor has the right to appeal the Division's not approvable letter to the Office level.
5. The Division will discuss internally the communication issues cited by the sponsor.

Action Item:

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

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 may have regarding the meeting outcomes.

Signature: Meeting Chair
See Electronic Signature Page
Shelley Slaughter, M.D., Ph.D.

Meeting Minutes
Page 5
NDA 21-211

Cc:
Original NDA/21-211
HFD-580/Division Files
HFD-580/Reddy/Gassman/Slaughter/Shames/Kober/Rhee/Tran/Jarugula
HFD-715/Castillo

Created by: Archana Reddy, July 28, 2003
Concurrence: st/sc/ag/July 28, 2003, ss/August 6, 2003, mk/July 30, 2003, das/August 7, 2003,
vj/August 1, 2003
Finalized: ar/August 7, 2003
Filename: C:\Data\My Documents\NDAs\n21211\TypeAminutes

Meeting Minutes

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/s/

Shelley Slaughter
8/7/03 02:55:15 PM
I concur



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-211

Organon USA, Inc.
Attention: Mr. John Leach
Director, Regulatory Affairs, Profertility
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Leach:

Please refer to your new drug application (NDA) dated January 28, 2000 received January 31, 2000 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim[®] - AQ Cartridge (follitropin beta for injection).

We acknowledge receipt of your submissions dated December 20, 2002, February 19, 21, 26, 27, March 13, 20, 21, 28, April 3, 7, May 16, 19, 20, 30, and June 17, 2003.

The December 20, 2002 submission, received on December 23, 2002, constituted a complete response to our November 29, 2000 action letter.

We completed our review and find that the clinical information presented is inadequate and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiency is summarized as follows:

Study 142-001 and Study 142-002, the two open-label, non-comparative comprehension studies for Follistim[®]-AQ Cartridge, provide insufficient safety and efficacy information for adequate labeling of Follistim[®]-AQ Cartridge.

To address the above deficiency, you will need to submit results from a blinded, randomized comparator trial that demonstrates therapeutic equivalence (non-inferiority of safety and efficacy) of Follistim[®]-AQ Cartridge to the approved product Follistim[®] for each proposed indication.

In addition, before this application may be approved, FDA must conduct an inspection of the manufacturing facilities referenced in the application to determine satisfactory compliance with CGMPs. Due to Agency-wide restrictions on foreign travel, we postponed the inspection of the following manufacturing facilities:

3. CFN 9612716: Organon Ireland Ltd., Swords, Ireland
4. CFN 9610342: Organon NV, 5340-BH, Oss, Netherlands

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. 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 this deficiency. 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 the Division of Reproductive and Urologic Drug Products 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 this application is approved.

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

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

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/s/

Donna Griebel
6/23/03 06:30:51 PM
Signed for Dr. Daniel Shames, MD

MEETING MINUTES

Date: February 6, 2003 **Time:** 1:00 – 1:30 P.M. **Location:** PKLN 17B-43

NDA: 21-211 **Drug Name:** Follistim AQ® (follitropin beta injection) Cartridge

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) Cartridge 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 to be used in conjunction with a pen injector. This new drug application received a not approvable action on January 28, 2000 due to chemistry and clinical issues. A complete response addressing all chemistry and clinical deficiencies was received on December 23, 2002. The user fee goal date for this new drug application is June 23, 2003.

Clinical

- The accuracy and precision of the pen needs to be addressed by CDRH.
- The NDA is fileable.

Chemistry

- The sponsor has provided responses to all chemistry issues as listed in the not approvable letter.
- The sponsor should submit the complete list of all manufacturing, testing, packaging, and labeling facilities and a statement regarding the current GMP compliance status for each site. Confirm that Organon Inc. of West Orange, NJ facilities are not alternate test and release sites for the drug product, but that both

facilities remain alternate test and release sites for the drug substance. Provide in writing the requested information within one week of receipt date of letter to sponsor.

- Manufacturing site in West Orange, NJ is not in compliance and is used only for appearance testing. The Office of Compliance will determine if this is acceptable from a GMP standpoint.
- The amendment dated 12/20/02 states that the drug substance manufacturing site has changed as provided for in Supplement S-007 for NDA 20-582. However, that supplement provides for only a change in the site of the drug substance purification. Clarification of whether this still holds true or if the new site at Veersemeer 4 in Oss responsible for the entire drug substance manufacture is needed from the sponsor.
- The NDA is fileable.

Microbiology

- The status of review needs to be confirmed with microbiology reviewer.

Decision Reached:

- NDA is fileable

Action Items:

- The Project Manager will request a DMETS consult for tradename review, a DDMAC consult of the package insert and a DSRCS consult for the patient package insert and video included with the pen injector.

Cc:

Archival NDA 21-211
HFD-580/Division Files
HFD-580/Reddy/Lin/Slaughter/Willett/Gassman/Tran/Crisostomo

Created by: Archana Reddy, 3.19.03
Concurrence: dtl/4.01.03, ag/.03, st/4.07.03, 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 01:06:33 PM
I concur.



NDA 21-211

DISCIPLINE REVIEW LETTER

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

Dear Dr. Starke:

Please refer to your January 31, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim AQ Cartridge (follitropin beta injection).

We have identified the following deficiency in the labeling:

Implement labeling revisions (package insert and container labels) that were discussed in the 20-NOV-2000 amendment and submit the revised labeling.

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.

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

Sincerely,

{see appended electronic signature page}

David Lin, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug
Products
DNDC II, 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/

David T. Lin
5/14/03 03:35:26 PM
I concur.

14 Page(s) Withheld

0 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



Food and Drug Administration
Rockville MD 20857

NDA 21-211

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

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated January 28, 2000, received January 31, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim® - AQ Cartridge (follitropin beta for injection).

We acknowledge receipt of your submissions dated March 7, 23 (facsimile) and 30, April 5, May 9, September 26 and 28, October 27 (3), 30, and 31, November 6 (facsimile) 16, 2000.

We also acknowledge receipt of your submission dated November 20, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical

1. Sufficient information to support the safe and effective use of Follistim®-AQ Cartridge was not provided in the current NDA submission.
2. The proposed draft labeling for Follistim®-AQ Cartridge (including the incorporated conversion table) contains several inaccuracies, is incomplete and is not applicable to all patients who would use this product for the indications proposed. These inaccuracies and omissions pose an unacceptable risk for prescribing and dosing errors.

Information needed to address clinical deficiencies:

1. Clinical trials using Follistim®-AQ Cartridge must be conducted in patients undergoing Assisted Reproductive Technology (ART) and Ovulation Induction (OI) protocols. The studies must demonstrate the safety and effectiveness of the product for the proposed indications, including demonstration of patient comprehension of a proposed patient instruction manual, patient ability to correctly handle and assemble the pen injector device prior to dose administration, and patient ability to determine and administer the correct dose of Follistim®-AQ Cartridge as indicated by a health care provider.
2. The information included in the patient instruction manual should also be included in the Physician Insert under INFORMATION FOR THE PATIENT.

Chemistry

1. Data on actual content of Polysorbate 20 to demonstrate that there is no loss of Polysorbate 20 during stability testing was not provided.
2. The proposed release specifications for oxidation products (calculated by oxidized subunits) and the proposed shelf-life specifications for subunit content, oxidation products (calculated by oxidized subunits) and benzyl alcohol content are not acceptable.
3. Your testing facility in West Orange, New Jersey (NJ) is not in compliance with cGMP.
4. Information contained in the MAF — and Organon NDA 21-211 volumes 1.3 and 1.6 does not describe the operating features of the device and its performance characteristics sufficiently to demonstrate that the BD Pen \ is safe and effective for its intended use. Because the BD Pen — is a Microfine — pen injector that has been modified with a new indication for use that would normally require a 510(k) submission (administration of Follistim instead of insulin), the BD pen — cannot rely on the marketing status of the Microfine — device for a safety and effectiveness determination.
5. The dose measure and incrementing unit of the BD Pen — was not identified. In addition, the dose scale and dose display of the BD Pen — was not described.
6. An evaluation of the comparative dosing accuracy of the BD Pen — injector to the syringe and needle for both formulations of Follistim® was not provided.
7. The ability to fit either the 300 IU FSH-containing cartridge or the 600 IU FSH-containing cartridge into the same injector device presents an unacceptable risk of dosing error to the user.
8. The pen injector device is an integral component of the drug product, Follistim® – AQ Cartridge, and since it is not a stand-alone device approved by CDRH, marketing the drug product, Follistim® – AQ Cartridge, separately from the pen injector is not acceptable.
9. The biological indicators (BIs) used for validation of the autoclave cycles for containers, closures and filling machine parts were not described in the application.
10. The sensitivity of the container closure integrity test was not indicated in the application.

Information needed to address the deficiencies:

1. Data on the actual content of polysorbate 20 during stability testing must be provided.
2. The release and shelf-life specifications for Follistim®-AQ Cartridge must be revised as follows:
 - a. Drug product release total oxidation (calculated by oxidized subunits): —
 - b. Drug product shelf-life total oxidation (calculated by oxidized subunits): —
 - c. Drug product shelf-life subunit content: —
 - d. Drug product shelf-life benzyl alcohol content: —
3. Your Organon Inc. facility in West Orange, NJ must have a satisfactory cGMP inspection.
4. Additional information about the device and its performance must be submitted to the MAF — to support the new intended use for the BD Pen — or the equivalent information must be submitted to CDER to support the new intended use.

5. A description of the dose measure that the BD Pen[®] injector is calibrated to deliver must be provided. The dose measure for the BD Pen[®] injector should be directly related to the international unit. A description of the incrementing dose unit and the accuracy tolerance for the BD Pen[®] injector must be provided. This should include a description of the difference in dose volume and quantity between adjacent clicks of the device.
6. Bench testing data to demonstrate the dosing accuracy of the BD Pen[®] for both Follistim[®] formulations must be provided. A comparison of the dosing accuracy of the BD Pen[®] and the dosing accuracy of conventional administration by syringe and needle must be provided for both such formulations.
7. An evaluation and mitigation of the patient risks that may arise from two different formulations being available in the same container type that fits into the same injector device must be provided.
8. A description of operations performed by the secondary packaging facility for co-packaging the device and cartridges must be provided.
9. The BIs used for validation of the _____ for containers, closures and filling machine parts must be identified. The results of the BIs in the validation cycles must be provided. The organism, source, spore concentration and D-value must be included in this information.
10. The sensitivity of the container closure integrity test must be indicated and data about the sensitivity of the _____ test must be provided.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. 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) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further 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, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Susan Allen

11/29/00 04:45:20 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 9, 2000
FROM: Karen Lechter, HFD-42 
TO: Lisa Stockbridge, HFD-42
SUBJECT: Follistim device instructions
NDA 21-211

I have reviewed the instructions for the Follistim device and have the following brief comments. At a later stage in the approval process, I will be happy to provide more detailed comments.

There are a number of instances in which the language can be simplified and the graphics improved. I also recommend some explanations of information to clarify it. I can give you specific recommendations for these changes.

If the medication used with this device does not already come with a PPI explaining the benefits risks of using the medication, I recommend a full PPI that contains benefit and risk information and general instructions about the medication to help patients learn to identify signs of problems and to decide if the medication is appropriate for them to use.

Please let me know when you want me to give you complete comments for this product.

cc:
HFD-42/Lechter/Ostrove/Reading
NDA 21-211

KLlechter 11/9/00
NON-RELEASABLE

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process



CONFIDENTIAL

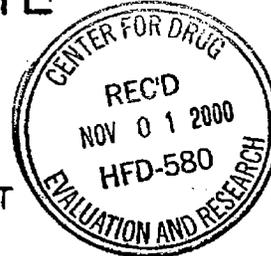
October 31, 2000

Organon Inc.

AKZO NOBEL

DUPLICATE

Mrs. F. Deguia, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



ORIG AMENDMENT

B13

NDA No. 21-211
Follistim® - AQ (follitropin beta injection)
Cartridge
Content Uniformity Data

Dear Freshnie:

Reference is made to our NDA No. 21-211 for Follistim® - AQ (follitropin beta injection) Cartridge, submitted January 28, 2000, and NDA No. 21-273 for Follistim® - AQ (follitropin beta injection), submitted July 21, 2000. Further reference is made to the phone call I received from Mrs. Mercier and Dr. Jarugula, on October 27, 2000, during which Dr. Jarugula requested content uniformity data for the batches used in the BE study (Protocol No. 37626, submitted in NDA No. 21-211) and in the *in vitro* study (submitted in NDA 21-273).

Please find attached respectively:

- Certificate of Analysis of Batch CP 097034 (Follistim Cake used in BE study 37626)
- Certificate of Analysis of Batch CP 097012 (Follistim Cartridge used in BE study 37626)
- Certificate of Analysis of Lot Number 0900306 A (Follistim Cake used in *in vitro* study)
- Certificate of Analysis of Lot Number FVA.05.00/D-A (Follistim Liquid used in *in vitro* study)

In addition, please find included for Dr. Jarugula's review the Certificate of Analysis of Lot Number 2800306 B, which pertains to the Follistim Cake used in the second *in vitro* study (PDTSR-055.00, report submitted October 31, 2000 under separate cover).

Please give me a call if you have any questions regarding this submission.

With kind regards,

Peter G. Stokman
Associate Director, Regulatory Affairs

PST/bl

Submitted via Federal Express Airbill



Organon Inc.
375 Mt. Pleasant Pk
West Orange
New Jersey 07052
0001
Tel: (973) 325-45
Fax: (973) 325-45

COPY 2



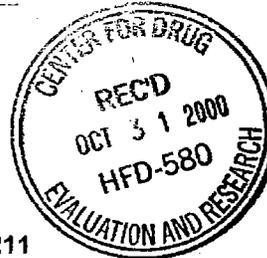
AKZO NOBEL

CONFIDENTIAL

October 30, 2000

Organon Inc.

Susan Allen, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B20
5600 Fishers Lane
Rockville, Maryland 20857



DUPLICATE

NDA 21-211
Follistim®-AQ (follitropin beta injection)
Cartridge
General correspondence

ORIG AMENDMENT

Dear Dr. Allen:

BL

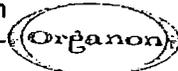
Reference is made to our Original New Drug Application (NDA 21-211) for Follistim®-AQ (follitropin beta injection) Cartridge, submitted January 28, 2000. Reference is also made to phone conversations on October 19, 2000, between Mrs. Freshnie DeGuia of your Division and Al Mayo, and on October 26, 2000, between Mrs. DeGuia and the undersigned.

During these phone conversations Mrs. DeGuia requested a revised version of the annotated labeling, including the conversion table that was submitted on March 30, 2000. The table and related text are included under *Dosage and Administration*, Pages 24 and 25 of the revised labeling. The revised annotated labeling is included as Attachment 1 to this letter.

Based on the teleconference held between the DRUDP and Organon, on September 28, 2000 (minutes issued by the division on October 10, 2000), an additional *in vitro* study will be carried out to establish the actual dose loss during regular handling of the cake/syringe. The outcome of this study may be a more accurate estimation of the proper adjustment of the dose to correct for the higher bioavailability of the Cartridge/Pen-Injector system. Hence, based upon the outcome of further discussions with your Division, it may be needed to revisit the conversion table.

During the mentioned phone conversations, Mrs. DeGuia requested the texts of the European labeling of Follistim® (Marketed in Europe under the trade name "Puregon®"). The European labeling of the 300 IU and the 600 IU presentation is included in this submission as Attachments 2 and 3 respectively.

Further, Mrs. DeGuia requested to be informed on the name and NDA number of any other products that are being administered with the B-D Pen-Injector device. Upon request, B-D indicated that Humalog® Insulin Lispro Injection (Eli Lilly, NDA No. 20-563) and Novolog® Insulin Aspart Recombinant Injection (Novo Nordisk, NDA No. 20-986) are two products that are used with the B-D Pen-Injector device. The Follistim® Cartridge will be used with a slightly remodeled Pen-Injector.



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 5-4500
Fax: (973) 525-4589

CONFIDENTIAL

Susan Allen, M.D., Acting Director
October 30, 2000
page 2

Please contact the undersigned at (973) 325-5214 with any questions you may have on this submission.

Sincerely,

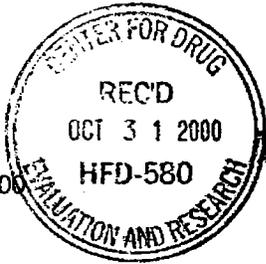


Peter G. Stokman, Associate Director
Regulatory Affairs

Attachments: - Proposed text of the Labeling with Annotations (Revised)
- European Labeling Puregon® Cartridge 300 IU
- European Labeling Puregon® Cartridge 600 IU

Submitted in Duplicate via Federal Express Airbill

0002



AKZO NOBEL

DUPLICATE

Organon Inc.

October 27, 2000

CONFIDENTIAL

Susan Allen, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B20
5600 Fishers Lane
Rockville, Maryland 20857



BL

NDA No. 21-211

Follistim[®] - AQ (follitropin beta injection) Cartridge

Dear Dr. Allen:

Reference is made to Organon's pending NDA No. 21-211, submitted January 21, 2000, for Follistim[®]- AQ (follitropin beta injection) Cartridge. Reference is also made to the telephone conversation between Dr. D. Lin of your Division and Mr. A. Mayo of Organon on October 19, 2000, regarding the Letter of Authorization from the manufacturer of the glass barrel (immediate container) used for Follistim[®]- AQ Cartridge. During that conversation, Dr. Lin requested clarification regarding the DMF numbers cited in that Letter of Authorization.

The authorization letter

provided in NDA No. 21-211, makes reference to two separate DMF numbers. In fact the DMF ~~1~~ references the immediate container, which is intended for the commercial finished product Follistim[®]- AQ Cartridge. The second DMF ~~2~~ referenced in the letter does not apply to NDA No. 21-211.

Should you have any questions regarding this correspondence, please contact the undersigned at (973) 325-5214.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Yours sincerely,

for

Peter G. Stokman
Associate Director, Regulatory Affairs



PGS/cjw

Submitted in Duplicate
via Federal Express Airbill

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973) 325-4588

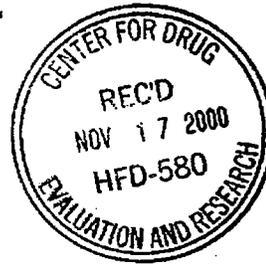


CONFIDENTIAL

Organon Inc.

November 16, 2000

Susan Allen, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B20
5600 Fishers Lane
Rockville, Maryland 20857



DUPLICATE

**NDA 21-211
Follistim[®]-AQ (follitropin beta injection) Cartridge
Safety Update**

ORIG AMENDMENT

Dear Dr. Allen:

Reference is made to our Original New Drug Application (NDA 21-211) for Follistim[®]-AQ (follitropin beta injection) Cartridge, submitted January 28, 2000. Reference is also made to the phone conversation of November 15, 2000, between Mrs. Freshnie DeGuia of your Division, and the undersigned.

During this conversation, Mrs. DeGuia asked why the aforementioned NDA does not contain a Safety Update for the use of Follistim[®]-AQ Cartridge with the Pen-Injector Device. I informed Mrs. DeGuia that such an update is not available due to the recency of market introduction, and hence the very limited post-marketing experience.

Per Mrs. DeGuia request we herewith submit this statement in writing.

Please contact the undersigned at (973) 325-5214 with any questions you may have on this correspondence.

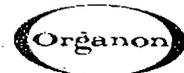
Sincerely,

Peter G. Stokman,
Associate Director, Regulatory Affairs

PST/bl

Attachment - Form FDA 356h

Submitted in duplicate to NDA 21-211
via Federal Express Airbill



Organon Inc.
275 Mt. Pleasant Avenue
Kenilworth, NJ 07033
New Jersey 07033
Tel: (973) 325-5214
Fax: (973) 325-5214



Food and Drug Administration
Rockville MD 20857

NDA 21-211

DISCIPLINE REVIEW LETTER

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

NOV 14 2000

Dear Mr. Stokman :

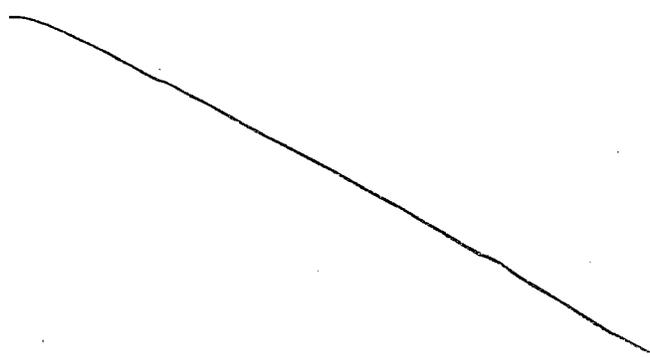
Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim AQ (follitropin beta for injection) Cartridge.

Our review of the Chemistry and Microbiology sections of your submission is complete, and we have identified the following deficiencies.

1. Based on data provided in the NDA, the total oxidation of subunits specification should be revised from _____
2. Due to the functional importance of polysorbate 20, please propose a drug product regulatory and stability test and specification for this excipient.
3. Please provide a drug product content uniformity test, based on protein content.
4. Please explain why iso-electric focusing (pI distribution) is not performed at release of the drug product.
5. Based on the stability provided to the NDA, the following stability specifications should be revised as follows:
 - a. Subunit content from _____
 - b. Oligomer content from _____
 - c. Total oxidation from _____
 - d. L-methionine content from _____
 - e. Benzyl alcohol content from _____
6. Based on the method of calculation for oxidation products, it is more accurate to revise the wording of the specification from "total oxidation" to "total oxidation of subunits".
7. The specification for particulate matter should refer to "per cartridge" and not "per vial".

8. Please clarify whether the reference standard used in the *in-vivo* bioassay is an in-house or WHO reference standard.
9. The proposed 24-month expiry date is not acceptable. Based on the data provided, we recommend an 18-month expiry date. However, if additional real time stability data at 5° C are available, they could be used to support a longer expiry date.
10. 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.
11. This drug product should be packaged in secondary packaging in three configurations: 1) pen injector plus drug product cartridge (either 437.5 IU or 737.5 IU presentation), 2) 437.5 IU cartridge, and 3) 737.5 IU cartridge. Please confirm that the secondary packaging facilities can perform this packaging operation.
12. The following paragraph should be added after the first paragraph in the **DESCRIPTION** section of the package insert in order to be consistent with the label for approved Follistim drug product:
"The amino acid sequence and tertiary structure of the product are indistinguishable from that of human follicle-stimulating hormone (hFSH) of urinary source. Also, based on available data derived from physio-chemical tests and bioassay, follitropin beta and follitropin alfa, another recombinant follicle-stimulating hormone product, are indistinguishable."
13. In the **DESCRIPTION** section of the package insert the following sentence should be added before the listing of the inactive ingredients:
"The recombinant protein in Follistim AQ Cartridge has been standardized for FSH *in-vivo* bioactivity in terms of the First International Reference Preparation for human menopausal gonadotropins (code 70/45), issued by the World Health Organization Expert Committee on Biological Standardization (1982)."

14.



15. In the package insert, cartridge label and carton label, the dash between Follistim ® and AQ should be removed in order to be consistent with similar current approved products. In addition, the registered mark, ®, should be placed after AQ.

16. The How Supplied section should be revised to the following:

17. A more detailed description of the appearance of the drug product cartridges, including the volume of the two presentation (437.5 IU and 737.5 IU) cartridges should be included in the How Supplied section of the package insert.

18. Please include the quantitative composition of the drug product on the cartridge and carton labels.

19. The total quantity of recombinant protein in International Units (IU) is needed on the label. It is recommended that it be placed before the word "Cartridge". The wording should be as follows: "438 IU Cartridge" or "738 IU Cartridge". The deliverable quantity of recombinant protein can be specified on the label following the list of components.

20. The "1.5 mL" statement is misleading. This implies that the volume of the drug product solution in the cartridge is 1.5 mL. The actual volume in the cartridge is 0.525 mL and 0.885 mL in the 437.5 IU and 737.5 IU presentations, respectively. The statement should be revised to "sterile prefilled cartridge 0.525 mL in 1.5 mL" or sterile prefilled cartridge 0.885 mL in 1.5 mL".

21. The Biological Indicators (BIs) used for the validation of the _____ were not described. Please identify the BIs and include _____ Also, please include the results of the BIs in the validation cycles.

22. The sensitivity of the _____ integrity test was not indicated. Please provide data about the sensitivity of the _____ test.

23. For the container and carton labels, we recommend the differentiation of the product strengths with the use of boxing, contrasting colors or some other means.

24. In the container label, we recommend the inclusion of the "Rx Only" statement.

25. Each carton contains one prefilled cartridge plus a carton containing disposable needles. The presentation of the name strength on the principle display panel leads the health care practitioner and/or consumer to believe the drug is the only item supplied in the carton. We recommend relocating the net quantity statement to appear below the strength and revise to read as follows:

The carton contains the following items:

- 1 sterile prefilled cartridge containing XXX International units of Follitropin Beta Injection

per X mL.

- 1 carton containing seven disposable needles

26. The proprietary name is displayed prominently on the needle carton. This is misleading in that it appears the drug is contained in the needle itself. The panels should be revised to indicate that the needles are for use with the cartridge. We recommend the following:

DISPOSABLE NEEDLES 30 gauge x 1/2"

27. The proprietary name is displayed incorrectly on the pen carton as "B-D Follistim Pen". This is misleading in that there is a marketed product "Follistim" which is a lyophilized version of "Follistim AQ". The pen is for the administration of "Follistim AQ" rather than "Follistim". The carton labeling should be revised to reflect not only the correct proprietary name but also not to indicate the drug is not included with the pen. We recommend the following:

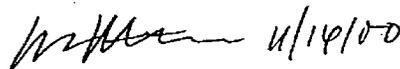
B-D Pen

For use with Follistim A@@ (Follitropin Beta Injection) 1.5 mL cartridges.

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.

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

Sincerely,



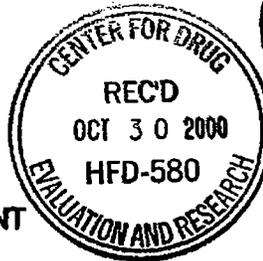
Moo Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research



Organon Inc.

October 27, 2000

Susan Allen, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B20
5600 Fishers Lane
Rockville, Maryland 20857



CONFIDENTIAL

ORIG AMENDMENT
BC

NDA No. 21-211
Follistim® - AQ (follitropin beta injection) Cartridge

Dear Dr. Allen:

Reference is made to Organon's pending NDA 21-211, submitted January 21, 2000, for Follistim®- AQ (follitropin beta injection) Cartridge. Reference is also made to the voice mail left by Mrs. DeGuia and Dr. Lin of your Division for the undersigned on October 25, 2000, regarding the Letter of Authorization for the _____ DMF number _____ provided in NDA No. 21-211.

The Letter of Authorization that was provided in NDA No. 21-211 only makes reference to the _____. The same DMF number is also applicable to the _____. Please find attached to this letter the Letter of Authorization of _____ Services we received today, for the _____

Should you have any questions regarding this correspondence, please contact the undersigned at (973) 325 5214.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Yours sincerely,

for

Peter G. Stokman
Associate Director, Regulatory Affairs

SGP/cjw

Form FDA 356h
Submitted in Duplicate
via Federal Express Airbill

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS DATE



Organon Inc.
375 Mt. Pleasant A
West Orange
New Jersey 07052
USA
Tel.: (973) 325-45
Fax: (973)-325-45



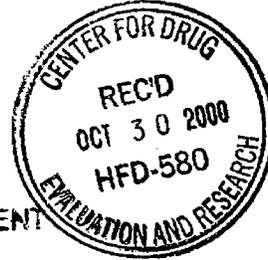
AKZO NOBEL

DUPLICATE CONFIDENTIAL

October 27, 2000

Organon Inc.

Susan Allen, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B20
5600 Fishers Lane
Rockville, Maryland 20857



ORIG AMENDMENT

BPM

**NDA 21-211
Follistim®-AQ (follitropin beta injection) Cartridge
Request for Pediatric Waiver**

Dear Dr. Allen:

Reference is made to our Original New Drug Application (NDA 21-211) for Follistim®-AQ (follitropin beta injection) Cartridge, submitted January 28, 2000. Reference is also made to our letter of September 25, 2000, General Correspondence related to NDA 21-273, Follistim-AQ (follitropin beta injection), in which a pediatric waiver was requested for both NDA No. 21-273 and NDA No. 21-211.

Further reference is made to the phone conversation of October 26, 2000, between Mrs. Freshnie DeGuia and the undersigned, during which Mrs. DeGuia indicated that the pediatric waiver for NDA 21-211 (Follistim®-AQ (follitropin beta injection) Cartridge) should be submitted under separate cover.

Pursuant to 21 CFR 314.55 we herewith request a full waiver of the requirements defined in 21 CFR 314.55(a) for NDA 21-211 Follistim®-AQ (follitropin beta injection) Cartridge, as the drug product does not represent a meaningful therapeutic benefit for pediatric patients, and is not likely to be used in pediatric patients.

Please contact the undersigned at (973) 325-5214 with any questions you may have on this correspondence.

Sincerely,

Peter G. Stokman, Associate Director
Regulatory Affairs

PST/cs

Submitted via Federal Express Airbill



Organon Inc.
P.O. Box 1000
Kenilworth, NJ 07033
Tel: (973) 325-5214

(973) 325-5214



ORIGINAL

Organon Inc.

September 28, 2000

Mrs. F. Deguia, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



NEW CORRESP

NIC

Follistim® - AQ (follitropin beta injection)
NDA No. 21-271: Instruction Manual
[redacted] participants T-con

Dear Freshnie,

Per your request of a 09/28/00, please find attached two additional copies of the Instruction Manual for the Follistim® Pen Injector.

In addition to this, please find herewith the names of the Organon participants to our September 28, 2000 teleconference regarding Follistim®-AQ, NDA No. 21-273, as I did not finish my minutes as fast as I anticipated I would...

Main Office (Oss, the Netherlands)
Cees Timmer
Gerrit Voortman, M.Sc.
Joost van Zutven, M.Sc.

Drug Metabolism & Pharmacokinetics
Clinical Development Department
Product Development Department

US Office (West Orange, New Jersey)
Eric Orlemans, Ph.D.
Vinod Gupta, Ph.D.
Peter Stokman, M.Sc.

Project Team Leader
Manufacturing Technology Department
Regulatory Affairs Department (Reporter)

Should you have any questions regarding this correspondence, please contact me at (973) 325-5214.

Best regards,

Peter G. Stokman
Associate Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____



PST/cs

Submitted via Federal Express Airbill # _____

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973)-325-4589

D/F

MEETING MINUTES

Date: September 27, 2000 **Time:** 2:00 – 3:00 PM

Location: Parklawn, Room 17B-43

NDA 21-211

Indication: Assisted Reproductive Technology (ART)

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

Sponsor: Organon, Inc.

Type of Meeting: Status Meeting (8-month)

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)

Daniel Shames, M.D. – Acting Deputy Director, 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)

David Lin, Ph.D. – Chemistry Reviewer, Division of New Drug Chemistry II (DNDC II)

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

Meeting Objectives: To discuss the status of the review of this pending NDA.

Background:

Follistim – AQ (follitropin beta for injection) cartridge is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA 20-582.

Decisions reached:

Clinical

- review is on-going
- recommendation for labeling comprehension will be included in the review

Chemistry

- review is on-going
- facility inspections are not yet completed

Biopharmaceutics

- review is on-going
- inconsistency in the percentage of drug loss was noted in the bioequivalence (BE) study submitted to support this pending NDA and the *in-vitro* study submitted to support the new NDA (NDA 21-273) for the liquid formulation; sponsor based their argument on assay data

Action Items: none

E De Guia 10/23/00
Signature, minutes preparer

Susan Allen, MD 10/23/00
Concurrence, Chair

cc:

NDA Arch:

HFD-580

HFD-580/SAllen/DShames/Bennett/Jarugula/Slaughter/Parekh/Lin

drafted: DeGuia/09.27.00

concurrences:

DMoore10.12.00/VJarugula,DShames10.16.00/RBennett,SSlaughter,DLin10.19.00/SAllen10.20.00

final: EDeGuia10.23.00

MEETING MINUTES

entered in DFS
10/23/00 ED



CONFIDENTIAL

September 26, 2000

Organon Inc.

Susan Allen, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B20
5600 Fishers Lane
Rockville, Maryland 20857

ORIGINAL

ORIG AMENDMENT
DC



NDA No. 21-211
Follistim® -AQ (follitropin beta Injection) Cartridge
General Correspondence:
Pen-Injector Instruction Manual

Dear Dr. Allen:

Reference is made to Organon's pending NDA 21-211, submitted January 21, 2000, for Follistim® -AQ (follitropin beta Injection) Cartridge.

Reference is also made to the recent discussion with your Division, during which it was decided that a Device Master File (MAF) should be submitted for the Pen-Injector device, rather than a 510(k) submission as was initially planned. Becton Dickinson, the manufacturer of the Pen-Injector, is planning on submitting the MAF by the end of this week.

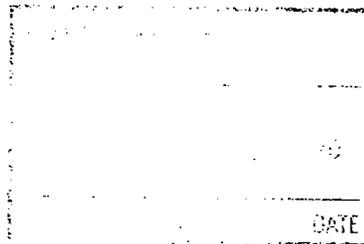
Further reference is made to a conversation of September 19, 2000, with Mrs. Freshnie DeGuia regarding the review of the Instruction Manual (IM) for the Pen-Injector. (In the original plan, the IM would be part of the 510(k) submission; in the new approach the regulatory status of the IM was not clear.) After consulting Dr. Rhee, Mrs. DeGuia indicated that the IM should be submitted as an amendment to the NDA.

Please find attached the proposed IM. It was agreed with Becton-Dickinson that they will supply Organon Inc. with a letter of authorization related to their MAF, upon receipt of a Device Master File number. As agreed with Mrs. DeGuia, I will forward this letter to the Division as soon as possible.

Please contact the undersigned at (973) 325-5214 with any questions you may have on this submission.

Sincerely,

Peter G. Stokman
Associate Director
Regulatory Affairs



Attachment: Follistim® Pen Instruction Manual, Version 18 September 2000

Submitted in Duplicate via Federal Express Airbill No _____

Organon Inc.
475 Mt. Pleasant Ave.
West Orange
New Jersey 07067
USA
Tel: (973) 425-4500
Fax: (973) 425-4591

D/F

MEETING MINUTES

Date: August 23, 2000 **Time:** 2:00 – 3:00 PM **Location:** Parklawn; Room 17B-43

NDA 21-211

Indication: Assisted Reproductive Technology (ART)

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

Sponsor: Organon, Inc.

Type of Meeting: Status Meeting (7-month)

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. - Medical 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)

David Lin, Ph.D. - Chemistry Reviewer, Division of New Drug Chemistry II (DNDC II)

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

Meeting Objectives: To discuss the status of the review of this pending NDA.

Background:

Follistim - AQ (follitropin beta for injection) cartridge is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA20-582.

Decisions reached:

Clinical

- review is on-going
- the application may not be approvable
- there are safety concerns on packaging configuration and delivery system and on the proposed pen injector and labeling recommendations (Please see OPDRA review dated August 4, 2000)

Chemistry

- review is on-going
- this NDA was consulted out to CDRH (Center for Devices and Radiologic Health) which advised Becton Dickinson (supplier of the pen injector) to submit a Device Master File on the pen injector for review instead of submitting a 510K application

Pharmacology/Toxicology

- review has been completed on March 24, 2000

Biopharmaceutics

- review is on-going
- this drug product has a higher bioavailability than the approved Follistim

OPDRA

- review has been completed (August 4, 2000)

Action Items:

- the next Status labeling meeting is scheduled for September 27, 2000.

E DeGuia 10/19/00
Signature, minutes preparer

Concurrence, Chair

1-120/20

cc:

NDA Arch:

HFD-580

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

drafted: DeGuia/09.06.00

concurrences: DMoore10.12.00/DShames, VJarugula10.16.00/RBennett, SSlaughter, DLin10.19.00

final: EDeGuia10.19.00

MEETING MINUTES

D/F

MEETING MINUTES

Date: May 9, 2000 **Time:** 2:00 – 3:00 PM **Location:** Room 17B-43

NDA 21-211

Indication: Assisted Reproductive Technology (ART)

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

Type of Meeting: Guidance/Status (internal meeting)

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

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

Florence Houn, M.D., M.P.H. - Director, Office of Drug Evaluation III

Victor Raczkowski, M.D. - Deputy Director, Office of Drug Evaluation III

Marianne Mann, M.D. - Deputy Director, 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)

Ferri 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

Karen Davis-Bruno, Ph.D. - Pharmacologist, DRUDP (HFD-580)

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

Meeting Objectives: To assess the feasibility that patients could accurately use the provided pen injector following instructions in the label and to determine the review strategy for this pending NDA.

Background:

Follistim - AQ (follitropin beta for injection) cartridge 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 Cartridge in an injectable aqueous solution of 300 IU and 600 IU follitropin beta in a multidose cartridge to be administered with a pen injector.

Organon, Inc. stated at the pre-NDA meeting on March 18, 1999, that Becton Dickinson will supply the pen device that will be used with their injection cartridge and that all information regarding the device will be included in a 510K application that will be filed by Becton Dickinson. The pen injector is virtually identical to the one supplied to Novo Nordisk for delivery of insulin. This 510K application has not been submitted to Center for Devices and Radiological Health for review.

The application was filed March 31, 2000.

Discussion points:

- after DRUDP conveyed its concerns to the sponsor regarding the lack of bioequivalence between this product and the currently marketed Follistim formulation, the sponsor amended the current NDA submission by providing a conversion table for the observed difference in dose administered by the two formulations (e.g., the Cartridge/pen injector and the Vial/syringe dose); the Division believes that modifying the pen injector dial scale as proposed by the sponsor would lead to extremely confusing dosing recommendations for providers and for patients
- the proposed conversion table provided is too difficult for patients and providers to interpret and could result in medication errors
 - with the conversion table and the markings proposed, it is not possible to determine the amount of drug remaining in the pen following each injection; the pen cannot be dialed backwards following forward dialing, making readjustment for appropriate dose delivery not possible

Decision Reached:

- the application does not appear to be approvable as proposed with the calibrated device and proposed conversion table
- review of the application will proceed as scheduled

Action Items: none

E De Guia 6/20/00

signature, minutes preparer

Susan Allen, MD
Concurrence, Chair

6/20/00

cc:

NDA Arch:

HFD-580

HFD-580/Allen/Rumble/Bennett/Rhee/Jarugula/Slaughter/Parekh/Mann

drafted: DeGuia

concurrences: TRumble, Fhoun, MMann, MRhee, KDavis-

Bruno06.02.00/Vraczkowski06.04.00/DLin06.07.00/SAllen06.09.00/VJarugula06.14.00

final: EDeGuia06.16.00

MEETING MINUTES



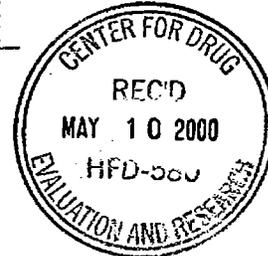
CONFIDENTIAL

Organon Inc.

May 9, 2000

Mrs. F. Deguia, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Documentation Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

ORIGINAL



NDA No. 21-211
Follistim® - AQ (follitropin beta injection)
Cartridge

ORIG AMENDMENT
BL

Dear Mrs. Deguia:

With reference to our NDA No. 21-211 for Follistim® - AQ (follitropin beta injection) Cartridge, submitted January 28, 2000, and our today's phone conversation, I herewith supply you with samples of the draft Packaging Labeling for review by OPTRA.

Should you have any questions regarding this correspondence, please contact the undersigned at (973) 325-5214.

Sincerely,

Peter G. Stokman
Associate Director
Regulatory Affairs

PST/esp

- Attachments:
- 300 IU Cartridge Roll Label 5308738 (1/00 06)
 - 300 IU Blister Label 5308739 (1/00 04)
 - 600 IU Cartridge Roll Label 5308740 (1/00 04)
 - 600 IU Blister Label 5308741 (1/00 03)
 - 300 IU Folding Carton 5315389 (1/00 05)
 - 600 IU Folding Carton 5315390 (1/00 03)
 - Cartridge Folding Needle Carton 5315392 (1/00 06)
 - B-D Follistim Pen Folding Carton 5315391 (12/99 04)

REVIEWS COMPLETED	
CRO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
OSO INITIALS	DATE



Submitted in duplicate via Federal Express Airbill # _____

Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973) 325-4589



CONFIDENTIAL

Done
4/28/00

April 5, 2000

Mrs. F. DeGuia, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



Handwritten initials: JRC

1. NDA No. 21-211 Follistim® - AQ (follitropin beta injection) Cartridge
2. Follistim® - AQ (follitropin beta injection): Request for a biowaiver

Dear Mrs. DeGuia:

Reference is made to our NDA No. 21-211 for Follistim® - AQ (follitropin beta injection) Cartridge, submitted January 28, 2000, and the teleconference on this NDA between FDA-DRUDP and Organon on March 22, 2000.

Further reference is made to our Request for a Biowaiver regarding Follistim® - AQ (follitropin beta injection) submitted on January 11, 2000, and the teleconference regarding this request between FDA-DRUDP and Organon on March 31, 2000. During this last meeting also NDA No. 21-211 was briefly discussed.

In addition to the minutes of the March 22, 2000, meeting, submitted to you by fax transmission on March 23, 2000, it is my pleasure to herewith provide you with paper copies of Organon's minutes of both meetings.

We believe that these minutes accurately reflect the discussions and agreements reached during this meeting and we request that they be taken into consideration in the preparation of the official minutes.

Should you have any questions regarding this correspondence, please contact the undersigned at (973) 325-5214.

Sincerely,

Peter G. Stokman
Associate Director, Regulatory Affairs

PST/bl

- Attachments:
- Form FDA 356h
 - Teleconference Minutes March 22, 2000
 - Teleconference Minutes March 31, 2000

Minutes Submitted via Federal Express Airbill #



Organon Inc.
575 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel: (973) 325-4500
Fax: (973) 325-4589

0001



noted
4/4/00
R13

CONFIDENTIAL

Organon Inc.

March 30, 2000

ORIGINAL



Dr. Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-211 **ORIG AMENDMENT**
Follistim® - AQ (follitropin beta injection)
Cartridge

B2

Dear Dr. Allen,

Reference is made to our NDA No. 21-211, submitted January 28, 2000, and the teleconference between FDA-DRUDP and Organon on March 22, 2000.

Further reference is made to the Organon Minutes from the above referenced meeting, which were submitted for your reference by fax transmission to Mrs. Deguia on March 23, 2000.

During the teleconference it was made clear that one of the preferred options available to Organon would be to ensure that the dose administered by the pen could be modified in such a way that it equals the dose administered by the approved product (Follistim (follitropin beta for injection), NDA No. 20-582) and the syringe. However, according to Beckton Dickinson experts regarding device regulations, this approach – leading to a discrepancy between nominal and actual dose - may not be viable as it conflicts with pertinent ISO guidances.

As the essence of this approach is to administer the same dose with the Cartridge/Pen-Injector system as with the conventional syringe, we further explored how this could be achieved. We propose an additional option.

This option entails a more prominent inclusion in the labeling of the difference in bioavailability of follitropin beta from the Cartridge/Pen-Injector system, as compared to the approved product administered with the conventional syringe. To this end, we propose to include a conversion table indicating the numerical relationship between the Vial/Syringe dose and the dose delivered by the Cartridge/Pen-Injector system. This table will allow physicians to make a proper adjustment of the dose to correct for the higher bioavailability of the Cartridge/Pen-Injector system. Inclusion of these changes, including this table, should eliminate any confusion that might arise from the difference in bioavailability.



We propose adding the following text and table to the labeling:

Organon Inc.
375 Mt. Pleasant Ave
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973)-325-4589

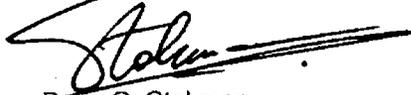
Dr. Susan Allen, MD, Acting Director
March 30, 2000
Page 2

CONFIDENTIAL

We appreciate that this correspondence may interfere with the administrative finalization of the 90-day response period. However, as we feel that the high accuracy and precision of the Cartridge/Pen-Injector system reduces the variability associated with the use of the conventional syringe, we request that this proposal - which obviously will have to be worked out in more detail in consultation with your division - be taken into consideration.

Should you have any questions regarding the above, please call me at (973) 325-5214.

Sincerely,



Peter G. Stokman
Associate Director, Regulatory Affairs

Submitted via Federal Express Airbill # _____

REVIEWS COMPLETED	
CDO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> MAIL <input type="checkbox"/> MEMO
DATE	



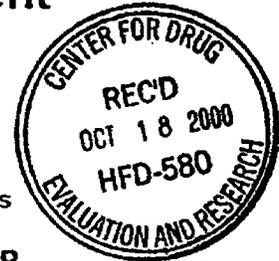
ORIGINAL

Telefax Transmittal
Cover Sheet

Organon Inc.

**Organon Inc.
Regulatory Affairs Department**

375 Mt. Pleasant Avenue
West Orange, New Jersey 07052
Telephone No.: (973) 325-5214
Telefax No.: (973) 325-4769



To: FDA-Division of Reproductive and Urologic Drug Products
Attn. Mrs. Eufrecina P. Deguia

NEW CORRESP

From: Peter G. Stokman

Date: March 23, 2000

AK

Subject: Minutes Teleconference Follistim[®]- AQ (follitropin beta Injection)
NDA No. 21-211

Total Number of Pages Sent, Including Cover Sheet: 3

Dear Mrs. Deguia,

Reference is made to our NDA No. 21-211, submitted January 28, 2000, and the teleconference between FDA-DRUDP and Organon on March 22, 2000.

We are herewith providing Organon's minutes from the above referenced meeting. We believe these minutes accurately reflect the discussions and agreements reached during this meeting.

If you have any questions regarding the attached please feel free to contact me at (973) 325 5214.

With kind regards,

Peter G. Stokman
Associate Director, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

DeGua

*entered in DFS
6/22/00
ED*

Teleconference Minutes

Date: March 22, 2000 Time: 9:00 - 9:30 AM Location: Room 17B-43

NDA 21-211

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

Indication: Assisted Reproductive Technology (ART)

Sponsor: Organon, Inc.

Type of Meeting: Guidance (clinical)

Meeting Chair: Dr. Marianne Mann

External Participant Lead: Peter Stokman

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, 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
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Participants:

Organon, Inc., Oss, the Netherlands
Gerrit Voortman, M.Sc. - Team Leader, International Clinical Development
Cees Timmer - Pharmacokineticist
Eric Orlemans, Ph.D. - Team Leader, International Project
Marjo Peters, Ph.D. - Regulatory Affairs

Organon, Inc. West Orange, NJ

Carol Anne Cartier - Regulatory Affairs Assistant Manager
Joel Krasnow, M.D., Ph.D. - Director, Women's Healthcare
Keith Gordon, Ph.D. - Assistant Director, Medical Services
Peter Stokman, M.Sc. - Associate Director, Regulatory Affairs
Loree Levine, Drug Information Specialist

Meeting Objectives: To discuss the issues and concerns regarding the fileability of this NDA.

Background:

Follistim - AQ (follitropin beta for injection) cartridge is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA20-582. The currently approved product is available as a freeze-dried cake, to be administered after reconstitution with Water for Injection. Follistim- AQ Cartridge is

an injectable aqueous solution of 300 IU and 600 IU follitropin beta in a multidose cartridge to be administered with a pen injector.

Organon, Inc. mentioned at the pre-NDA meeting on March 18, 1999, that Becton Dickinson will supply the pen device that will be used with their injection cartridge and all information regarding the device is included in a 510K application that will be filed by Becton Dickinson

Discussion Points:

- Dr. Mann made reference to the minutes of the pre-NDA meeting held on March 18, 1999 and reiterated that although the pen injector delivers efficiently, the issue of not meeting bioequivalence still exists; she emphasized to the sponsor that in the pre-NDA meeting, it was clearly stated that:
 - the dose delivered by the two formulations must be addressed by conducting another bioequivalence study after altering the dose delivered by the pen injector to match the dose delivered by the cake formulation
 - a significant risk could exist for patients who switch from cake to pen and *vice-versa*
 - since it would be difficult to change the label in the approved product, the delivery volume issue would need to be clearly addressed in the label for the pen injector NDA
 - BE issues should be resolved before the NDA application is submitted
- the bioequivalence study between the pen injector formulation vs. the approved formulation was conducted following single-dose subcutaneous administration of 150 IU; both C_{max} and AUC for the pen injector were 20% higher than that noted with subcutaneous administration

Decisions reached:

The following options were conveyed to the sponsor:

- safety and efficacy of the pen injector must be linked to the old product by establishing bioequivalence
- one option is to adjust the dose down in the pen injector to match the dose delivered by syringe and label the product in a way to convey bioequivalence to the more familiar dose (and this can be illustrated by tables); should the sponsor decide to adjust the dose, the BE study requirement would be waived; should this option be chosen, the pen injector device (made by Becton Dickinson) would need to be recalibrated to facilitate ease of use by patients and physicians
- a second option was to generate clinical trial data with the more bioavailable pen device to show that the 18% higher dose is safe and effective; the sponsor was advised to meet with us to discuss a proposed protocol for a reasonable design for a clinical trial; a third option was to change the concentration of drug while maintaining the same administration volume; since it will be a new formulation, stability data will be required
- the pen injector device could be re-calibrated to administer less volume, and should reflect the doses that physicians and patients are used to
- the sponsor's belief that treatment is primarily guided by ovarian response and that the observed difference is of no clinical concern is not acceptable to the Division; since there is already high variability, the Division cannot accept increased variability of the product which will make it difficult to predict outcome in individual subjects; the sponsor has an option to appeal this although it was made clear that these issues had been discussed at the Office level
- further discussions will take place on whether this application will be refused to file or whether the ongoing issues will be a review issue

Meeting Minutes

Page 3

Action Items:

- the Division will follow up with Organon, Inc. before March 31, 2000 (filing date)
- meeting minutes will be sent to the sponsor in 30 days

Ed de Guiz 4.17.00
Signature, minutes preparer

W. Alan Man, MD
Concurrence, Chair 4/17/00.

NOTE: 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.

Meeting Minutes
Page 4

cc:

NDA Arch:

HFD-580/DeGuia

HFD-580/Bennett/Rhee/Jarugula/Slaughter/DLin/Mann

drafted: DeGuia/03.23.00

concurrences: TRumble03.28.00/MMann03.29.00/SSlaughter04.04.00/RBennett04.05.00/
DLin04.11.00/VJarugula04.13.00

final: EDeGuia04.14.00

MEETING MINUTES

TELECONFERENCE MINUTES
FDA / ORGANON
MARCH 22, 2000

Follistim[®] -AQ (follitropin beta injection) Cartridge
NDA # 21-211

FDA attendees:

Marianne Mann, MD, Ph.D.	Deputy Director
Eufrecina DeGuia	Regulatory Project Manager
Venkateswa Jarugula, Ph.D.	Pharmacokinetics Reviewer
Ridgeley Bennett, MD, Ph.D.	Medical Officer
David Lin, Ph.D.	Chemical Reviewer
Shelley Slaughter, MD, Ph.D.	Chief Medical Officer
Moo Jhong Rhee, Ph.D.	Chemistry Team Leader

Organon attendees:

Main Office (Oss, the Netherlands)

Gerrit Voortman, M.Sc.	International Clinical Development Team Leader
Cees Timmer	Pharmacokineticist
Eric Orlemans, Ph.D.	International Project Team Leader
Marjo Peters, Ph.D.	Regulatory Affairs, Oss

US Office (West Orange, New Jersey)

Carole Ann Cartier	Assistant Manager Regulatory Affairs
Joel Krasnow, MD, Ph.D.	Director Women's Healthcare
Keith Gordon, Ph.D.	Associate Director Reproductive Medicine
Peter Stokman, M.Sc.	Associate Director Regulatory Affairs (Reporter)
Lauree Levine	Drug Information Specialist

Background

After the Meeting with FDA on March 18, 1999, it was decided by Organon to follow the approach perceived as being acceptable for the Division (i.e., to substantiate that the observed difference between the cake/syringe and the cartridge/Pen-Injector is clinically not noticeable, and to address this difference in the labeling).

On January 26, 2000, an NDA along these lines was submitted (NDA # 21-211). On March 20, 2000, FDA's internal Filing Meeting took place, and the current teleconference was convened to share the outcome of the Filing Meeting with Organon.

Meeting

After the introduction of the participants, Dr. Mann gave the highlights of the Filing Meeting. She indicated that it was clear to the Division that the Pen-Injector is a more accurate device and that the observed 18% difference in bioavailability between cake/syringe and cartridge/Pen-Injector is the consequence of the higher administration efficiency of the latter, and not of a difference in volume or concentration.

Dr. Mann referred to the March 18, 1999 discussion, during which - according to the FDA interpretation - it was concluded that a dose reduction of 18% per administration would be the way to resolve this issue. She quoted from the FDA meeting minutes, *Decisions Reached*, first bullet item: "bioequivalence issue should be resolved before the NDA application is submitted." She considered this issue not to be resolved in our NDA.

Dr. Mann reiterated the previously suggested solution as the first option: reduce the administered dose by recalibrating the Pen-Injector in such a way that it would administer 18 % less than the nominal dose. This would lead to a device that per administration is bioequivalent to the syringe, and hence would permit reference to NDA 20-582 (Follistim cake). Dr. Mann indicated that we would not need to carry out a bioequivalence study after implementing this dose reduction.

Dr. Krasnow remarked that a reduction of the concentration could lead to an 18% dose reduction while maintaining the same administration volume. This was also acceptable for the Division. However, as Dr. Rhee indicated, a reduction of concentration would formally lead to a new formulation, requiring new stability data.

Dr. Mann indicated that the Division realizes that there is a high inter and intra subject variability regarding response, and that our reasoning focusing on individual titration guided by ovarian response makes good sense. However, because of the already high variability, the Division would feel very uncomfortable with adding another source of variability (i.e., an 18% difference between two nominally identical doses).

The third option, suggested by Dr. Krasnow, was to generate new Clinical data regarding the safety and efficacy of the use of the Pen-injector (and the associated higher dose). Dr. Mann indicated that the Division would gladly be willing to discuss a protocol proposal, to come to a reasonable trial design.

Since the Division agreed that the difference between cake/syringe and cartridge/Pen-Injector is caused by the actual amount administered, Dr. Peters suggested to substantiate the clinical efficacy and safety of the Pen-Injector with data generated in syringe studies in which different dose levels were used. This would be done without submitting data obtained with the Pen-injector.

Dr. Mann indicated that if Organon would choose this fourth option, it would imply an appeal to the Division's decision thereby taking the issue to a higher level (i.e., the Office level). Dr. Mann made it clear that the issue was amply discussed with Office representatives, and that the Division was backed in it's decision by the Office.

Dr. Mann indicated that the discussion is still ongoing on whether NDA 21-211 will be refused to file, or whether the outstanding issue will be considered to be a review issue. FDA will follow up with Organon before March 31, 2000, which ends the 90-day response period.

The participants were thanked for their time and contribution and the teleconference then ended.

D-file

MEETING MINUTES

Date: March 20, 2000 **Time:** 4:00 – 5:00 PM **Location:** Room 17B-43

NDA 21-211

Indication: Assisted Reproductive Technology (ART)

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

Type of Meeting: Filing Meeting

Meeting Chair: Dr. Marianne Mann

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

- Marianne Mann, 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
- meeta Parekh, Ph.D., - Team Leader, Office of Clinical Pharmacology and Biopharmaceutics

Meeting Objectives: To discuss the fileability of this NDA.

Background:

Follistim – AQ (follitropin beta for injection) cartridge is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA20-582. The currently approved product is available as a freeze-dried cake, to be administered after reconstitution with Water for Injection. Follistim- AQ Cartridge in an injectable aqueous solution of 300 IU and 600 IU follitropin beta in a multidose cartridge to be administered with a pen injector.

Organon, Inc. mentioned at the pre-NDA meeting on March 18, 1999, that Becton Dickinson will supply the pen device that will be used with their injection cartridge and all information regarding the device is included in a 510K application that will be filed by Becton Dickinson. The pen injector is virtually identical to the one supplied to Novo Nordisk for delivery of insulin.

Discussion Points:

- the bioequivalence study between the pen injector formulation vs. approved formulation was conducted following single-dose subcutaneous administration of 150 IU; both Cmax and AUC for the pen injector were 20% higher than with Follistim delivered by the syringe
- sponsor claimed that in the BE study, the pen injector efficiently delivered the amount that it was set to deliver, whereas, the conventional syringe delivered an amount of FSH, that, on the average, was lower than the nominal dose of 150 IU; this is due to filling, excess air being removed and dead volume of the



syringe; the actual dose delivered was determined by weighing the syringe before and after injection to the subjects

- concentration of the drug is higher in the pen injector formulation (833 IU/mL) than the approved reconstituted product (75-300 IU/mL)
- the BE issue was discussed in the pre-NDA meeting and the sponsor was told that they could address this issue by doing another BE study after correcting the pen injector dose to match the dose delivered from the approved product; however, following a meeting with the Biopharm supervisors, it was noted that another BE study may not be required if the dose of pen injector is adjusted appropriately to match the dose delivered by conventional syringe
- risk of Ovarian Hyperstimulation Syndrome (OHSS) should be taken into account although it is not always a dose-dependent phenomenon

Decisions reached:

The following options will be conveyed to the sponsor:

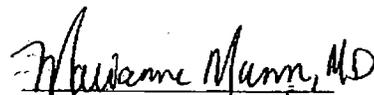
- to support honesty in labeling, the dose could be adjusted down in the pen injector by removing the 18% of FSH and rewriting the label to describe how the new dose (delivered by the pen injector) is bioequivalent to the more familiar dose (delivered by syringe)
- alternatively, perform a clinical trial to show that the 20% higher concentration is safe and effective
- the sponsor could reformulate the solution to be less concentrated to achieve administration of dose that is identified to the approved Follistim
- if the first option were chosen, the pen injector device would need to be recalibrated to give less drug
- the NDA is fileable from Biopharm perspective because it consists of BE study (although the BE study failed, this is a review issue)
- from CMC perspective, the application is fileable
- from pharm/tox perspective, the application is fileable

Action Items:

- fileability from the clinical perspective will be discussed further with Dr. Houn at the Office level.

Post-Meeting Addendum: A teleconference with the sponsor is scheduled for March 22, 2000.


Signature, minutes preparer


Concurrence, Chair

cc:

NDA Arch:

HFD-580

HFD-580/Allen/Rumble/Bennett/Rhee/Jarugula/Slaughter/Parekh/Mann

drafted: DeGuia/03.10.00

concurrences: TRumble03.28.00/RBennett,MRhee03.31.00/

MMann04.03.00/AParekh,VJarugula04.13.00

final: EDeGuia04.14.00

MEETING MINUTES

Date: March 18, 1999 **Time:** 1:00-2:30 pm **Location:** Conference Room "L"

NDA 20-582 **Drug Name:** Follistim (follitropin beta form injection)

Indication: Assisted Reproductive Technology (ART)

External Participant: Organon, Inc.

Type of Meeting: pre-NDA (guidance)

Meeting Chair: Dr. Lisa Rarick

External Participant Lead: Mr. Albert Mayo

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

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

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

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

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

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

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

Du Gong Wu, Ph.D. - Chemistry, Division of Metabolic and Endocrine Drug Products

Sam Haidar, R.Ph., Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

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

External Constituents:

Albert Mayo, Executive Director, Regulatory Affairs, Organon, Inc.

Carole Anne Cartier, Regulatory Affairs, Organon, Inc.

Jay Rheingold Ph.D. - Product Development, Organon, Inc.

Eric Orlemans Ph.D. - Program Management, NV Organon

Mario Peters, Ph.D. - Regulatory Affairs, NV Organon

Joost van Zutven, Ph.D. - Technology Department, NV Organon

Meeting Objectives: To discuss the specific requirements and concerns regarding a bioequivalence study to support the new formulation which is an aqueous solution to be supplied in a cartridge and administered with a special pen injector.

Background:

- meeting package provided for the review of the new formulation and new administration

- responses to the sponsor's questions posed on the meeting package were conveyed to the sponsor via teleconference on March 5, 1999, to provide them the opportunity to decide whether a face-to-face meeting is still warranted

Discussion Points:

- the sponsor provided their explanation for the non-equivalent results for the lyophilized formulation (approved product) and the pen injector formulation (new product)
- the sponsor justified the use of a "dose correction factor" which changed the results of the study to bioequivalent
- by weighing the syringe before and after delivery of the cake formulation, the sponsor determined that 18% of the labeled dose was lost during reconstitution and delivery to patient and this 18% loss appears to be excessive
- the pen injector is designed to deliver 100% of the labeled dose
- the sponsor can address the differences in the dose delivered by the two formulations by conducting another bioequivalence study after altering the dose delivered by the pen injector to match the dose delivered by the cake formulation
- a significant risk could exist for the patients who switch from cake to pen or vice versa; this issue should be addressed by providing a justification for the use of either product and allowing the physician to decide the choice of product, dose and mode of administration
- since it would be difficult to change label in the approved product, the delivery volume should be clearly addressed in the label for the pen injector NDA
- with the use of L-methionine as a _____ an adequate amount of stability with oxidation data are needed for the NDA submission

Decisions reached:

- bioequivalence issues should be resolved before the NDA application is submitted
- this application qualifies as a New Drug Application and therefore requires a User Fee; the Agency will determine if a full or half User Fee is required
- after consulting with their marketing personnel, Organon, Inc. will formally submit a new format of the tradename which will then be submitted to LNC (Labeling and Nomenclature Committee)
- 12-month stability data (including 6-month accelerated data) will be submitted prior to the NDA submission

Action Items:

- provide a copy of industry meeting minutes to the sponsor within 30 days
- convey need for full or half User Fee for this application

EP de Guid 4.6.99
Signature, minutes preparer

Manuel 4/9/99
Concurrence, Chair

01-File

MEETING MINUTES

Date: March 8, 2000 **Time:** 9:00 – 10:00 AM **Location:** Room 17B-43

NDA 21-211

Indication: Assisted Reproductive Technology (ART)

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

Type of Meeting: pre-Filing Meeting

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

- Susan Allen, M.D., M.P.H. – Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
- Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
- Shelley Slaughter, M.D., Ph.D. – Team Leader, 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

Meeting Objectives: This meeting was requested by the Biopharm Team to discuss some fileability issues with the Medical Officers regarding a new formulation of Follistim to be supplied in a cartridge and administered with a special pen injector.

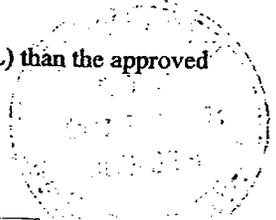
Background:

Follistim – AQ (follitropin beta for injection) cartridge is a new pharmaceutical presentation of the approved product, Follistim (follitropin beta for injection) NDA20-582. The currently approved product is available as a freeze-dried cake, to be administered after reconstitution with Water for Injection. Follistim- AQ Cartridge in an injectable aqueous solution of 300 IU and 600 IU follitropin beta in a multidose cartridge to be administered with a pen injector.

Organon, Inc. mentioned at the pre-NDA meeting on March 18, 1999, that Becton Dickinson will supply the pen device that will be used with their injection cartridge and all information regarding the device is included in a 510K application that will be filed by Becton Dickinson. The pen injector is virtually identical to the one supplied to Novo Nordisk for delivery of insulin.

Discussion Points:

- the concentration of the drug is higher in the pen injector formulation (833 IU/mL) than the approved reconstituted product (75-300 IU/mL)



- the bioequivalence study between the pen injector formulation vs. approved formulation was conducted following single-dose subcutaneous administration of 150 IU; both C_{max} and AUC for the pen injector were 20% higher than for the currently marketed formulation
- in the BE study, the sponsor stated that the pen injector accurately delivered the amount that it was set to deliver, whereas the conventional syringe delivered an amount of FSH that, on the average, was lower than the nominal dose of 150 IU; this is due to losses in filling, excess air removed and the dead volume of the syringe; the actual dose delivered was determined by weighing the syringe before and after injection to the subjects
- following the correction of dose delivered by syringe (retrospectively), the two formulations were shown bioequivalent
- the pen injector results in higher bioavailability when compared to the approved product/dose
- the BE issue was discussed in the pre-NDA meeting and the sponsor was told that they could address this issue by doing another BE study
- the risk of Ovarian Hyperstimulation Syndrome (OHSS) should be taken into account although the incidence of this syndrome does not appear to be strictly dose-dependent

Decisions reached:

- three options are possible for sponsor to address the dosing issues:
 - perform another study to demonstrate bioequivalence between the old and new formulations
 - adjust the dose down in the pen injector and label it as such (without BE study)
 - perform a clinical trial to show that the 18% higher dose is safe and effective
- the NDA is fileable from Biopharm perspective because it consists of a BE study (although the BE study failed, it is not a filing issue) and sponsor's proposed clinical justification

Action Items:

- the fileability of this application will be determined following further discussion with Dr. Houn, ODE III Office Director

Post-Meeting Addendum: The Filing Meeting is re-scheduled for March 20, 2000. A teleconference with the sponsor is scheduled for March 22, 2000.

E De Guia 4.17.00
Signature, minutes preparer

Manna Ma, M.D. (for S. Allen)
Concurrence, Chair 4/17/00

cc:

NDA Arch:

HFD-580

HFD-580/Allen/Rumble/Bennett/Rhee/Jarugula/Slaughter/Parekh/Mann

drafted: DeGuia/03.10.00

concurrences:

TRumble03.28.00/MMann03.29.00/MRhee, RBennett03.31.00/SSlaughter04.04.00/SAllen04.06.00/

AParekh04.11.00/VJarugula04.13.00

final: EDeGuia04.13.00



CONFIDENTIAL

Organon Inc.

March 7, 2000

ORIGINAL

Mrs. F. Deguia, Project Manager
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation III
Documentation Control Room 17B45
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-211
Follistim® - AQ (follitropin beta injection)
Cartridge

BC

Dear Mrs. Deguia:

With reference to our NDA No. 21-211 for Follistim® - AQ (follitropin beta injection) Cartridge, submitted January 28, 2000, and your phone call of March 7, 2000, I'm happy to herewith supply you with a sample of the Beckton-Dickinson Follistim Pen (bearing the European tradename 'Puregon®'), and some samples of the Follistim® - AQ (follitropin beta injection) Cartridge.

Please be informed that the Pen-Injector device concerns a prototype, which merely gives an impression of the eventual pen. Both the Pen-Injector and the unlabeled cartridges are supplied as impromptu samples, and the way they are packaged is obviously not representative for the way the eventual products will be packaged.

Being part of the 510(k) submission, the Instruction Manual is still in preparation but the pictograms in the included manual indicate how the Pen-Injector and the cartridge have to be handled.

I apologize that I cannot supply you with samples of the final products at short notice. (Juggling feathers in a hurricane may be an achievement, but the act in the circus will be better!).

Should you have any questions regarding this correspondence, please contact the undersigned at (973) 325-5214.

Sincerely,

Peter G. Stokman
Associate Director, Regulatory Affairs

PST/bl

Submitted via Federal Express Airbill #

REVIEWS COMPLETED	
CSD ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
INITIALS	DATE



Organon Inc.
375 Mt. Pleasant Avenue
West Orange
New Jersey 07052
USA
Tel.: (973) 325-4500
Fax: (973)-325-4589

Dequina

NDA 21-211

FEB 2 2000

Organon, Inc.
Attention: Albert P. Mayo
Executive Director, Regulatory Affairs
375 Mt. Pleasant Ave.
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 cartridge) 300IU/600IU

Therapeutic Classification: Standard (S)

Date of Application: January 28, 2000

Date of Receipt: January 31, 2000

Our Reference Number: NDA 21-211

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 30, 2000 and the secondary user fee goal date will be January 31, 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 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

Appears This Way
On Original

NDA 21-211
Page 3

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301)
827-5424.

Sincerely,

 2/9/00

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

Appears This Way
On Original

NDA 21-211

Page 4

cc:

Archival NDA 21-211

HFD-580/Div. Files

HFD-580/E.DeGuia/TRumble

HFD-580/RBennett

DISTRICT OFFICE

Drafted by: ED/February 2, 2000

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ACKNOWLEDGEMENT (AC)

Appears This Way
On Original

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January 28, 2000

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852 -1833



Organon Inc.



NDA 21-211
Follistim® - AQ (follitropin beta injection)
Cartridge
ORIGINAL NEW DRUG APPLICATION

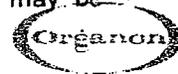
Dear Sir / Madam:

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, Organon Inc. herewith submits an original New Drug Application, Form 356h and supporting documentation for Follistim® - AQ (follitropin beta injection) Cartridge. Please note that the above referenced NDA number has been pre-assigned to this application. The trade name Follistim® - AQ (follitropin beta injection) Cartridge was proposed in our July 28, 1999 correspondence to FDA.

Follistim® - AQ (follitropin beta injection) Cartridge is a new pharmaceutical presentation of the approved Follistim® (follitropin beta for injection), NDA No. 20-582. The currently approved product is formulated as a freeze-dried cake, to be administered after reconstitution with Water for Injection, whereas Follistim® - AQ (follitropin beta injection) Cartridge is an injectable aqueous solution of 300 IU and 600 IU follitropin beta in a glass rubber multidose cartridge, to be administered with a Pen-Injector device.

A multidose ready-to-use presentation is considered to be more convenient than the approved product since its use requires less handling. The use of the Pen-Injector provides a more accurate and precise method of dosing as compared to the conventional syringe. This allows a greater dosing flexibility and a more subtle treatment of hyper responders. Patient comfort is enhanced by the smaller needle and dosing volume. The use of the cartridge presentation with the Pen-Injector facilitates self-administration by patients.

The concentration of follitropin beta of the Follistim® - AQ (follitropin beta injection) Cartridge is higher than the concentration range obtained with the reconstituted lyophilized FDA-approved Follistim® (follitropin beta for injection) product. For the Cartridge the concentration is 833 IU/ml, whereas reconstitution of the lyophilized cake yields a solution in the concentration range between 75 and 300 IU/mL. (In line with the approved labeling up to 4 cakes may be reconstituted in 1 mL of Water for Injection.)



Organon Inc.
575 N. Pleasant Avenue
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0001
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Since absorption from the injection site may be influenced by the concentration of the drug and injection volume, the pharmacokinetics of FSH were compared after subcutaneous administration of Follistim® - AQ (follitropin beta injection) Cartridge by a Pen-Injector, and subcutaneous administration of reconstituted Follistim® (follitropin beta for injection) by a syringe (Study 37626, submitted in this NDA under 315.50(d)(3) Human Pharmacokinetics and Bioavailability and 315.50(d)(5) Clinical Data.)

In this open-label, single-center, single-dose, cross-over study a single-dose of 150 IU recombinant FSH was subcutaneously administered as Follistim® - AQ (follitropin beta injection) Cartridge by a Pen-Injector, and as reconstituted Follistim® (follitropin beta for injection) by a syringe. The concentrations were 150 IU/mL and 833 IU/mL respectively.

After normalization of the pharmacokinetic data for the dose of reconstituted Follistim® (follitropin beta for injection) actually administered, bioequivalence could be proven for dose-corrected C_{max} and AUC. This leads to the conclusion that the bioavailability of follitropin beta is not influenced by the concentration in the tested dose range.

However, in the same study it was found that the Pen-Injector accurately delivered the dose to which it was set, whereas the conventional syringe, due to filling, removing of excess air and the dead volume of the syringe, actually delivered an amount of FSH that on average was lower than the nominal dose of 150 IU. Consequently, due to the high accuracy and precision of the device, Pen-Injector dosing resulted in an approximately 18% higher dose than the conventional syringe.

This finding was discussed with the Agency on March 18, 1999 during a pre-NDA (guidance) meeting (minutes issued by the DRUDP on April 12, 1999). Several approaches to resolve the bioequivalence issues were identified:

- the sponsor can address the differences in the dose delivered by the two formulations by conducting another bioequivalence study after altering the dose delivered by the pen injector to match the dose delivered by the cake formulation
- a significant risk could exist for patients who switch from cake to pen or vice versa; this issue should be addressed by providing a justification for the use of either product and allowing the physician to decide the choice of the product, dose and mode of administration
- since it would be difficult to change label in the approved product, the delivery volume should be clearly addressed in the label for the pen injector

In the referenced pharmacokinetics study it was shown that both preparations are bioequivalent when the administered doses are the same. This was established by retrospectively correcting the plasma concentrations for the actually administered volume. Carrying out another

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January 28, 2000
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bioequivalence study in which the dose delivered by the pen is reduced to match the dose delivered by the syringe (prospective correction) would confirm that the Pen-Injector has a higher level of accuracy of administration.

Modifying the Pen-Injector dial scale to decrease the actual delivered dose to the low accuracy level of the conventional syringe (keeping the nominal dose however identical) would lead to extremely confusing situations.

Therefore, it was chosen to pursue the approach to address the clinical relevance of the difference between administering Follistim[®] - AQ (follitropin beta injection) Cartridge with a Pen-Injector and administering reconstituted Follistim[®] (follitropin beta for injection) with a syringe.

A pertinent assessment is included in this submission under 314.50(d)(5) Clinical Relevance of Observed Difference. Focusing on the fact that treatment with follitropin beta is essentially guided by ovarian response, this document substantiates that the observed difference is of no clinical concern when the Pen-Injector is used throughout the treatment cycle. In line with the approach described under the second bullet item changes to the labeling are proposed to address the cases in which the observed difference might be of clinical relevance (i.e., when a switch is made between the Pen-injector and the conventional syringe within one treatment cycle). This is also addressed sub 314.50(c)2(i), Annotated Proposed Labeling. In line with the approach given under the third bullet item, the increased delivery volume and associated increased plasma levels of FSH are also included in the Proposed Labeling.

The aforementioned pharmacokinetics study was conducted outside of the United States. Therefore, Follistim[®] - AQ (follitropin beta injection) Cartridge has not been investigated clinically under an IND.

Follistim[®] - AQ (follitropin beta injection) Cartridge differs from the approved Follistim[®] (follitropin beta for injection) in its pharmaceutical presentation only. Therefore, except for section 314.50(d)(1)(ii) Chemistry, Manufacturing and Control (Drug Product), data contained in NDA No. 20-528 are incorporated into NDA 21-211 by cross-reference. In addition, new information is submitted in sections 314.50(d)(3) Human Pharmacokinetics and Bioavailability, and 314.50(d)(5) Clinical Data, and the pertinent Application Summaries, section 314.50(c).

In accordance with 21 CFR 314.50(k)(3), an identical field copy of the Chemistry, Manufacturing and Controls section of this NDA has been prepared for simultaneous submission to the FDA Newark District Office. Enclosed is a copy of the field copy transmittal letter and the signed certification that the copy submitted to the District Office is a true copy of that submitted to FDA headquarters.

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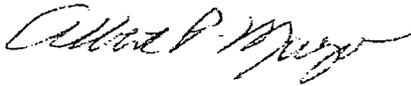
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Central Document Room
January 28, 2000
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This NDA is provided entirely in paper (18 Volumes). However, a copy of the Package Insert has been included in electronic format as a review aid. It is supplied on one (1) diskette in Microsoft Word 7.0 format, and it has been checked for viruses using McAfee Virus Shield version 4.0.3.

We believe that the enclosed NDA is complete and organized to facilitate the ease of review. Therefore, review and evaluation at your earliest convenience would be greatly appreciated. Should you have any questions or comments regarding this submission, please do not hesitate to contact the undersigned at (973) 325-5214.

Please note that Organon Inc. considers this application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Sincerely,



Albert P. Mayo
Executive Director, Regulatory Affairs

Enclosures: Form 356h

Copy to: District Office
Food and Drug Administration
120 North Center Drive, Bldg. C
North Brunswick, NJ 08902
Attention: Pre-Approval Coordinator

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Organon Inc.

January 10, 2000

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

**Re: Prescription Drug User Fee Act of 1997
Application Fee Payment for NDA 21-211:
Original New Drug Application for
Follistim[®] - AQ (follitropin beta injection) Cartridge
Organon Inc., 375 Mount Pleasant Avenue, West Orange, New Jersey 07052**

Dear Sir/Madam:

Pursuant to the above referenced Act, please find enclosed on behalf of Organon Inc., 375 Mount Pleasant Avenue, New Jersey as follows:

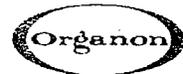
Check No. _____ in the amount of \$ 142,870.00 related to the Application Fees for NDA 21-211, Follistim[®] - AQ (follitropin beta injection) Cartridge, an original New Drug Application, not requiring clinical data, to be submitted on or about January 26, 2000.

Should you have any questions please contact the undersigned at (973) 325-4833.

Sincerely,

Albert P. Mayo
Executive Director, Regulatory Affairs

Submitted via Federal Express Airbill _____



Organon Inc.
375 Mount Pleasant Avenue
West Orange
New Jersey 07052
0012
973-325-4830
973-325-4880

NDA 21-211
Follistim® - AQ (follitropin beta injection)
Organon, Inc.

Advisory Committee Meeting Minutes

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

NDA 21-211
Follistim® - AQ (follitropin beta injection)
Organon, Inc.

Federal Register Notices

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Albert P. Mayo Organon Inc. 375 Mt. Pleasant Ave. West Orange, NJ 07052	3. PRODUCT NAME Follistim® - AQ (follitropin beta injection) Cartridge
2. TELEPHONE NUMBER (Include Area Code) (973) 325-4833	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 3890	6. LICENSE NUMBER / NDA NUMBER 21-211

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, on reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

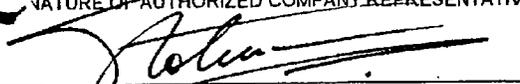
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

NATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Albert P. Mayo Executive Director, Regulatory Affairs	DATE 01/10/00 0013
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◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review)	Materials requested in AP letter
◆ Post-marketing Commitments	N/A
Agency request for Phase 4 Commitments.....	N/A
Copy of Applicant's commitments	N/A
◆ Was Press Office notified of action (for approval action only)?.....	Yes X No
Copy of Press Release or Talk Paper.....	N/A
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)].....	N/A
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	N/A
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	N/A
Disclosable information – indicate where review is located	See memo
◆ Correspondence/Memoranda/Faxes	X
◆ Minutes of Meetings	X
Date of EOP2 Meeting <u>Not held</u>	
Date of pre NDA Meeting <u>March 18, 1999</u>	
Date of pre-AP Safety Conference <u>N/A</u>	
◆ Advisory Committee Meeting	N/A
Date of Meeting	
Questions considered by the committee	
Minutes or 48-hour alert or pertinent section of transcript	
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, <u>Group Leader's memo</u>)	X
◆ Clinical review(s) and memoranda	X

Continued

- ◆ Safety Update review(s) N/A
- ◆ Pediatric Information
 Waiver/partial waiver (Indicate location of rationale for waiver) D e f e r r e d
 Pediatric Page..... X
 Pediatric Exclusivity requested? D e n i e d G r a n t e d N o t A p p l i c a b l e
- ◆ Statistical review(s) and memoranda N/A
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) N/A
 Recommendation for scheduling
- ◆ Microbiology (efficacy) review(s) and memoranda N/A
- ◆ DSI Audits N/A
 Clinical studies X bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable),
 X (completed), or add a
 comment.

- ◆ CMC review(s) and memoranda X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability N/A
- ◆ DMF review(s) X
- ◆ Environmental Assessment review/FONSI/Categorical exemption N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda X
- ◆ Facilities Inspection (include EES report)
 Date completed Acceptable X Not Acceptable
- ◆ Methods Validation Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable),
 X (completed), or add a
 comment.

- ◆ Pharm/Tox review(s) and memoranda X
- ◆ Memo from DSI regarding GLP inspection (if any) N/A

Continued

◆ Statistical review(s) of carcinogenicity studies N/A

◆ CAC/ECAC report N/A