

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-211

CHEMISTRY REVIEW(S)

NDA 21-211

**Follistim® AQ Cartridge
(follitropin beta injection)**

Organon Inc.

**Suong Tran, PhD
Division of Reproductive and Urologic Drug
Products**



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Chemistry Review Data Sheet

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1. NDA 21-211
2. REVIEW #: 4
3. REVIEW DATE: 9-MAR-2004
4. REVIEWER: Suong Tran PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	28-JAN-2000
Amendment	9-MAY-2000
Amendment	26-SEP-2000
Amendment	27-OCT-2000
Amendment	27-OCT-2000
Chemistry Review #1	30-OCT-2000
Chemistry Review Letter	14-NOV-2000
Amendment	20-NOV-2000
Chemistry Review #2	27-NOV-2000
Action (non-approval) Letter	29-NOV-2000
Amendment	19-MAR-2001
Amendment	20-DEC-2002
Amendment	19-FEB-2003
Amendment	21-FEB-2003
Amendment	26-FEB-2003
Amendment	16-MAY-2003
Amendment	19-MAY-2003
Chemistry Review #3	30-MAY-2003
Addendum to Chem. Review #3	23-JUN-2003
Action (non-approval) Letter	23-JUN-2003
Formal dispute resolution	24-NOV-2003
Action (approvable) Letter	23-DEC-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	30-MAY-2003
Amendment	22-JAN-2004
Amendment	29-JAN-2004
Amendment	24-FEB-2004

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Amendment

26-FEB-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Organon Inc.

Address: 375 Mt. Pleasant Ave., West Orange, NJ 07052

Representative: Lawrence Starke, PhD

Telephone: 973-325-4921

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Follistim AQ Cartridge
- b) Non-Proprietary Name (USAN): Follitropin beta injection
- c) Code Name/# (ONDC only): Org 32489
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Follicle stimulating hormone (FSH), recombinant

11. DOSAGE FORM: Sterile aqueous solution

12. STRENGTH/POTENCY: 300 IU and 600 IU FSH activity per cartridge

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product Form Completed

Not a SPOTS product

CHEMISTRY REVIEW

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

Recombinant human follicle stimulating hormone (rhFSH) is composed of alpha and beta subunits which are bound together in a non-covalent association of high affinity without interchain disulfide bonds or covalent bonds. The alpha subunit is common to all four members of a glycoprotein hormone family, including pituitary luteinizing hormone (LH), pituitary thyroid stimulating hormone (TSH) and placental human chorionic gonadotropin (hCG). The amino acid sequences for the beta subunit, which determines the specific biological properties of the heterodimer, are different among the four glycoprotein hormones.

Alpha Subunit:

The alpha subunit consists of 92 amino acid residues. Structurally, there are two glycosylation sites (Asn 52 and 78, see underlined amino acid residues below) and five internally cross-linked disulfide bonds.

The molecular weight is estimated to be approximately 21,000-22,000 dalton for both subunits.

1	Ala-Pro-Asp-Val-Gln-Asp-Cys-Pro-Glu-Cys	10
11	Thr-Leu-Gln-Glu-Asn-Pro-Phe-Phe-Ser-Gln	20
21	Pro-Gly-Ala-Pro-Ile-Leu-Gln-Cys-Met-Gly	30
31	Cys-Cys-Phe-Ser-Arg-Ala-Tyr-Pro-Thr-Pro	40
41	Leu-Arg-Ser-Lys-Lys-Thr-Met-Leu-Val-Gln	50
51	Lys- <u>Asn</u> -Val-Thr-Ser-Glu-Ser-Thr-Cys-Cys	60
61	Val-Ala-Lys-Ser-Tyr-Asn-Arg-Val-Thr-Val	70
71	Met-Gly-Gly-Phe-Lys-Val-Glu- <u>Asn</u> -His-Thr	80
81	Ala-Cys-His-Cys-Ser-Thr-Cys-Tyr-Tyr-His	90
91	Lys-Ser	92

Beta Subunit:

The beta subunit consists of 111 amino acid residues with two carbohydrate moieties linked to amino acid residues (Asn 7 and 24, see underlined amino acid residues below) and six internally cross-linked disulfide bonds.

1	Asn-Ser-Cys-Glu-Leu-Thr- <u>Asn</u> -Ile-Thr-Ile	10
11	Ala-Ile-Glu-Lys-Glu-Glu-Cys-Arg-Phe-Cys	20
21	Ile-Ser-Ile-Asn-Thr-Thr-Trp-Cys-Ala-Gly	30
31	Tyr-Cys-Tyr-Thr-Arg-Asp-Leu-Val-Tyr-Lys	40
41	Asp-Pro-Ala-Arg-Pro-Lys-His-Gln-Lys-Thr	50
51	Cys-Thr-Phe-Lys-Glu-Leu-Val-Tyr-Glu-Thr	60
61	Val-Arg-Val-Pro-Gly-Cys-Ala-His-His-Ala	70
71	Asp-Ser-Leu-Tyr-Thr-Tyr-Pro-Val-Ala-Thr	80
81	Gln-Cys-His-Cys-Gly-Lys-Cys-Asp-Ser-Asp	90
91	Ser-Thr-Asp-Cys-Thr-Val-Arg-Gly-Leu-Gly	100
101	Pro-Ser-Tyr-Cys-Ser-Phe-Gly-Glu-Met-Lys	110
111	Glu	

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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II		Recombinant FSH	3	Adequate	3-JUL-2002	By D. Lin
	III			3	Adequate	19-OCT-2000	By D. Lin
	III			3	Adequate and adequate, respectively	31-JAN-2003 and 16-FEB-2000, respectively	By R. Kasliwal and J Sieczkowski, respectively

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-582	Follistim (follitropin beta for injection)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	<i>Not Applicable</i>		
EES	Acceptable	19-NOV-2003	J. D'Ambrogio
Pharm/Tox	<i>Not Applicable</i>		
Clin.Pharm.	<i>Not Applicable</i>		
LNC	<i>Not Applicable</i>		
Methods Validation	Package will be submitted to FDA labs after test methods are finalized.		
DMETS	Acceptable proprietary name	8-MAR-2004	A. Mahmud
EA	<i>Not Applicable</i>		
Microbiology	Recommended "Approval"	8-JAN-2001	B. Riley
CDRH	Recommended "Approval"	11-APR-2003	V. Nakayama

The Chemistry Review for NDA 21-211

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is **APPROVAL**.

Refer to the Basis for Approval in Section C below for details.

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

None

II. Summary of Chemistry Assessments

- On 23-JUN-2003, a Non-Approval letter was issued for this NDA 21-211 for clinical deficiencies and a pending recommendation from the Office of Compliance for GMP of facilities. At the time of the action, labeling (package insert and container labels) were not yet reviewed by the Division. Therefore, the labeling amendment dated 30-MAY-2003 is now covered by this present Chem. Rev. #4.
- On 19-NOV-2003, an ACCEPTABLE recommendation was obtained from the Office of Compliance.
- On 24-NOV-2003, a formal dispute was satisfactorily resolved in favor of the applicant.
- On 23-DEC-2003, as a result of the formal dispute resolution, a letter was issued informing the applicant that this NDA 21-211 is considered Approvable as of 23-JUN-2003. Because the Office of Compliance already recommended ACCEPTABLE for the NDA on 19-NOV-2003, the only issue included in the Approvable letter was FDA's request for a safety update and draft labeling (package insert, container labels, etc.)
- On 22-JAN-2004, an amendment was submitted with the information requested in the 23-DEC-2003 letter. Because the Office of Compliance already recommended ACCEPTABLE for the NDA on 19-NOV-2003, no further action from OC is required (refer to the attached email from OC).

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

Drug product –

- Name: Follistim® AQ Cartridge (follitropin beta injection)
- For use only with Follistim Pen™, available only from physicians. The patient or physician loads the cartridge into the pen. The pen can be re-used with a new cartridge. [Note to reviewers: the pen cannot be used with Follistim AQ (packaged in vials; subject of the different NDA 21-273). This reviewer finds that there is no confusion about using the pen with the lyophilized Follistim product because 1) the pen is only available from the physician, with specific instructions on its use with Follistim AQ Cartridge; and 2) the statement "For

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use only with Follistim AQ Cartridge" is prominent on all the labels and on the pen itself (as requested by this reviewer, the applicant emphasizes the use of the pen with the cartridge product by putting both words "Pen" and "Cartridge" in red color). Therefore, "Follistim Pen" is acceptable as the name of the pen injector to be used with Follistim AQ Cartridge. The proposed label is acceptable.]

- Strength/Fill size: 300 IU per cartridge and 600 IU per cartridge (both presentations having the same concentration of 833 IU/mL)
- Dosage form: aqueous solution for subcutaneous injection
- Pharmacological category: Follicle stimulating hormone (FSH), recombinant
- Formulation - Inactive ingredients are sucrose NF, sodium citrate dihydrate USP, polysorbate 20 NF, benzyl alcohol NF, L-methionine USP, 0.1 N hydrochloric acid or sodium hydroxide NF, and water for injection USP.
- Packaging: The primary container/closure system for the drug product is a _____ tubing glass cartridge. At one end, the cartridge barrel is closed with

_____ an aluminum crimp-cap. The sealed cartridge is intended to fit into Follistim Pen, a Becton-Dickinson pen-injector, which features an adjustable dosing system for administering the drug (refer to the review of the pen-injector by the Center for Devices and Radiological Health). The secondary packaging configuration of the drug product is as follows: the sealed and labeled cartridge is packaged in a _____ plastic tray, which is then sealed with a lidding material. The sealed tray and 4 Becton-Dickinson Micro-Fine needles (29G) are packaged together in an outer carton. The Follistim Pen is packaged separately, for distribution by the physicians as professional samples.

- Expiry _____ months at 2-8 °C, protected from light, OR _____ months at 2-8 °C _____ months at 25 °C, protected from light (based on _____ month data at 5 °C for three production batches of each dosage strength and _____ month data at 25 °C/60% RH for one production batch of each dosage strength; both dosage strengths are filled from the same final blend, with the same concentrations of active and inactive ingredients). Refer to Chem. Rev. #3. In addition, once the stopper on the cartridge is pierced (during normal use), the product can be kept for up to _____ at 2-25 °C (based on data submitted in the original NDA submission on pages 0358-0360 Vol. 1.4, covered by Chem. Rev. #1, as well as data submitted in the 24-FEB-2004 amendment, covered by this Chem. Rev. #4).

Drug substances – follitropin beta

- The drug substance is a human follicle-stimulating hormone (hFSH), which is manufactured by recombinant DNA (rDNA) technology. This glycoprotein hormone has a dimeric structure containing two glycoprotein subunits (alpha and beta). Both the 92 amino acid alpha-chain and the 111 amino acid beta-chain have complex heterogeneous structures arising from two N-linked oligosaccharide chains. Follitropin beta is synthesized in a Chinese hamster ovary (CHO) cell line that has been transfected with a plasmid containing the two subunit DNA sequences encoding for hFSH. The purification process results in a highly purified preparation with a consistent hFSH isoform profile and high specific activity (as determined by the Ph. Eur. test for FSH *in vivo* bioactivity and on the basis of the molar extinction coefficient at 277 nm ($[\epsilon]_{277} = \text{mg}^{-1} \text{cm}^{-1}$) = 1.066. The biological activity is determined by measuring the increase in ovary weight in female rats. The intrinsic luteinizing hormone (LH) activity in follitropin beta is less than 1 IU per 40,000 IU FSH. The compound is considered to contain no LH activity. The amino acid sequence and tertiary structure of the product are indistinguishable from that of human follicle-stimulating hormone

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(hFSH) of urinary source. Also, based on available data derived from physico-chemical tests and bioassay, follitropin beta and follitropin alfa, another recombinant follicle-stimulating hormone product, are indistinguishable.

- Reference is made to Drug Master File — for all chemistry reviews of the drug substance. The DMF is adequate as of the last review dated 3-JUL-2002, by D. Lin. No amendment has been submitted since the last review.

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

- Dosage administration: subcutaneous injection only with Follistim Pen™
- Dosing schedule: as determined by physician

C. Basis for Approvability or Not-Approval Recommendation

- All chemistry issues were satisfactorily resolved as discussed in the Chem. Review #3. All labeling issues per chemistry perspective (e.g., packaging labels, inserts) are satisfactorily resolved as discussed in this current Chem. Review #4.
- A recommendation for approval was obtained from Microbiology on 8-JAN-2001 (see reviews in DFS).
- A recommendation for approval was obtained from CDRH for the pen injector Follistim Pen on 11-APR-2003 (see reviews in DFS).
- A recommendation for approval was obtained from the Office of Combination Products on 7-MAY-2003 (see Chem. Rev. #3) on the issue of packaging the product cartridge and the pen injector in the same secondary container. The Office determined by such co-packaging is not necessary even though the pen injector was approved specifically under this NDA. However, the Office recommends that the device labeling clearly indicate that the device is specifically indicated for use in administering this specific product cartridge. This recommendation is reflected in the device label submitted in the 24-FEB-2004 amendment, that the cap of Follistim Pen bears the statement "For use only with Follistim AQ Cartridge".
- Because the Office of Compliance already recommended ACCEPTABLE for the NDA on 19-NOV-2003, no further action from OC is required (refer to the attached email from OC). In addition, on 29-JAN-2004, the applicant submitted an amendment to remove the alternate drug substance testing site (only test performed here: Appearance) Organon in West Orange, NJ, CFN 2211109. The GMP status of the NDA is currently satisfactory.
- On 8-MAR-2004 DMETS found the proprietary name acceptable (see review in DFS).

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

Executive Summary Section

B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

12 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-1

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

/s/

Suong Tran
3/10/04 10:21:10 AM
CHEMIST

revised per your recommendations

Moo-Jhong Rhee
3/10/04 04:56:12 PM
CHEMIST
I concur

Addendum to Chemistry Review # 3

From: Suong Tran, PhD, Chemist
To: NDA 21-211 Follistim AQ Cartridge (follitropin beta injection)
Date: 19-JUN-2003
Subject: Final, second-cycle review of the NDA

The chemistry recommendation for NDA 21-211 is "APPROVABLE" pending satisfactory labeling and GMP status. The CMC approvability issues are delineated at the end of this addendum.

Pending GMP status - A final recommendation is pending from FDA Compliance. Due to Agency-wide restrictions on foreign travel, inspection of the following manufacturing facilities has been postponed:

3. CFN 9612716: Organon Ireland Ltd., Swords, Ireland (Drug product packager and release tester)
4. CFN 9610342: Organon NV, 5340-BH, Oss, Netherlands (Drug substance release tester)

The labeling amendment dated 30-MAY-2003 was found by Chemistry and DMETS to be deficient. Pending labeling issues are as follows:

- Cartridge carton labels should be revised to state the actual total quantity of recombinant protein per cartridge, (e.g., "438 IU Cartridge" or "738 IU Cartridge").
- All labeling should be revised to state "Follistim AQ Pen" instead of "Follistim Pen".
- It should be clarified whether the physician sample does include needles because the content statement of the physician carton label does not include needles. Per consult from the Clinical reviewer (A. Gassman), needles for use with the pen injector are not the ordinary needles usually found in a physician's office.

DRAFT CHEMISTRY APPROVABILITY ISSUES:

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

We will schedule and perform an inspection of this/these facility/facilities as soon as we can. Please notify us in writing when the inspection of these facilities has been completed.

The following is with regard to the labeling of the drug product:

- **Revise cartridge carton labels to state the actual total quantity of recombinant protein per cartridge, (e.g., "438 IU Cartridge" or "738 IU Cartridge").**
- **Revise all labeling to state "Follistim AQ Pen" instead of "Follistim Pen".**
- **Confirm that the physician sample does include needles because the content statement of the physician carton label does not include needles**

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

/s/

Suong Tran
6/23/03 11:17:17 AM
CHEMIST

David T. Lin
6/23/03 05:51:04 PM
CHEMIST
I concur.

NDA 21-211

Follistim AQ® Cartridge (follitropin beta injection)

Organon Inc.

Suong Tran, PhD
Division of Reproductive and Urologic Drug Products

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1. NDA 21-211
2. REVIEW #: 3
3. REVIEW DATE: 30-MAY-2003
4. REVIEWER: Suong Tran PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
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Action (non-approvable) Letter	29-NOV-2000

6. SUBMISSION(S) BEING REVIEWED:

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Amendment	26-FEB-2003
Amendment	16-MAY-2003
Amendment	19-MAY-2003

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Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Organon Inc.

Address: 375 Mt. Pleasant Ave., West Orange, NJ 07052

Representative: Lawrence Starke, PhD

Telephone: 973-325-4921

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Follistim AQ Cartridge
- b) Non-Proprietary Name (USAN): Follitropin beta injection
- c) Code Name/# (ONDC only): Org 32489
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Follicle stimulating hormone (FSH),
recombinant

11. DOSAGE FORM: Aqueous solution for injection

12. STRENGTH/POTENCY: 300 IU and 600 IU FSH activity per
cartridge

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product Form Completed

Not a SPOTS product

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

Recombinant human follicle stimulating hormone (rhFSH) is composed of alpha and beta subunits which are bound together in a non-covalent association of high affinity without interchain disulfide bonds or covalent bonds. The alpha subunit is common to all four members of a glycoprotein hormone family, including pituitary luteinizing hormone (LH), pituitary thyroid stimulating hormone (TSH) and placental human chorionic gonadotropin (hCG). The amino acid sequences for the beta subunit, which determines the specific biological properties of the heterodimer, are different among the four glycoprotein hormones.

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41	Leu-Arg-Ser-Lys-Lys-Thr-Met-Leu-Val-Gln	50
51	Lys- <u>Asn</u> -Val-Thr-Ser-Glu-Ser-Thr-Cys-Cys	60
61	Val-Ala-Lys-Ser-Tyr-Asn-Arg-Val-Thr-Val	70
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The beta subunit consists of 111 amino acid residues with two carbohydrate moieties linked to amino acid residues (Asn 7 and 24, see underlined amino acid residues below) and six internally cross-linked disulfide bonds.

1	Asn-Ser-Cys-Glu-Leu-Thr- <u>Asn</u> -Ile-Thr-Ile	10
11	Ala-Ile-Glu-Lys-Glu-Glu-Cys-Arg-Phe-Cys	20
21	Ile-Ser-Ile- <u>Asn</u> -Thr-Thr-Trp-Cys-Ala-Gly	30
31	Tyr-Cys-Tyr-Thr-Arg-Asp-Leu-Val-Tyr-Lys	40
41	Asp-Pro-Ala-Arg-Pro-Lys-His-Gln-Lys-Thr	50
51	Cys-Thr-Phe-Lys-Glu-Leu-Val-Tyr-Glu-Thr	60
61	Val-Arg-Val-Pro-Gly-Cys-Ala-His-His-Ala	70
71	Asp-Ser-Leu-Tyr-Thr-Tyr-Pro-Val-Ala-Thr	80
81	Gln-Cys-His-Cys-Gly-Lys-Cys-Asp-Ser-Asp	90
91	Ser-Thr-Asp-Cys-Thr-Val-Arg-Gly-Leu-Gly	100
101	Pro-Ser-Tyr-Cys-Ser-Phe-Gly-Glu-Met-Lys	110
111	Glu	

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17. RELATED/SUPPORTING DOCUMENTS:

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	III			3	Adequate	19-OCT-2000	By D. Lin
	III				3	Adequate and adequate, respectively	31-JAN-2003 and 16-FEB-2000, respectively

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-582	Follistim (follitropin beta for injection)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	<i>Not Applicable</i>		
EES	Ongoing by Compliance		
Pharm/Tox	<i>Not Applicable</i>		
Clin.Pharm.	<i>Not Applicable</i>		
LNC	<i>Not Applicable</i>		
Methods Validation	Package will be submitted to FDA labs after test methods are finalized.		
DMETS	Recommended changes to the container labeling	7-MAY-2003	A. Mahmud
EA	<i>Not Applicable</i>		

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Microbiology	Recommended "Approval"	8-JAN-2001	B. Riley
CDRH	Recommended "Approval"	11-APR-2003	V. Nakayama

Appears This Way
On Original

The Chemistry Review for NDA 21-211

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry recommendation for NDA 21-211 is "APPROVABLE" pending satisfactory labeling and GMP status.

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

None

II. Summary of Chemistry Assessments

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

Drug product –

- Name: Follistim AQ® (follitropin beta injection) Cartridge
- Strength: 300 IU and 600 IU
- Dosage form: aqueous solution for subcutaneous injection
- Pharmacological category: Follicle stimulating hormone (FSH), recombinant
- Formulation - Inactive ingredients are sucrose NF, sodium citrate dihydrate USP, polysorbate 20 NF, benzyl alcohol NF, L-methionine USP, 0.1 N hydrochloric acid or sodium hydroxide NF, and water for injection USP.
- Packaging: The primary container/closure system for the drug product is a _____ tubing glass cartridge. At one end, the cartridge barrel is closed with a _____ rubber piston. At the other end, the cartridge barrel is closed by a flat rubber inlay, which is secured in place by an aluminum crimp-cap. The sealed cartridge is intended to fit into a Becton-Dickinson pen-injector, which features an adjustable dosing system for administering the drug (refer to the review of the pen-injector by the Center for Devices and Radiological Health). The secondary packaging configuration of the drug product is as follows: the sealed and labeled cartridge is packaged in a _____ plastic tray, which is then sealed with a lidding material. The sealed tray and a carton containing 7 needles are packaged together in an outer carton. The Becton-Dickinson pen-injector is packaged separately from the cartridge and needles, for separate commercial distribution.

Drug substances – follitropin beta



Executive Summary Section

- The drug substance is a human follicle-stimulating hormone (hFSH), which is manufactured by recombinant DNA (rDNA) technology. This glycoprotein hormone has a dimeric structure containing two glycoprotein subunits (alpha and beta). Both the 92 amino acid alpha-chain and the 111 amino acid beta-chain have complex heterogeneous structures arising from two N-linked oligosaccharide chains. Follitropin beta is synthesized in a Chinese hamster ovary (CHO) cell line that has been transfected with a plasmid containing the two subunit DNA sequences encoding for hFSH. The purification process results in a highly purified preparation with a consistent hFSH isoform profile and high specific activity (as determined by the Ph. Eur. test for FSH *in vivo* bioactivity and on the basis of the molar extinction coefficient at 277 nm ($\epsilon_{277} = \text{mg}^{-1} \text{cm}^{-1}$) = 1.066. The biological activity is determined by measuring the increase in ovary weight in female rats. The intrinsic luteinizing hormone (LH) activity in follitropin beta is less than 1 IU per 40,000 IU FSH. The compound is considered to contain no LH activity. 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.
- Reference is made to Drug Master File — for all chemistry reviews of the drug substance. The DMF is adequate as of the last review dated 3-JUL-2002, by D. Lin. No amendment has been submitted since the last review.

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

- Dosage administration: subcutaneous injection
- Dosing schedule: as determined by physician; maximum daily dose is 600 IU
- Dosage strength: 300 IU and 600 IU
- Expiry: — months at 2-8 °C, protected from light, OR — months at 2-8 °C + — months at 25 °C, protected from light (based on — month data at 5 °C for three production batches of each dosage strength and — month data at 25 °C/60% RH for one production batch of each dosage strength; both dosage strengths are filled from the same final blend, with the same concentrations of active and inactive ingredients).

C. Basis for Approvability or Not-Approval Recommendation

- A recommendation for approval was obtained from Microbiology on 8-JAN-2001 (see reviews in DFS).
- A recommendation for approval was obtained from CDRH for the pen injector on 11-APR-2003 (see reviews in DFS). However, CDRH does not accept any — claim or any other superiority claim for this device. This issue will be addressed in the labeling review by the division.



CHEMISTRY REVIEW



Executive Summary Section

- A recommendation for approval was obtained from the Office of Combination Products on 7-MAY-2003 (see attached memo) on the issue of packaging the product cartridge and the pen injector in the same secondary container. The Office determined by such co-packaging is not necessary even though the pen injector was approved specifically under this NDA. However, the Office recommends that the device labeling clearly indicate that the device is specifically indicated for use in administering this specific product cartridge. This issue will be addressed in the labeling review by the division.
- A final recommendation is pending from FDA Compliance. The following establishments have not received any recommendation from the Office of Compliance (all foreign sites- delayed because of foreign travel restrictions):

- 
3. CFN 9612716: Organon Ireland Ltd., Swords, Ireland (Drug product packager and release tester)
 4. CFN 9610342: Organon NV, 5340-BH, Oss, Netherlands (Drug substance release tester)

- A recommendation on changes to the container labeling was obtained from the Office of Drug Safety on 7-MAY-2003. The issues will be addressed in the labeling review by the division.
- The chemistry recommendation is approvable pending satisfactory resolution of issues delineated above as well as the following:
 - Labeling revisions (package insert and container labels) that were discussed in the 20-NOV-2000 amendment should be implemented and the revised labeling submitted. These revisions were committed by the applicant in the 20-NOV-2000 amendment and found to be acceptable in Chem. Review #2. However, the latest labeling submission dated 20-DEC-2002 does not include these revisions. This deficiency was conveyed to the applicant in a Discipline Review letter dated 14-MAY-2003.
- Note: The revised drug product specification should be submitted and include all revisions committed by the applicant in the 19-MAY-2003 amendment and found to be acceptable in this Chem. Review #3.

III. Administrative

A. Reviewer's Signature

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B. Endorsement Block

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C. CC Block

Electronically captured in DFS

13 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Suong Tran
5/30/03 11:14:59 AM
CHEMIST

David T. Lin
5/30/03 11:29:20 AM
CHEMIST
I concur.

NOV 27 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA #: 21-211

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 27-NOV-2000

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	31-JAN-00	31-JAN-00	04-FEB-00
Amendment	27-OCT-00	30-OCT-00	
Amendment	27-OCT-00	31-OCT-00	
Amendment	20-NOV-00	21-NOV-00	

NAME & ADDRESS OF SPONSOR:

Organon Inc.
375 Mt. Pleasant
West Orange, NJ 07052

DRUG PRODUCT NAME:

Proprietary:

Nonproprietary/Established/USAN:

Code Name/#:

Chem. Type/Ther. Class:

Follistim AQ Cartridge
Follitropin beta injection
Org 32489
3S

PHARMACOLOGICAL CATEGORY/INDICATION:

Hormone, stimulating multiple ovarian follicular growth/Development of multiple follicles in ovulatory patients participating in a Assisted Reproductive Technology program and induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and is not due to a primary ovarian failure

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

DISPENSED:

SPECIAL PRODUCTS:

Aqueous solution for injection in cartridge
300 IU and 600 IU FSH activity per cartridge
Subcutaneous (SC) injection
 Rx OTC
 Yes No

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

See page 3.

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
NDA 20-582	Follistim (follitropin beta for injection)	Organon, Inc.	Approved 9/29/97	12/5/96,	N/A
DMF	Recombinant follicle stimulating hormone		Adequate; Reviewed by D.T. Lin	10/18/00	N/A
DMF			Adequate; Reviewed by D.T. Lin	10/18/00	N/A

DMF		Withdrawn*		N/A
DMF		Adequate; Reviewed by S.K. De and J. Sieczkowski	5/25/99 2/16/00	N/A

*This DMF is not relevant to this NDA and was withdrawn by the sponsor (10/27/00 amendment).

RELATED DOCUMENTS:

none

PATENT STATUS:

See Chemistry Review #1.

CONSULTS:

1. The EER was sent to the Office of Compliance on March 31, 2000. An overall withhold recommendation was issued on November 17, 2000 (see Appendix A).
2. The Microbiology Staff has been consulted for review of the Microbiology section. The review is pending.
3. Assessment of the injector pen has been consulted to the Center for Devices and Radiological Health. CDRH has recommended that the device not be approved for the proposed use (see CDRH review by Von Nakayama dated 11/6/00).

REMARKS/COMMENTS:

The October 27, 2000 amendment contains an amended letter of authorization for DMF

The October 27, 2000 amendment contains a request to withdraw DMF. This DMF is not relevant to this NDA.

The November 20, 2000 amendment contains the sponsor's response to the November 14, 2000 Discipline Review Letter.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is not approvable based on the recommendation from CDRH. Furthermore, satisfactory resolution of the issues delineated in the draft letter, satisfactory reviews from Microbiology, and satisfactory inspection reports from the Office of Compliance, are required before this NDA may be approved.

cc:

- Orig. NDA #21-211
- HFD-580/Division File
- HFD-580/EDeguia
- HFD-580/MRhee/DLin

WML 11/27/00

David T. Lin 11/27/00
David T. Lin, Ph.D.
Review Chemist

R/D Init by:
filename: nda21211.2 (doc)

/s/

David T. Lin
11/27/00 01:05:27 PM
CHEMIST

Moo-Jhong Rhee
11/29/00 03:38:42 PM
CHEMIST

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6 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-3

NOV 27 2000

Summary of Chemistry Review of NDA 21-211

A. Drug Substances:

Follitropin beta is a recombinant version of the human follicle stimulating hormone (FSH) genetically engineered from Chinese Hamster Ovary (CHO) cells and was previously approved for NDA 20-582. Since the approval of the NDA, there has been no significant manufacturing changes occurred in the NDA. It is manufactured, packaged, and tested by [redacted]. The facility is in compliance with cGMP.

The quality of follitropin beta is adequately controlled by extensive specifications and limits, which are appearance, color, molecular size, PI distribution, peptide mapping, biological in-vitro testing, water content, clarity of solution in water, pH of solution in water, content of CHO-derived proteins, content of FCS-derived proteins, content of bovine transferrin, content of porcine insulin, content of DNA, aerobic viable count, bacterial endotoxins, mycoplasma, biological in-vivo activity, and biological in-vivo fiducial limits.

B. Drug Product:

The drug products are pre-filled cartridges which are new aqueous versions of the previously approved lyophilized powder product (NDA 20-582), Follistim. The cartridge with either 0.525ml (300 IU) or 0.885ml (600 IU) contains sucrose, NF [redacted], sodium citrate dihydrate, USP ([redacted]), polysorbate 20, NF [redacted], benzyl alcohol, NF [redacted], L-methionine [redacted].

The pre-filled cartridges are manufactured by Vetter Pharma-Fertigung GmgH & Co. KG; packaged and tested by Organon Ltd (Ireland); testing is also to be done by Organon Inc (West Orange, NJ); and secondary packaging is to be done by Organon Inc (Allentown, PA). Bio-assay has been conducted by [redacted]; Sterility and bacterial endotoxins have been tested by Vetter Pharma-Fertigung GmgH & Co. KG. Organon Inc. in West orange, NJ is not in compliance with cGMP. The Office of Compliance sent a warning letter to the firm and made an overall recommendation of "Withhold".

The quality of the drug product was controlled by specifications including appearance, color, clarity, pH, extractable volume, particulate matter, identification, assays, subunit content, oligomer content, total oxidation, L-methionine content, benzyl alcohol content, bacterial endotoxins, and sterility. The sponsor's proposed release specification for oxidation products (calculated by oxidized subunits) is not acceptable. In addition, the sponsor's proposed shelf-life specifications for subunit content, oxidation products (calculated by oxidized subunits), and benzyl alcohol content are not acceptable.

The aqueous product is packaged into a [redacted] tubing glass barrel having a [redacted] rubber piston [redacted] at one end and the other end is closed by a flat rubber inlay [redacted] which is secured by an aluminum crimp cap [redacted]. Based on all available information from the suppliers of each component, it is considered to be adequate to protect the drug product during the shelf-life. This cartridge is to be fit into a pen-injector (Becton Dickinson). Since the pen-injector is a dedicated device for this cartridge, it must be co-packaged with the cartridges, but no adequate information is available as to how they are co-packaged.

The Becton-Dickinson pen-injector has been reviewed by CDRH and "Not Approval" of this device was recommended for various reasons.

Based on the available real time data up to 24 months from three full-scale production batches, an expiry date of 24-month is granted

The tradename, Follistim AQ, was accepted by OPDR.

C. Conclusion and Recommendation:

From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA is **not approvable** due to inadequacy of the pen-injector for the safe and effective use of the drug product. Furthermore, several issues noted in the Chemistry Review #2 including Microbiology issues and inspection reports also have to be resolved before this NDA can be approved.

 11/27/00

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

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2 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-4

DMF			Withdrawn*		N/A
DMF			Adequate; Reviewed by S.K. De and J. Sieczkowski	5/25/99 2/16/00	N/A

*This DMF is not relevant to this NDA and will be withdrawn by the sponsor.

RELATED DOCUMENTS:

none

PATENT STATUS:

Patent No.	Type	Expiration	Patent Owner
5,929,028	Drug product formulation	4/18/2018	Akzo Nobel N.V.
4,589,402	Method of use	7/26/2004	Serono Laboratories, Inc.
5,767,251	Drug product	6/16/2015	Genzyme Corp.

CONSULTS:

1. The EER was sent to Compliance on March 31, 2000 (the overall recommendation is pending; see Appendix A).
2. The proposed trademark, Follistim AQ Cartridge, was consulted to OPDRA and determined to be acceptable (see reviews dated August 4 and November 5, 2000).
3. The Microbiology Staff has been consulted for review of the Microbiology section. The review is pending.
4. Assessment of the injector pen has been consulted to the Center for Devices and Radiological Health.

REMARKS/COMMENTS:

Follistim AQ (follitropin beta for injection) Cartridge is a sterile drug product solution containing human follicle-stimulation hormone (hFSH). This glycoprotein is manufactured by recombinant DNA technology. Follitropin beta has a dimeric structure containing two glycoprotein subunits (alpha and beta). Both the 92 amino acid alpha-chain and the 111 amino acid beta-chain have complex heterogeneous structures arising from two N-linked oligosaccharide chains. Follitropin beta is synthesized in a Chinese hamster ovary (CHO) cell line that has been transfected with a plasmid containing the two subunit DNA sequences encoding for hFSH. The drug product solution contains as inactive ingredients, sucrose, sodium citrate, polysorbate 20, benzyl alcohol and L-methionine. The pH of the solution is adjusted to pH 7. The polysorbate 20 functions to reduce the adsorption of the drug substance protein to the walls of the glass cartridge container. The function of L-methionine is to reduce the amount of oxidized protein by acting as an antioxidant. Benzyl alcohol serves as an antimicrobial agent. This product is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program. It is also indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

The May 9, 2000 amendment contains an additional copy of the package insert, cartridge labels and carton labels for review by OPDRA.

NDA #21-211

Sponsor: Organon, Inc.

Drug: Follistim AQ Cartridge
(follitropin beta for injection)

The September 26, 2000 amendment contains instruction manual for the pen injector.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending satisfactory resolution of the issues delineated in the draft letter, satisfactory reviews from Microbiology and CDRH, and satisfactory inspection reports from the Office of Compliance.

cc:

Orig. NDA #21-211
HFD-580/Division File
HFD-580/EDegua
HFD-580/MRhee/DLin

MLC 10/31/00

David T. Lin

10/30/00

David T. Lin, Ph.D.
Review Chemist

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 § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry 6

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

Methods Validation

The analytical methods for only the drug product will be sent to the district laboratories for validation. Please see Chemistry Review, Page 24.