

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-273

CHEMISTRY REVIEW(S)

NDA 21-273

Follistim AQ (follitropin beta injection)

Organon Inc.

Suong Tran, PhD
Division of Reproductive and Urologic Drug Products

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Chemistry Review Data Sheet

1. NDA 21-273
2. REVIEW #: 4
3. REVIEW DATE: 14-JUL-2005
4. REVIEWER: Suong Tran PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	24-JUL-2000
Amendment	31-OCT-2000
Amendment	13-MAR-2001
Amendment	20-APR-2001
Amendment	3-MAY-2001
Amendment	3-MAY-2001
Amendment	8-MAY-2001
Amendment	16-MAY-2001
Amendment	17-OCT-2002
Amendment	21-FEB-2003
Amendment	4-MAR-2003
Amendment	26-MAR-2003
Amendment	28-MAR-2003
Amendment	9-APR-2003
Amendment	11-APR-2003
Amendment	29-APR-2003
Amendment	30-APR-2003
Approvable Letter	17-JUL-2003
Amendment	19-NOV-2004
Amendment	21-MAR-2005
Approvable Letter	17-MAY-2005

CHEMISTRY REVIEW

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Amendment

Document Date
24-JUN-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Organon Inc.

Address: 56 Livingston Avenue, Roseland NJ 07068

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: N/A

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

11. DOSAGE FORM: Aqueous solution for injection

12. STRENGTH/POTENCY: 75 IU or 150 IU FSH activity
per 0.5 mL/vial

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: Rx OTC

Chemistry Review Data Sheet

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

 x SPOTS product x 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.

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- <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	

CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT
1	II	[Redacted]	[Redacted]	3	Adequate	3-JUL-2002	
	III			3	Adequate	27-MAR-2001	
	III			3	Adequate	24-MAY-2004	

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	"Acceptable"	11-JUL-2005	S. Adams
Pharm/Tox	<i>Not Applicable</i>		
Clin.Pharm.	<i>Not Applicable</i>		
LNC	<i>Not Applicable</i>		
Methods Validation	<i>Not Applicable</i>		
EA	<i>Not Applicable</i>		
Microbiology	"Approval"	19-APR-2005	B. Riley

The Chemistry Review for NDA 21-273

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is Approval.

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

None

II. Summary of Chemistry Assessments

- This review is an assessment of the applicant's response to the Approvable letter dated 17-MAY-2005. The Approvable letter had one single deficiency: the "withhold" recommendation from the Office of Compliance for the manufacturing site of the drug product (Organon Ireland, Ltd. in Swords, Ireland).

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

Drug product –

- Name: Follistim AQ (follitropin beta injection)
- Strength: 75 IU or 150 IU per 0.5 mL/vial
- Dosage form: aqueous solution for subcutaneous injection
- Pharmacological category: Human follicle stimulating hormone (FSH), recombinant
- Formulation - Inactive ingredients are sucrose NF, sodium citrate 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 type I tubing glass vial with a rubber stopper.
- Stability: Acceptable stability data are provided for the U.S.-to-be-marketed 75 IU up to 24 months at 5 °C and 25 °C, ~~and for the U.S.-to-be-marketed 150 IU up to 24 months at 5 °C and 25 °C.~~

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 ($\epsilon_{277} = 1.066 \times 10^6 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$). 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: 75 IU or 150 IU per 0.5 mL/vial
- Expiry: 36 months at 2-8 °C, protected from light, OR 33 months at 2-8 °C + 3 months at 25 °C, protected from light.

C. Basis for Approvability or Not-Approval Recommendation

- A recommendation for approval was filed by Microbiology on 19-APR-2005 (see review in DFS).
- The labeling submitted in the current 24-JUN-2005 amendment is acceptable. It only differs from the previous 21-MAR-2005 labeling (found acceptable in the Chem. Review #3) in the change in the corporate address of the applicant.
- A final recommendation is "Acceptable" from the Office of Compliance on 11-JUL-2005.

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

3 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

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
7/22/05 09:27:15 AM
CHEMIST

paper sign-off 7/15/05

Moo-Jhong Rhee
7/22/05 12:26:14 PM
CHEMIST
I concur

NDA 21-273

Follistim AQ (follitropin beta injection)

Organon Inc.

Suong Tran, PhD
Division of Reproductive and Urologic Drug Products

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Chemistry Review Data Sheet

1. NDA 21-273
2. REVIEW #: 3
3. REVIEW DATE: 05-MAY-2005
4. REVIEWER: Suong Tran PhD

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	24-JUL-2000
Amendment	31-OCT-2000
Amendment	13-MAR-2001
Amendment	20-APR-2001
Amendment	3-MAY-2001
Amendment	3-MAY-2001
Amendment	8-MAY-2001
Amendment	16-MAY-2001
Amendment	17-OCT-2002
Amendment	21-FEB-2003
Amendment	4-MAR-2003
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Amendment	28-MAR-2003
Amendment	9-APR-2003
Amendment	11-APR-2003
Amendment	29-APR-2003
Amendment	30-APR-2003
Approvable Letter	17-JUL-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	19-NOV-2004

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Amendment

21-MAR-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Organon Inc.

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

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: N/A

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

11. DOSAGE FORM: Aqueous solution for injection

12. STRENGTH/POTENCY: 75 IU or 150 IU FSH activity per 0.5 mL/vial

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: Rx OTC

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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.

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- <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	

CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT
1	II	[Redacted]	[Redacted]	3	Adequate	3-JUL-2002	
1	III			3	Adequate	27-MAR-2001	
1	III			3	Adequate	24-MAY-2004	

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	"Withhold"	05-MAY-2005	R. Woods
Pharm/Tox	<i>Not Applicable</i>		
Clin.Pharm.	<i>Not Applicable</i>		
LNC	<i>Not Applicable</i>		
Methods Validation	<i>Not Applicable</i>		
EA	<i>Not Applicable</i>		
Microbiology	"Approval"	19-APR-2005	B. Riley

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 ($\epsilon_{277} = 1.066 \text{ mg}^{-1} \text{ cm}^{-1}$). 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 [redacted] 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: 75 IU or 150 IU per 0.5 mL/vial
- Expiry: 36 months at 2-8 °C, protected from light, OR 33 months at 2-8 °C + 3 months at 25 °C, protected from light.

C. Basis for Approvability or Not-Approval Recommendation

- A recommendation for approval was filed by Microbiology on 19-APR-2005 (see review in DFS).
- The labeling submitted in the 21-MAR-2005 amendment is acceptable (revised as FDA requested).

Executive Summary Section

- A final recommendation is "Withhold" from the Office of Compliance on 05-MAY-2005. The manufacturing site of the drug product, Organon Ireland in Swords, Ireland, is currently in violation of GMP.
- The final recommendation from Chemistry is approvable pending a satisfactory recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

11 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

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
5/5/05 03:17:25 PM
CHEMIST

Moo-Jhong Rhee
5/5/05 03:28:44 PM
CHEMIST
I concur

NDA 21-273

Follistim® AQ (follitropin beta injection)

Organon Inc.

**David T. Lin, Ph.D.
Division of Reproductive and Urologic Drug Products (HFD-
580)**



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Chemistry Review Data Sheet

1. NDA 21-273
2. REVIEW #: 2
3. REVIEW DATE: 16-July-2003
4. REVIEWER: David T. Lin, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Original
Amendment
Amendment
Amendment
Amendment

Document Date

24-JUL-2000
31-OCT-2000
13-MAR-2001
20-APR-2001
03-MAY-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment (BC)
Amendment (BC)
Amendment (BC)
Amendment (AZ) [Response to Approvable Letter]
Amendment (BC)
Amendment (BC)
Amendment (BC)
Amendment (C)
Amendment (C)
Amendment (AC)
Amendment (BC)
Amendment (BC)

Document Date

03-MAY-2001
08-MAY-2001
16-MAY-2001
17-OCT-2002
21-FEB-2003
04-MAR-2003
26-MAR-2003
28-MAR-2003
09-APR-2003
11-APR-2003
29-APR-2003
30-APR-2003

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Organon Inc.
Address: 375 Mt. Pleasant Avenue
West Orange, NJ 07052
Representative: N/A
Telephone: 973-325-4921

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Hormone, development of multiple follicles in ovulatory patients participating in a Assisted Reproductive Technology program and induction of ovulation in anovulatory infertile patients in whom the cause of infertility is functional and is not due to a primary ovarian failure

11. DOSAGE FORM: Injection, Solution

12. STRENGTH/POTENCY: 75 IU, 150 IU,

13. ROUTE OF ADMINISTRATION: Subcutaneous (SC) injection

14. Rx/OTC DISPENSED: x Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

SPOTS product – Form Completed

Not a SPOTS product

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

See page 8

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	2	/		3	Adequate	7/3/02	Reviewed by Dr. D.T. Lin
	3		3	Adequate	4/27/01	Reviewed by Dr. D.T. Lin	
	3		3	Adequate	4/27/01	Reviewed by Dr. D.T. Lin	
	3		3	Adequate	5/25/99 2/16/00	Reviewed by S.K. De and J. Sieczkowski	

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
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CHEMISTRY REVIEW



Chemistry Review Data Sheet

Original NDA	NDA 20-582	Organon's approved NDA for Follistim® [follitropin beta (rDNA origin) for injection]; approved 9/29/97
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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Withhold	7/15/03	Randall Woods
Pharm/Tox	N/A		
Biopharm	Acceptable	See Chem. Rev. #1	Venkat Jarugula, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated	5/4/01 See Chem. Rev. #1	David Lin, Ph.D.
DMETS	Acceptable Acceptable	8/1/00 3/19/03	Alina R. Mahmud, R.Ph.
EA	Categorical exclusion granted	5/4/01 See Chem. Rev. #1	David Lin, Ph.D.
Microbiology	Acceptable See Micro Rev. #3	4/10/03	David Hussong, Ph.D.



Chemistry Review Data Sheet

Structure:

Recombinant human luteinizing hormone (rhLH) 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 follicle stimulating hormone (FSH), 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 and bolded amino acid residues below) and five internally cross-linked disulfide bonds. The molecular weight is estimated to be approximately 23,000 dalton.

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- Asn -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- Asn -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 121 amino acid residues with one glycosylation site (Asn 30, see underlined and bolded amino acid residue below) and six internally cross-linked disulfide bonds. The molecular weight is estimated to be approximately 18,000 dalton.

1	Ser-Arg-Glu-Pro-Leu-Arg-Pro-Trp-Cys-His	10
11	Pro-Ile-Asn-Ala-Ile-Leu-Ala-Val-Glu-Lys	20
21	Glu-Gly-Cys-Pro-Val-Cys-Ile-Thr-Val- Asn	30
31	Thr-Thr-Ile-Cys-Ala-Gly-Tyr-Cys-Pro-Thr	40
41	Met-Met-Arg-Val-Leu-Gln-Ala-Val-Leu-Pro	50
51	Pro-Leu-Pro-Gln-Val-Val-Cys-Thr-Tyr-Arg	60
61	Asp-Val-Arg-Phe-Glu-Ser-Ile-Arg-Leu-Pro	70
71	Gly-Cys-Pro-Arg-Gly-Val-Asp-Pro-Val-Val	80
81	Ser-Phe-Pro-Val-Ala-Leu-Ser-Cys-Arg-Cys	90
91	Gly-Pro-Cys-Arg-Arg-Ser-Thr-Ser-Asp-Cys	100
101	Gly-Gly-Pro-Lys-Asp-His-Pro-Leu-Thr-Cys	110
111	Asp-His-Pro-Gln-Leu-Ser-Gly-Leu-Leu-Phe	120
121	Leu	

The Chemistry Review for NDA 21-273

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From chemistry, manufacturing, and controls point of view, this NDA is **Approvable**. The sponsor's West Orange, NJ facility will need to be in cGMP compliance before an approval recommendation can be issued. In addition, all relevant facilities in the application need to remain in cGMP compliance.

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

N/A

II. Summary of Chemistry Assessments

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

This review is an assessment of the sponsor's response to the Agency's approvable letter dated October 17, 2002.

Drug Product:

Follistim® AQ is a sterile aqueous solution intended for subcutaneous injection. Each vial contains 75, 150, [REDACTED] IU follitropin beta [recombinant human follicle-stimulating hormone (r-hFSH)] in 0.5 mL volume. 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 [REDACTED]

[REDACTED] The function of L-methionine [REDACTED]
[REDACTED] Benzyl alcohol [REDACTED] The drug product is manufactured as a sterile solution and filled into [REDACTED] Type I glass vials. The vials [REDACTED]

[REDACTED] All manufacturing operations and release testing, except for the bioassay test, are conducted at Organon Inc. in West Orange, NJ. [REDACTED]

[REDACTED] The proposed specifications are acceptable and adequate to control the quality of the product.

The relevant DMFs for the glass vial and rubber stopper have been reviewed and determined to be adequate as a container/closure system for this drug product. In addition, the Microbiology Reviewer has determined the integrity of the container/closure system to be acceptable.



Executive Summary Section

Based on the stability data provided, a 24-month expiration dating period is granted, when stored at 2-8°C. OPDRA has determined that the tradename, Follistim® AQ, is acceptable. In addition, adequate chemistry information is presented in the labeling and labels of primary as well as secondary packaging labels.

Drug Substance:

Human follicle-stimulating hormone (hFSH) is a protein hormone whose pharmacodynamic action stimulates ovarian follicular growth in women. The protein is required for normal follicular growth, maturation and gonadal steroid production.

This glycoprotein is manufactured by recombinant DNA technology. Follitropin beta has a dimeric structure containing two glycoprotein subunits, designated alpha (α) and beta (β). 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.

Physico-chemical characterization of recombinant-hFSH demonstrated that the glycoprotein is highly complex, ~~_____~~

This recombinant glycoprotein ~~_____~~ is manufactured, packaged and tested by ~~_____~~. A letter of authorization has been provided to cross-reference DMF ~~_____~~.

Data have been provided to support the re-test period proposed in the DMF.

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

Follistim® AQ is a sterile solution intended for subcutaneous injection. Each vial of drug product contains 75, 150, ~~_____~~ IU follitropin beta (r-hFSH) in a 0.5 mL volume. Follistim® AQ is administered to patients participating in an Assisted Reproductive Technology (ART) program. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles is induced by administering hCG.

The drug product has an expiration dating period of 24 months when stored under refrigerated conditions (2-8°C). Additionally, the product can be stored at 2-8°C for 21 months plus 3 months of storage at 25°C.

C. Basis for Approvability or Not-Approval Recommendation

Due to sterility assurance issues at the sponsor's West Orange, NJ drug product manufacturing facility the District Office recommended a **withhold** on the basis of non-compliance with cGMP. Therefore, this NDA may not be approved. This facility needs to have a satisfactory inspection report before an approval recommendation can be made.

The first review cycle, completed on May 4, 2001, also resulted in an Approvable recommendation from a CMC point of view, due to non-compliance with cGMP at the West Orange, NJ facility.



Executive Summary Section

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: DLin/
ChemistryTeamLeaderName: DLin/
ProjectManagerName: AReddy

C. CC Block

HFD-580/Division File/NDA 21-273
HFD-580/D.T. Lin, Ph.D.
HFD-580/A. Reddy, M.P.H.

18 Page(s) Withheld

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/s/

David T. Lin
7/16/03 09:37:52 AM
CHEMIST

Summary of Chemistry Review of NDA 21-273

A. Drug Substances:

Follitropin beta is a recombinant version of the human follicle stimulating hormone (FSH) genetically engineered from Chinese Hamster Ovary (CHO) cells by [REDACTED] (DMF [REDACTED]) and was previously approved for NDA 20-582. Although there has been an update on the DMF, it is still adequate to support the NDA. The facility is **in compliance to cGMP**.

B. Drug Product:

Unlike the previously approved Follistim (NDA 20-582), which is in a form of lyophilized powder in vials, the proposed new products are aqueous solutions containing 75 IU, 150IU, [REDACTED] IU in 0.5 ml filled in [REDACTED] vials. This solution version has L-methionine in the formulation as an antioxidant to stabilize the protein in solution. Each strength of the product has sucrose (25mg), sodium citrate dihydrate (7.35mg), polysorbate 20 (0.1mg), L-methionine (0.25mg), and water for injection (to 0.5ml).

The drug products are manufactured by Organon Inc., West Orange, NJ, packaged by Organon Inc., Allentown, PA, and tested for quality controls by three facilities: Organon Inc., West Orange, NJ; N.V. Organon, Netherlands; and [REDACTED]. All, but **Organon, Inc., West Orange, NJ, are in compliance to CGMP**.

Organon, Inc. West Orange, NJ received a Warning Letter from the Agency due to serious cGMP violations and this resulted in an overall recommendation of **"Withhold"** for this application.

The quality of the product is controlled by specifications such as appearance, color, clarity, pH, extractable volume, particulate matter, identification (in-vivo assay), assay, subunit content, [REDACTED] content, total oxidation, L-methionine content, bacterial endotoxins, and sterility. According to the Microbiologist's review, **sterility assurance is not adequately established** and this should be clarified before approval of the application.

The proposed acceptance criteria for "total oxidation" is based on the sum of oxidized alpha and beta subunits, [REDACTED]

Stability studies show that the amount of L-methionine decreased to not less than [REDACTED] of the label claim, therefore, the **proposed acceptance criteria should be revised to [REDACTED]**. Since the amount of methionine is important for the stability of the drug product, this should be clarified, unless justified.

The acceptance criteria for the subunit during stability studies **should be revised to [REDACTED] unless justified.**

[REDACTED]

Based on primary and supporting stability data, the proposed shelf-life of _____ is not acceptable, _____ can be granted, during which it can be stored at controlled room temperature (25°C) for up to three months.

One of the statements in the stability protocol has to be revised so that the product can be stored at room temperature for 3 months **only after** being stored at 2-8°C so that the patients can store the drug product at room temperature after being dispensed from a pharmacy. The current statement says it can be stored at room temperature for 3 months either prior to or after storage at 2-8°C.

The tradename, **Follistim AQ Vial** was accepted by OPDRA, but there are several pending labeling issues including labels for container and carton.

C. Conclusion and Recommendation:

From chemistry, manufacturing, and controls point of view, as the primary reviewer recommends, this NDA is **approvable** pending resolution of the following issues:

1. Revision of acceptance criteria for total oxidation products, L-methionine, and subunit content during the stability studies.
2. Revision of the storage statement in the stability protocol
3. Reduction of expiration date of the drug product from _____
4. Sterility assurance of the product
5. Satisfactory inspection results for Organon facility at West Orange, NJ
6. Revision of labeling (Description and How Supplied sections) as well as labels of container and carton

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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/s/

Moo-Jhong Rhee
5/22/01 09:59:02 AM
CHEMIST

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

NDA #: 21-273

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 04-MAY-2001

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	24-JUL-00	25-JUL-00	26-JUL-00
Amendment	31-OCT-00	01-NOV-00	
Amendment	13-MAR-01	14-MAR-01	
Amendment	20-APR-01	23-APR-01	
Amendment	03-MAY-01	04-MAY-01	

NAME & ADDRESS OF SPONSOR:

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

DRUG PRODUCT NAME:

Proprietary: Follistim AQ Vial
Nonproprietary/Established/USAN: Follitropin beta injection
Code Name/#: Org 32489
Chem.Type/Ther.Class: 3S

PARMACOLOGICAL 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:

Aqueous solution for injection in vial

STRENGTHS:

75, 150, _____ IU FSH activity per 0.5 mL (vial)

ROUTE OF ADMINISTRATION:

Subcutaneous (SC) injection

DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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

See page 4

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	_____		Adequate; Reviewed by D.T. Lin	10/18/00	N/A

DMF		Adequate; Reviewed by D.T. Lin	4/27/01	N/A
DMF		Adequate; Reviewed by D.T. Lin	4/27/01	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:

See Chemistry Reviews for NDA 21-211 (Follistim AQ Cartridge).

PATENT STATUS:

[Redacted content]

CONSULTS:

1. The EER was sent to Compliance on September 30, 2000. An overall **withhold** recommendation was issued on October 30, 2000 (see Appendix A).
2. The proposed trademark, Follistim AQ Vial, was consulted to OPDRA and determined to be acceptable (see review dated October 5, 2000). However, some recommendations were made to minimize potential user error (see Labeling section).
3. The Microbiology Staff has been consulted for review of the Microbiology section. The review is pending (see Microbiology Review by Dr. D. Hussong dated 3/29/01).

REMARKS/COMMENTS:

Follistim AQ (follitropin beta for injection) Vial 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

The function of L-methionine is [redacted]. Benzyl alcohol [redacted]. 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.

NDA #21-273

Sponsor: Organon, Inc.

Drug: Follistim AQ Vial
(follitropin beta for injection)

The October 31, 2000 amendment contains the sponsor's response to Microbiology deficiencies.

The March 13, 2001 amendment contains a corrected letter of authorization for DMF. _____

The April 20, 2001 amendment contains the sponsor's response to Microbiology deficiencies.

The May 3, 2001 amendment contains updated stability data. _____

CONCLUSIONS & RECOMMENDATIONS:

From a Chemistry, Manufacturing and Controls point of view this NDA is approvable. The NDA may be approved pending satisfactory resolution of the issues delineated in the draft letter, satisfactory reviews from Microbiology, and satisfactory inspection reports from the Office of Compliance.

cc:

Orig. NDA #21-273
HFD-580/Division File
HFD-580/DSpell-LeSane
HFD-580/MRhee/DLin

David T. Lin, Ph.D.
Review Chemist

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/s/

David T. Lin

5/4/01 04:31:48 PM

CHEMIST

Chemistry Review #1 of original NDA; Approvable from CMC point of view

Moo-Jhong Rhee

5/7/01 03:11:02 PM

CHEMIST

I concur