

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-273

MICROBIOLOGY REVIEW

Product Quality Microbiology Review

Review for HFD-580

11 APRIL 2005

NDA: 21-273 (resubmission) and Amendment (dated 28 March 2005)

Drug Product Name

Proprietary: Follistim AQ

Non-proprietary: follitropin beta for injection

Drug Product Priority Classification: P

Review Number: 4

Subject of this Review

Submission Dates: 19 November 2004 and 28 March 2005

Receipt Date: 22 November 2004

Consult Date: 1 December 2004

Date Assigned for Review: 16 December 2004

Submission History

**Date(s) of Previous Submission(s): 21 July 2000, 20 April 2001,
29 October 2002**

**Date(s) of Previous Micro Review(s): 29 March 2001, 15 May 2001,
10 April 2003**

Applicant/Sponsor

Name: Organon USA, Inc.

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

Representative: Albert P. Mayo

Telephone: 973-325-4833

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval with a comment for the Applicant (see Section H. "List of Microbiology Deficiencies and Comments" on page 8)

Executive Summary**I. Recommendations**

- A. Recommendation on Approvability** – This submission is recommended for approval on the basis of product quality microbiology. Please see comment for applicant at the end of this review (Section H. on page 8)
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is _____
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
David Hussong, Ph.D. (Microbiology Supervisor)
- C. CC Block**
N/A

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/s/

Bryan Riley
4/18/05 12:40:44 PM
MICROBIOLOGIST

David Hussong
4/19/05 08:18:58 AM
MICROBIOLOGIST

Product Quality Microbiology Review

Review for HFD-580

10 April 2003

NDA: 21-273

Drug Product Name

Proprietary: Follistim® AQ

Non-proprietary: follitropin beta injection

Drug Product Classification: Standard

Review Number: 3

Subject of this Review

Submission Date: 17 OCT 2003

Receipt Date: 29 OCT 2002

Consult Date: 29 OCT 2002

Date Assigned for Review: 07 NOV 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): 21 JUL 2000 and 20 APR 2001

Date(s) of Previous Micro Review(s): 29 Mar 2001 and 15 MAY 2001

Applicant/Sponsor

Name: Organon, Inc

**Address: 375 Mt Pleasant Ave
Orange, NJ 07052**

Representative: John Leach

Telephone: (973)325-4706

Name of Reviewer: David Hussong

Conclusion: APPROVE

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUPPLEMENT:** N/A (this is an amendment to an original NDA)
 2. **SUPPLEMENT PROVIDES FOR:** N/A
 3. **MANUFACTURING SITE:** The drug is manufactured by _____
in the Sterile Production Area at:
Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** The drug product is a recombinant protein in an aqueous solution of 0.5 mL volume, contained in a _____ glass vial closed with a rubber stopper and an aluminum seal. This solution is for subcutaneous or intramuscular injection. The NDA covers strengths from 75 IU _____ Each vial of Follistim-AQ contains 75, 150, _____ IU of follicle stimulating factor FSH activity.
 5. **METHOD(S) OF STERILIZATION:** _____
 6. **PHARMACOLOGICAL CATEGORY:** Synthetic hormone for inducing or enhancing ovulation.
- B. **SUPPORTING/RELATED DOCUMENTS:** none
- C. **REMARKS:** This is the third microbiology review cycle for the application. Microbiologist's Review #2 produced 4 questions that were forwarded as part of the chemistry deficiencies, (items 6, 7, 8 and 9 of "chemistry").

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Executive Summary**I. Recommendations**

- A. Recommendation on Approvability - APPROVE**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This product is processed under _____ conditions and is the aqueous form of another approved product that is marketed in a _____ . To stabilize the solution, the formulation was modified slightly.**
- B. Brief Description of Microbiology Deficiencies – N/A**
- C. Assessment of Risk Due to Microbiology Deficiencies - none**

III. Administrative

- A. Reviewer's Signature _____**
- B. Endorsement Block**
 - David Hussong/Microbiologist
 - Peter Cooney/Microbiology Supervisor
- C. CC Block**
 - cc:
 - Original NDA 21-273
 - HFD- 580/Division File/NDA 21-273

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Withheld Track Number: Microbiology-2

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/s/

David Hussong
4/11/03 09:50:52 AM
MICROBIOLOGIST

Peter Cooney
4/11/03 01:14:18 PM
MICROBIOLOGIST

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA

May 15, 2001

- A. 1. NDA 21-273
- APPLICANT Organon, Inc.
375 Mount Pleasant Avenue
Orange, NJ 07052
2. PRODUCT NAMES: Folistim® – AQ (recombinant follicle stimulating hormone)
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Glass vial, _____ that is sealed with a rubber stopper, containing 0.5 mL of an aqueous solution for subcutaneous or intramuscular injection. The product is available in strengths of 75 IU, 150 IU, _____ per vial.
4. METHOD(S) OF STERILIZATION: _____
5. PHARMACOLOGICAL CATEGORY: Synthetic hormone for inducing or enhancing ovulation.
6. DRUG PRIORITY CLASSIFICATION: Standard
- B. 1. DATE OF INITIAL SUBMISSION: July 21, 2001 (subject of Microbiologist's Review #1)
2. DATE OF AMENDMENT: April 20, 2001 (subject of this review)
3. RELATED DOCUMENTS: none
4. ASSIGNED FOR REVIEW: May 4, 2001
- C. REMARKS: The NDA provides for an aqueous presentation of an approved product that is _____. The approved product is Follistim, NDA 20-582. NDAs for products manufactured by similar processes at this facility have been approved by reference to previous applications, resulting in no comprehensive review of the facility's _____ processes since 1994 (NDA 20-328).
- Microbiologist's Review #1 resulted in substantial deficiency questions that were conveyed to the applicant in an Information Request Letter (by FAX, April 3, 2001). Additionally, the New Jersey District issued a Warning Letter to the facility on September

19, 2000, containing many microbiology observations, and is the basis of a Compliance recommendation to withhold approval of the NDA. The drug is manufactured by _____

Organon, Inc.
375 Mount Pleasant Avenue
West Orange, NJ

- D. CONCLUSIONS: The application is APPROVABLE. Deficiencies are provided at the end of this review (see "List of Microbiology Deficiencies and Comments"). For detailed information, see section, "E. Review Notes."

David Hussong, Ph.D.

cc: Original **NDA 21-273**
HFD 160/Consult File
HFD 580/Division File
HFD 580/CSO/E. Deguia
HFD 580/Chemist/D. Lin
HFD 805/D. Hussong

Drafted by: D. Hussong, 05/15/2001
R/D initialed by: P. Cooney

Filename, d:\nda\21-273rv2.DOC

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/s/

David Hussong
5/15/01 03:05:48 PM
MICROBIOLOGIST

Peter Cooney
5/16/01 09:23:30 AM
MICROBIOLOGIST

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

March 29, 2001

- A. 1. NDA 21-273
- APPLICANT Organon, Inc.
375 Mount Pleasant Avenue
Orange, NJ 07052
2. PRODUCT NAMES: Folistim® – AQ (recombinant follicle stimulating hormone)
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Glass vial _____ that is sealed with a rubber stopper, containing 0.5 mL of an aqueous solution for subcutaneous or intramuscular injection. The product is available in strengths of 75 IU, 150 IU, _____ per vial.
4. METHOD(S) OF STERILIZATION: _____
5. PHARMACOLOGICAL CATEGORY: Synthetic hormone for inducing or enhancing ovulation.
6. DRUG PRIORITY CLASSIFICATION: Standard
- B. 1. DATE OF INITIAL SUBMISSION: July 21, 2001
2. DATE OF AMENDMENT: none
3. RELATED DOCUMENTS: none
4. ASSIGNED FOR REVIEW: October 20, 2000
- C. REMARKS: The NDA provides for an aqueous presentation of an approved product that is _____. The approved product is Follistim, NDA 20-582. Volumes 5 and 7 were initially sent for review. Additional volumes were needed to enable a complete review. The NDA does not provide information for microbiology in sections that “stand alone” and critical information is found in other sections. Volume 5 contains subsection 2.4 “Sterilization Process Validation” including its Table of Contents. However, the page numbers in the Table of Contents are wrong, and there are no page numbers listed for the Appendices.
- NDA's for products manufactured by similar processes at this facility have been approved by reference to previous applications, resulting in no comprehensive review of the facility's _____ processes since 1994 (NDA 20-328).

- D. CONCLUSIONS: The application is APPROVABLE pending resolution of deficiencies (see "List of Microbiology Deficiencies and Comments"). For detailed information, see section, "E. Review Notes."

David Hussong, Ph.D.

cc: Original **NDA 21-273**
HFD 160/Consult File
HFD 580/Division File
HFD 580/CSO/E. Deguia
HFD 580/Chemist/D. Lin
HFD 805/D. Hussong

Drafted by: D. Hussong, 03/29/2001
R/D initialed by: P. Cooney

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/s/

David Hussong
4/2/01 08:54:11 AM
MICROBIOLOGIST

Peter Cooney
4/2/01 09:47:25 AM
MICROBIOLOGIST