CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-684

CHEMISTRY REVIEW(S)

NDA 21-684

Gonal-f® Pen
(follitropin alfa injection)

Serono, Inc.

Suong Tran, PhD
Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-684

2. REVIEW #: 3

3. REVIEW DATE: 26-APR-2004

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS: Chem. Reviews #1 and #2

6. SUBMISSION(S) BEING REVIEWED:

Submission reviewed	Submission date
Amendment	25-MAR-2004
Amendment	19-APR-2004
Amendment	17-MAY-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Serono Inc.

Address: One Technology Place
Rockland MA 02370

Telephone: 781-681-2273

8. DRUG PRODUCT NAME/CODE/TYPE:
Gonal-f Pen (follitropin alfa injection)
a) Proprietary Name: Gonal-f Pen
b) Non-Proprietary Name: follitropin alfa injection
c) Code Name/# (ONDC only): not applicable
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: not applicable

Chemistry Review Data Sheet

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

11. DOSAGE FORM: Aqueous solution

12. STRENGTH/POTENCY: the fill volume is at least 300 IU, 450 IU, or 900 IU (total deliverable) per multiple-dose pen. All three pens have the same concentration of 625 IU/mL and are differentiated by fill volumes.

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: _x_Rx ___OTC

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 (r-hFSH), follitropin alfa, is composed of two polypeptide subunits (alpha- and beta-) bound together non-covalently. The alpha-subunit consists of 92 amino acid residues. Structurally, there are two N-glycosylation sites (Asn 52 and Asn 78), no O-glycosylation sites, and five internal disulfide bonds. The beta-subunit consists of 111 amino acid residues with 2 N-glycosylation sites (Asn 7, Asn 24), no O-glycosylation sites, and six internal disulfide bonds.

Follitropin alfa (alpha subunit): $C_{437}H_{682}N_{122}O_{134}S_{13}$ MW = 10,205.88 Da
Follitropin alfa (beta subunit): $C_{538}H_{833}N_{145}O_{171}S_{13}$ MW = 12,485.34 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	III	/	/	4	N/A	N/A	
/	III	/	/	3	Adequate	3-MAY-2000	By D. Lin

			cap				

[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	20-378	Gonal-f (follitropin alfa for injection)
NDA	21-765	follitropin alfa injection

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**Acceptable.**	17-NOV-2003	S. Adams
Pharm/Tox	*Not Applicable*		
Biopharm	*Not Applicable*		
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs.		
DMETS	**Pending**		
EA	*Not Applicable*		
Microbiology	**Sterile — drug product is acceptable.**	21-NOV-2003	B. Riley
CDRH	**Pen injector is acceptable.**	16-SEP-2003	V. Nakayama

19. ORDER OF REVIEW (OGD Only) not applicable

Chemistry Executive Summary

The Chemistry Review for NDA 21-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from Chemistry is APPROVAL.

(The review of the proposed proprietary name is pending from the Division of Medication Errors and Technical Support.)

Refer to the Basis for Approvability 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

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

The solution dosage form is packaged in sterile pre-filled cartridges, which are assembled into disposable, multi-dose, pen injectors at the manufacturing site.

Drug product –

- Name: Gonal-f Pen (follitropin alfa injection)
- Strengths: the fill size is at least 300 IU, 450 IU, or 900 IU (total deliverable) per multiple-dose pen. All three pens have the same concentration of 625 IU/mL and are differentiated by fill volumes. [Note to reviewer: the designation of the fill sizes to be dosage strengths on the labeling is historical per DRUDP; refer to other approved multiple-dose containers of this type of product in this division.]
- Dosage form and administration: sterile aqueous solution for subcutaneous injection
- Pharmacological category: Follicle stimulating hormone (FSH), recombinant human
- Formulation - Inactive ingredients are Poloxamer 188 USP, sucrose NF methionine USP,
  USP, m-cresol USP, 0-phosphoric acid 85% USP, sodium hydroxide USP, and

- Packaging: The drug product is packaged in a pre-filled multi-dose disposable pen-injector, which is enclosed in a carton with 29G x 0.5 in. needles. The pen injector 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). Inside each pen-injector is a — glass cartridge pre-filled with the solution product. At one

end, the cartridge barrel is closed with a — lunger stopper. At the other end, the cartridge barrel is closed by a — — crimp-cap. The assembly of the pre-filled cartridge and pen-injector is completed at the manufacturing site.

- Expiry:
  - 12 months at 2-8 °C (including the option of storing at 20-25 °C for up to one month or until expiry, whichever occurs first). This expiry is based on satisfactory — data at 5 °C and — data at 25 °C for 6 batches (2 batches for each dosage strength), and
  - 1 month at room temperature during use and within the 12-month expiry. This in-use storage is based on satisfactory — data at 25 °C with used pen injectors (punctured closures) from 4 batches (2 batches of 300 IU and 2 batches of 900 IU) and satisfactory — data at 25 °C for 1 developmental batch (closed pen injectors with and without the outside carton).

Drug substances – follitropin alfa

- The drug substance is a human follicle-stimulating hormone (hFSH), which is manufactured by recombinant DNA (rDNA) technology. Recombinant human follicle stimulating hormone (r-hFSH), follitropin alfa, is composed of two polypeptide subunits (alpha- and beta-) bound together non-covalently. The alpha-subunit consists of 92 amino acid residues. Structurally, there are two N-glycosylation sites (Asn 52 and Asn 78), no O-glycosylation sites, and five internal disulfide bonds. The beta-subunit consists of 111 amino acid residues with 2 N-glycosylation sites (Asn 7, Asn 24), no O-glycosylation sites, and six internal disulfide bonds. Follitropin alfa is synthesized in a Chinese hamster ovary (CHO) cell line. The biological activity is determined by measuring the increase in ovary weight in female rats. 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 NDA 20-378 for all chemistry reviews of the drug substance. It is stated on page 84 of Volume 1 that "No changes have been made in the currently approved drug substance manufacturing process."

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 300 IU for ovulation induction or 450 IU for Assisted Reproductive Technologies.
- Expiry: 12 months at 2-8 °C (including the option of storing at 20-25 °C for up to one month or until expiry, whichever occurs first) and 1 month at room temperature during use and within the 12-month expiry.

C. Basis for Approvability or Not-Approval Recommendation

- A recommendation for approval was obtained from CDRH on the pen injector on 16-SEP-2003 (see review in DFS).
- A recommendation for approval of the proprietary name "Gonal-f Pen" was obtained from the Division of Medication Errors and Technical Support on 6-OCT-2003 (see review in DFS). A re-review of the name is pending from DMETS.
- A recommendation for approval was obtained from the Office of Compliance on the GMP status of manufacturing facilities on 17-NOV-2003 (see attached report).
- A recommendation for approval was obtained from the Microbiology Team on the sterility assurance of the drug product on 21-NOV-2003 (see review in DFS).
- The Chemistry Review #2 found the NDA approvable pending the approval of NDA 20-378 S-015 and S-032 (efficacy supplement S-032 was converted to NDA 21-765). NDA 20-378 S-015 and NDA 21-765 were both approved on 25-MAR-2004. In order to have consistent labeling among all three NDAs, this reviewer requested changes in the packaging labels (letter dated 15-APR-2004; see details in the attached Chemistry Assessment) and Description and How Supplied sections of the packaging inserts (revised inserts were sent to the applicant by DRUDP electronically; see details in the attached Chemistry Assessment). Revisions of the packaging labels as FDA requested were implemented in the 19-APR-2004 amendment, and revisions of the Description and How Supplied sections of the packaging inserts as FDA requested were implemented in the 17-MAY-2004 amendment. All are found to be satisfactory is this final Chemistry Review #3.

III. Administrative

A. Reviewer's Signature
Electronically captured in DFS

B. Endorsement Block
Electronically captured in DFS

C. CC Block
Electronically captured in DFS

5 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

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/s/

Suong Tran
5/20/04 10:01:49 AM
CHEMIST

revised per your recommendations 5/20/04

Moo-Jhong Rhee
5/20/04 10:23:57 AM
CHEMIST
I concur

NDA 21-684

Gonal-f® Pen
(follitropin alfa injection)

Serono, Inc.

Suong Tran, PhD
Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-684

2. REVIEW #: 2

3. REVIEW DATE: 25-NOV-2003

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS: none

6. SUBMISSION(S) BEING REVIEWED:

Submission reviewed	Submission date
Amendment	22-OCT-2003
Amendment	30-OCT-2003
Amendment	18-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Serono Inc.

Address: One Technology Place
Rockland MA 02370

Telephone: 781-681-2273

8. DRUG PRODUCT NAME/CODE/TYPE:
Gonal-f Pen (follitropin alfa injection)
a) Proprietary Name: Gonal-f Pen
b) Non-Proprietary Name: follitropin alfa injection
c) Code Name/# (ONDC only): not applicable
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: not applicable

Chemistry Review Data Sheet

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

11. DOSAGE FORM: Aqueous solution for injection

12. STRENGTH/POTENCY: 300 IU (22 µg/0.5 mL), 450 IU (33 µg/0.75 mL), or 900 IU (66 µg/1.5 mL) per cartridge

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: _x_Rx ___OTC

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 (r-hFSH), follitropin alfa, is composed of two polypeptide subunits (alpha- and beta-) bound together non-covalently. The alpha-subunit consists of 92 amino acid residues. Structurally, there are two N-glycosylation sites (Asn 52 and Asn 78), no O-glycosylation sites, and five internal disulfide bonds. The beta-subunit consists of 111 amino acid residues with 2 N-glycosylation sites (Asn 7, Asn 24), no O-glycosylation sites, and six internal disulfide bonds.

Follitropin alfa (alpha subunit): $C_{437}H_{682}N_{122}O_{134}S_{13}$ MW = 10,205.88 Da
Follitropin alfa (beta subunit): $C_{538}H_{833}N_{145}O_{171}S_{13}$ MW = 12,485.34 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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—	III	—	/	3	Adequate	3-MAY-2000	By D. Lin

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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	20-378	Gonal-f (follitropin alfa for injection)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**Acceptable.**	17-NOV-2003	S. Adams
Pharm/Tox	*Not Applicable*		
Biopharm	*Not Applicable*		
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs.		
DMETS	**The proprietary name Gonal-f Pen is acceptable.** **Labeling changes are recommended.**	7-NOV-2003	M. Lee
EA	*Not Applicable*		
Microbiology	**Sterile — . drug product is acceptable.**	21-NOV-2003	B. Riley
CDRH	**Pen injector is acceptable.**	16-SEP-2003	V. Nakayama

19. ORDER OF REVIEW (OGD Only) not applicable

The Chemistry Review for NDA 21-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from Chemistry is APPROVABLE pending the approval of NDA 20-378 S-015 and S032.

Refer to the Basis for Approvability 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

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

The drug product Gonal-f Pen is a new dosage form, a solution, of the currently approved Gonal-f (NDA 20-378), a powder for reconstitution. The solution dosage form is packaged in sterile pre-filled cartridges, which are assembled into disposable, multi-dose, — pen injectors at the manufacturing site.
Note: The proprietary name for NDA 20-378 changed from "Gonal-F" to "Gonal-f" in the supplement SLR-026 dated 23-AUG-2002 and approved on 16-JUL-2003.

Drug product –

- Name: Gonal-f Pen (follitropin alfa for injection)
- Strengths: 300 IU, 450 IU, or 900 IU. All three strengths have the same concentration of 625 IU/mL and are differentiated by fill volumes of the cartridges.
- Dosage form: sterile aqueous solution for subcutaneous injection
- Pharmacological category: Follicle stimulating hormone (FSH), recombinant
- Formulation - Inactive ingredients are Poloxamer 188 USP, sucrose NF methionine USP, —
  — , m-cresol USP, 0-phosphoric acid USP, sodium hydroxide USP, and
  —
- Packaging: The drug product is packaged in a pre-filled multi-dose disposable pen-injector, which is enclosed in a carton with 29G x 0.5 in. needles. The pen injector 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). Each pen-injector delivers at minimum the labeled dosage strength of 300 IU, 450 IU, or 900 IU . Inside each pen-injector is a — glass cartridge pre-filled with the solution product. At one end, the cartridge barrel is closed with a —
  — plunger stopper. At the other end, the cartridge barrel is closed by a

crimp-cap. The assembly of the pre-filled cartridge and pen-injector is completed at the manufacturing site.

- Expiry:
  - 12 months at 2-8 °C (including the option of storing at 20-25 °C for up to one month or until expiry, whichever occurs first). This expiry is based on satisfactory data at 5 °C and data at 25 °C for 6 batches (2 batches for each dosage strength), and
  - 1 month at room temperature during use and within the 12-month expiry. This in-use storage is based on satisfactory data at 25 °C with used pen injectors (punctured closures) from 4 batches (2 batches of 300 IU and 2 batches of 900 IU) and satisfactory data at 25 °C for 1 developmental batch (closed pen injectors with and without the outside carton).

Drug substances – follitropin alfa

- The drug substance is a human follicle-stimulating hormone (hFSH), which is manufactured by recombinant DNA (rDNA) technology. Recombinant human follicle stimulating hormone (r-hFSH), follitropin alfa, is composed of two polypeptide subunits (alpha- and beta-) bound together non-covalently. The alpha-subunit consists of 92 amino acid residues. Structurally, there are two N-glycosylation sites (Asn 52 and Asn 78), no O-glycosylation sites, and five internal disulfide bonds. The beta-subunit consists of 111 amino acid residues with 2 N-glycosylation sites (Asn 7, Asn 24), no O-glycosylation sites, and six internal disulfide bonds. Follitropin alfa is synthesized in a Chinese hamster ovary (CHO) cell line. The biological activity is determined by measuring the increase in ovary weight in female rats. 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 NDA 20-378 for all chemistry reviews of the drug substance. It is stated on page 84 of Volume 1 that "No changes have been made in the currently approved drug substance manufacturing process."

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 300 IU for ovulation induction and 450 IU for Assisted Reproductive Technologies.
- Expiry: 12 months at 2-8 °C (including the option of storing at 20-25 °C for up to one month or until expiry, whichever occurs first) and 1 month at room temperature during use and within the 12-month expiry.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry Executive Summary

- The 21-OCT-2003 Chemistry Review # 1 of the NDA found deficiencies which were conveyed to the applicant on 24-OCT-2003 (see DFS review and letter). Subsequently, the applicant submitted amendments dated 22-OCT-2003 AND 30-OCT-2003 in response which satisfactorily resolved the chemistry deficiencies. Of the chemistry deficiencies discussed in the Chemistry Review #1, the more germane issues are as follows:
  - In the original submission of the NDA, the composition of the drug product per cartridge was incorrect because [redacted] As FDA requested, the correct information was submitted in the 30-OCT-2003 amendment.
  - In the original submission of the NDA, it was not stated whether the drug product manufacturer [redacted]

    As FDA requested, the affirmation was submitted in the 30-OCT-2003 amendment.
  - Because the drug product can be stored for one month at room temperature, FDA requested a revision of the post-approval stability protocol to include this storage condition. The protocol was satisfactorily revised in the 30-OCT-2003 amendment.
- Chemistry comments on the labeling (container labels and physician insert sections Description and How Supplied) were sent to the applicant in the Chemistry Review letters dated 24-OCT-2003 and 14-NOV-2003. The labeling issues included in the 24-OCT-2003 were satisfactorily resolved by the 30-OCT-2003 amendment. Per DMETS' recommendation on 7-NOV-2003, additional revisions to the container labels were sent to the applicant on 14-NOV-2003 (see letter in DFS) and the applicant satisfactorily revised all labels in the 18-NOV-2003 amendment.
- A recommendation for approval was obtained from CDRH on the pen injector on 16-SEP-2003 (see review in DFS).
- A recommendation for approval of the proprietary name "Gonal-f Pen" was obtained from the Division of Medication Errors and Technical Support on 6-OCT-2003 (see review in DFS).
- A recommendation for approval was obtained from the Office of Compliance on the GMP status of manufacturing facilities on 17-NOV-2003 (see attached report).
- A recommendation for approval was obtained from the Microbiology Team on the sterility assurance of the drug product on 21-NOV-2003 (see review in DFS).
- The chemistry recommendation for NDA 21-684 is approvable pending the approval of NDA 20-378 S-015 and S-032. This NDA has data from one bioequivalence study to support the drug product. In the study, the solution drug product (batch GGC101 - 900 IU) was compared to the modified lyophilized product that is currently under review in NDA 20-378 S-032 and S-015. S-032 is an efficacy supplement that refers to the chemistry information in S-015. S-015 was found to be approvable on 28-FEB-2002 with chemistry and biopharmaceutics deficiencies. The chemistry deficiencies were subsequently addressed in the amendments dated 18-MAR-2002, 8-JUL-2002, 30-AUG-2002, 30-JAN-2003, AND 26-MAR-2003 (currently being reviewed by Chemist Y. Yang, HFD-510). The biopharmaceutics deficiency was that the modified lyophilized product was

not bioequivalent to the original, approved lyophilized product, and this deficiency resulted in a clinical study with clinical data submitted in S-032 (currently being reviewed by MO A. Gassman, HFD-580). Approvability of S-015, the chemistry supplement for the modified lyophilized product, depends on the regulatory action on S-032, the efficacy supplement for the modified lyophilized product. Therefore, approvability of this NDA 21-684 depends on the regulatory actions on NDA 20-378 S-032 and S-015 because the solution product of this NDA is compared to the modified lyophilized product subject of those supplements

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III. Administrative

A. Reviewer's Signature
Electronically captured in DFS

B. Endorsement Block
Electronically captured in DFS

C. CC Block
Electronically captured in DFS

17 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

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
11/25/03 01:25:48 PM
CHEMIST

paper sign-off 11/25/03

Moo-Jhong Rhee
11/25/03 03:21:17 PM
CHEMIST
I concur

NDA 21-684

Gonal-f® Pen
(follitropin alfa injection)

Serono, Inc.

Suong Tran, PhD
Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-684

2. REVIEW #: 1

3. REVIEW DATE: 6-OCT-2003

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS: none

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-JUL-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Serono Inc.
Address:	One Technology Place Rockland MA 02370
Telephone:	781-681-2273

8. DRUG PRODUCT NAME/CODE/TYPE:
   Gonal-f Pen (follitropin alfa injection)
   a) Proprietary Name: Gonal-f Pen
   b) Non-Proprietary Name: follitropin alfa injection
   c) Code Name/# (ONDC only): not applicable
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: not applicable

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

11. DOSAGE FORM: Aqueous solution for injection

12. STRENGTH/POTENCY: 300 IU (22 µg/0.5 mL), 450 IU (33 µg/0.75 mL), or 900 IU (66 µg/1.5 mL) per cartridge

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: _x_Rx ___OTC

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 (r-hFSH), follitropin alfa, is composed of two polypeptide subunits (alpha- and beta-) bound together non-covalently. The alpha-subunit consists of 92 amino acid residues. Structurally, there are two N-glycosylation sites (Asn 52 and Asn 78), no O-glycosylation sites, and five internal disulfide bonds. The beta-subunit consists of 111 amino acid residues with 2 N-glycosylation sites (Asn 7, Asn 24), no O-glycosylation sites, and six internal disulfide bonds.

Follitropin alfa (alpha subunit): $C_{437}H_{682}N_{122}O_{134}S_{13}$ MW = 10,205.88 Da
Follitropin alfa (beta subunit): $C_{538}H_{833}N_{145}O_{171}S_{13}$ MW = 12,485.34 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	/	/	4	N/A	N/A	
—	III	/	/	3	Adequate	3-MAY-2000	By D. Lin

[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	20-378	Gonal-f (follitropin alfa for injection)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**Ongoing review**		
Pharm/Tox	*Not Applicable*		
Biopharm	*Not Applicable*		
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs.		
DMETS	**Ongoing review**		
EA	*Not Applicable*		
Microbiology	**Ongoing review**		
CDRH	**Pen injector is acceptable.**	16-SEP-2003	V. Nakayama

19. ORDER OF REVIEW (OGD Only) not applicable

Executive Summary Section

The Chemistry Review for NDA 21-684

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from Chemistry is APPROVABLE pending satisfactory resolution of the chemistry issues delineated in the draft letter as well as satisfactory recommendations from the Microbiology Team on the sterility assurance, from the Office of Compliance on the GMP status of manufacturing facilities, and from the Division of Medication Errors and Technical Support on the proprietary name.
Refer to the Basis for Approvability 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

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

The drug product Gonal-f Pen is a new dosage form, a solution, of the currently approved Gonal-f (NDA 20-378), a powder for reconstitution. The solution dosage form is packaged in sterile pre-filled cartridges, which are assembled into disposable, multi-dose, — pen injectors at the manufacturing site.
Note: The proprietary name for NDA 20-378 changed from "Gonal-F" to "Gonal-f" in the supplement SLR-026 dated 23-AUG-2002 and approved on 16-JUL-2003.

Drug product –

- Name: Gonal-f Pen (follitropin alfa for injection)
- Strengths: 300 IU, 450 IU, or 900 IU. All three strengths have the same concentration of 625 IU/mL and are differentiated by fill volumes of the cartridges.
- Dosage form: sterile aqueous solution for subcutaneous injection
- Pharmacological category: Follicle stimulating hormone (FSH), recombinant
- Formulation - Inactive ingredients are Poloxamer 188 USP, sucrose NF methionine USP, — m-cresol USP, 0-phosphoric acid — USP, sodium hydroxide USP, and —
- Packaging: The drug product is packaged in a pre-filled multi-dose disposable pen-injector, which is enclosed in a carton with 29G x 0.5 in. needles. The pen injector 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). Each pen-injector delivers at minimum the labeled dosage strength of 300 IU, 450 IU, or 900 IU . Inside each pen-injector is a — glass cartridge pre-filled with the solution product. At one end, the

cartridge barrel is closed with a — plunger stopper. At the other end, the cartridge barrel is closed by a — crimp-cap. The assembly of the pre-filled cartridge and pen-injector is completed at the manufacturing site.

- Expiry:
  - 12 months at 2-8 °C (including the option of storing at 20-25 °C for up to one month or until expiry, whichever occurs first). This expiry is based on satisfactory — data at 5 °C and — data at 25 °C for 6 batches (2 batches for each dosage strength), and
  - 1 month at room temperature during use and within the 12-month expiry. This in-use storage is based on satisfactory data at 25 °C with used pen injectors (punctured closures) from 4 batches (2 batches of 300 IU and 2 batches of 900 IU) and satisfactory — data at 25 °C for 1 developmental batch (closed pen injectors with and without the outside carton).

Drug substances – follitropin alfa

- The drug substance is a human follicle-stimulating hormone (hFSH), which is manufactured by recombinant DNA (rDNA) technology. Recombinant human follicle stimulating hormone (r-hFSH), follitropin alfa, is composed of two polypeptide subunits (alpha- and beta-) bound together non-covalently. The alpha-subunit consists of 92 amino acid residues. Structurally, there are two N-glycosylation sites (Asn 52 and Asn 78), no O-glycosylation sites, and five internal disulfide bonds. The beta-subunit consists of 111 amino acid residues with 2 N-glycosylation sites (Asn 7, Asn 24), no O-glycosylation sites, and six internal disulfide bonds. Follitropin alfa is synthesized in a Chinese hamster ovary (CHO) cell line. The biological activity is determined by measuring the increase in ovary weight in female rats. 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 NDA 20-378 for all chemistry reviews of the drug substance. It is stated on page 84 of Volume 1 that "No changes have been made in the currently approved drug substance manufacturing process."

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 300 IU for ovulation induction and 450 IU for Assisted Reproductive Technologies.
- Expiry: 12 months at 2-8 °C (including the option of storing at 20-25 °C for up to one month or until expiry, whichever occurs first) and 1 month at room temperature during use and within the 12-month expiry.

C. Basis for Approvability or Not-Approval Recommendation

- A recommendation for approval was obtained from CDRH on the pen injector on 16-SEP-2003 (see review in DFS).

- A recommendation is pending from the Microbiology Team on the sterility assurance of the drug product.
- A recommendation is pending from the Office of Compliance on the GMP status of manufacturing facilities.
- A recommendation is pending from the Division of Medication Errors and Technical Support on the proprietary name.
- The chemistry recommendation is approvable pending satisfactory resolution of issues delineated in the draft letter.

III. Administrative

A. Reviewer's Signature
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B. Endorsement Block
Electronically captured in DFS

C. CC Block
Electronically captured in DFS

34 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

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/s/

Suong Tran
10/17/03 03:36:58 PM
CHEMIST

revised per paper copy 10/17/03

Moo-Jhong Rhee
10/21/03 04:38:26 PM
CHEMIST
I concur

NDA: 21-684
Drug: Gonal-f® RFF Pen (follitropin alfa injection)
Sponsor: Serono, Inc.

Environmental Assessment

This new drug application was granted a categorical exclusion.

4. ENVIRONMENTAL RISK ASSESSMENT

The active medicinal moiety in liquid r-hFSH is follitropin alfa. Follitropin alfa is produced by mammalian cells (Chinese hamster ovary cells) into which a recombinant DNA expression cassette has been inserted. Under controlled cell culture conditions follitropin alfa is expressed by CHO cells. The active moiety is harvested from the cell culture media and purified for subsequent preparation into a suitable formulation for injection.

The primary structure of follitropin alfa is identical to human follicle stimulatin hormone (hFSH), a naturally occurring human protein that is derived from the urine of pregnant women. Thus, pursuant to 21 CFR 25.31(a) Serono, Inc. claims categorical exclusion for the preparation and submission of an Environmental Assessment.