CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-684

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

14. PATENT CERTIFICATION

Pursuant to Title 21 of the United States Code Section 355(b)(1), Serono, Inc. has reviewed the records of the U.S. Patent and Trademark Office and is of the opinion that there are no United States patents to which Serono, Inc. does not have a license which claim recombinant human Follicle Stimulating Hormone (r-hFSH) or a method of using r-hFSH with respect to which a claim of patent infringement could reasonably be asserted against Serono, Inc. in connection with the manufacture, use or sale of r-hFSH for the treatment of patients with infertility.

Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and
Quality Assurance, North America

7/28/03
Date

EXCLUSIVITY SUMMARY for NDA # 21-684 **SUPPL #** N/A

Trade Name Gonal-f® RFF Pen
*revised formulation female
Generic Name follitropin alfa injection
Applicant Name Serono, Inc. **HFD-**580
Approval Date May 25, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

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

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

   YES /___/ NO /_X_/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.
   The sponsor has submitted a single bioequivalence study (# 23572)to show bioequivalence between the fill-by-mass formulation (NDA 21-765)and the new liquid formulation delivered via the Pen (NDA 21-684).

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

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

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

YES /___/ NO /_X_/

If yes, NDA # Drug Name

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

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety

(including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

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

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

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

YES /__/ NO /_X_/

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source,

including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /__/

If yes, explain:

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

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a

previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /__/

Investigation #3 YES /___/ NO /___/

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

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

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

Investigation #1 YES /___/ NO /__/

Investigation #2 YES /___/ NO /__/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

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

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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

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

Investigation #1

IND # _____ YES /__/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /__/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the

sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__/

If yes, explain: _____

_____

_____

Archana Reddy, M.P.H.
Signature of Preparer

5/26/04
Date

Title: Regulatory Project Manager

cc:
Archival NDA 21-684
HFD- 580/Division File
HFD- 580/Reddy
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

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/s/

Archana Reddy
5/27/04 04:44:08 PM

16. DEBARMENT CERTIFICATION

Debarment Certification Statement

In accordance with Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act, the undersigned hereby certifies that Serono, Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application.

Rosann J. Reinhart
Executive Director, Regulatory Affairs

28-JUL-03
Date

002

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-684 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: March 26, 2004 **Action Date:** May 25, 2004

HFD 580 **Trade and generic names/dosage form:** Gonal-f® RFF Pen (follitropin alfa injection)

Applicant: Serono, Inc. **Therapeutic Class:** 3s

Indication(s) previously approved: Ovulation Induction and Assisted Reproductive Technologies

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Ovulation Induction and Assisted Reproductive Technologies

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

This page was completed by:

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

cc: NDA 21-684
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

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/s/

Archana Reddy
5/26/04 12:41:14 PM

5600 Fishers Lane, Rockville, Maryland 20857

Food & Drug Administration
Division of Reproductive and Urologic Drug Products

Fax

To: Lisa S. Mills	**From:** Archana Reddy
Fax: 781-681-2924	**Pages:** 31
Phone: 781-681-2273	**Date:** 5/25/04
Re:	**CC:**

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Attached is the approval letter for NDA 21-684 Gonal-f® RFF Pen 3. Please confirm that you have received all pages.

Archana Reddy

5/01/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your July 28, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename ® (follitropin alfa injection).

We also refer to your submission dated March 25, 2004, containing a complete response to our November 25, 2003, Not Approvable letter.

We are reviewing your proposed labeling submitted on May 17, 2004. We request a prompt written response to the attached labeling comments in order to continue our evaluation of your NDA.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

A

76 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Margaret Kober
5/21/04 04:49:59 PM
Chief, Project Management Staff

3 Page(s) Withheld

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__✓ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

5/10/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your July 28, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename ® (follitropin alfa for injection).

We also refer to your submission dated March 25, 2004, containing a complete response to our November 25, 2003 Not Approvable letter.

We are reviewing your proposed labeling submitted on March 25, 2004. We request a prompt written response to the attached labeling comments in order to continue our evaluation of your NDA.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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✓ § 552(b)(5) Draft Labeling

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/s/

Margaret Kober
5/10/04 06:31:27 PM
Chief, Project Management Staff

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 19, 2004

To: Pamela Williamson Joyce Vice President, Regulatory Affairs Cc: Lisa Mills, Manager, Regulatory Affairs	**From:** Archana Reddy, M.P.H. Regulatory Project Manager
Company: Serono, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 781-681-2947	**Fax number:** 301-827-4267
Phone number: 781-681-2273	**Phone number:** 301-827-4260

Subject: Clinical pharmacology information request letter

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your March 25, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f Pen ™ (follitropin alfa injection).

We are reviewing the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We are unable to locate a table which details individual patient PK parameters (AUC_{last}, C_{max}, and T_{max}) from each of the 2 periods. If such a table exists in the submission, provide the location of the table within the submission. If such a table does not exist, provide an EXCEL table with the patient IDs in the rows and AUC_{last}, C_{max}, and T_{max} in columns (2 sets of those, one each for Period 1 and 2) in each row against each of the patient IDs. You can provide this information as an electronic submission to the NDA.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
4/19/04 10:59:55 AM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your March 25, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f Pen™ (follitropin alfa injection).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA.

Cartridge Labels:

1. Revise as follows (delete the strikeout and add the underlined):

   300 IU~~/0.5 mL~~
   Contains 415 IU to deliver 300 IU/0.5 mL

   450 IU~~/0.75 mL~~
   Contains 568 IU to deliver 450 IU/0.75 mL

   900 IU~~/1.5 mL~~
   Contains 1026 IU to deliver 900 IU/1.5 mL

Carton Labels:

1. In the Contents section, delete "\ ' from the applicable label. Add '

2. Replace the individual quantities of the inactive ingredients with their concentrations in mg/mL.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Suong Tran
4/15/04 09:35:23 AM
for Moo-Jhong Rhee, Team Leader

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

Serono, Inc.
Attention: Pamela Williamson Joyce
Vice President, U.S. Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

We acknowledge receipt on March 26, 2004, of your March 25, 2004, resubmission to your new drug application for Gonal-f® Pen (follitropin alfa injection).

We consider this a complete, class 1 response to our November 25, 2003, action letter. Therefore, the user fee goal date is May 26, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
4/8/04 03:29:16 PM

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: November 21, 2003

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products, HFD-580

FROM: John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, DRUDP, HFD-580

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 21-684
Gonal-f™ Pen (follitropin alfa injection)

Study/Site Identification:

As discussed with you, the following study/site pivotal to approval has been identified for inspection:

Study #	Clinical Site	Analytical Site
Bioequivalence Study # IMP 23572 (CRO Study # RD 494/23374)		/

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

___X__There is a lack of domestic data that solely supports approval;

_____Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **February 16, 2004**. We intend to issue an action letter on a related application NDA 20-378/S-032 by **March 26, 2004**.

Should you require any additional information, please contact John Kim at 301-827-3003 or Archana Reddy at 301-827-7514.

Concurrence:
Henry Malinowski, Ph.D., Director, Clinical Pharmacology Biopharmaceutics (OCPB)
John Hunt, Ph.D., Deputy Director, OCPB
Ameeta Parekh, Ph.D., Team Leader, OCPB
Sayed Al Habet, Ph.D., Reviewer, OCPB

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/s/

Daniel A. Shames
11/21/03 03:02:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your new drug application (NDA) dated July 28, 2003, received July 29, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f™ Pen (follitropin alfa injection).

We acknowledge receipt of your submissions dated August 18 (2), 21, 29, September 15, October 22, 30 (2), and November 4, 13 (2), 18 (2), 2003.

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

1. A non-approved drug product was used as the reference product in Study 23572, the bioequivalence trial submitted to support this application.
2. Inspection of the clinical trial site(s) for Study 23572 is pending.

To address these deficiencies:

1. The data from Study 23572 may be resubmitted with an approved reference product.
2. A satisfactory inspection of the clinical trial site(s) for Study 23572 must be obtained.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Donna Griebel
11/25/03 05:02:57 PM
I have signed this letter for Dr. Daniel Shames, MD in has absence.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your July 28, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f Pen ™ (follitropin alfa injection).

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Additional comments may be forwarded as we progress with our review.

1. Revise to read "mcg" rather than the symbol for "micro" throughout labels and labeling.

2. The — . is distracting and interferes with the readability of the proprietary name. We request — be deleted from the proprietary name.

3. The font style of the letter "f" is inconsistent among the labels and labeling. The letter "f" — , while on the container label it appears in a lower case font. We recommend revising the labels and labeling so that the "f" appears uniform throughout the labels and labeling.

Cartridge Label:

4. See 1. and 3. above.

5. Increase the differentiation of the dosage strengths by use of font style, highlighting, or bolding to make this information more prominent and minimize the likelihood of confusion among the various dosage strengths of Gonal-f Pen.

Carton Label:

6. See 1. 2. 3. and 5. above.

7. Define the abbreviation "S.C." located on the back panel of the carton.

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

Sincerely,

{see appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Margaret Kober
11/14/03 11:20:02 AM
Chief, Project Management Staff

11/7/03

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: AUG-20-2003	**DUE DATE:** OCT-30-2003 **PDUFA DATE:** NOV-27-2003	**ODS CONSULT #:** 03-0151

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

CC: Archana Reddy, MPH
Project Manager
HFD-580

PRODUCT NAME: Gonal-f Pen (Follitropin Alfa Injection) 300 International Units 450 International Units 900 International Units **NDA #:** 21-684	**NDA SPONSOR:** Serono, Inc.

SAFETY EVALUATOR: Marci Lee, PharmD

SUMMARY: In response to a request from the Division of Reproductive and Urologic Drug Products, HFD-580, the Division of Medication Errors and Technical Support (DMETS) has reviewed the proposed proprietary name, Gonal-f Pen.

DMETS RECOMMENDATION:

1. DMETS has no objection to the use of the proprietary name, Gonal-f Pen. However, DMETS has concerns with the design and labeling of the Pen (See Sections II and III of the review). This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.
2. DMETS recommends implementation of the labeling revisions as outlined in Section III.
3. DDMAC did not have concerns about the name, Gonal-f Pen, with regard to promotional claims.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 6, 2003

NDA: 21-684

NAME OF DRUG: Gonal-f Pen (Follitropin Alfa Injection)
300 International Units, 450 International Units,
900 International Units

NDA SPONSOR: Serono Inc.

I. INTRODUCTION

This consult is written in response to a request from the Division of Reproductive and Urologic Drug Products, HFD-580, for evaluation of the proposed proprietary name, Gonal-f Pen. The sponsor withdrew the alternate proposed names, Gonal-f — and Gonal-f — In January 2003, DMETS reviewed the sponsors' proposal to change the presentation of the letter 'F' (from a capital F to a small f). DMETS recommended label and labeling changes but did not have any objections to the revised presentation of the letter F. The sponsor submitted container label, carton labeling, cartridge labels, patient information leaflet, professional package insert labeling, and a sample Gonal-f Pen device with this review for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

"Gonal-F" was approved on September 29, 1997 (NDA 20-378). The sponsor has marketed "Gonal-F" in multidose vials and ampules. The sponsor has since proposed to revise the capital letter "F" to appear as a lowercase letter "f" in the proprietary name.

Gonal-f is a human follicle stimulating hormone (FSH) preparation of recombinant DNA origin. Gonal-F is indicated in women for the induction of ovulation and pregnancy in the anovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure.

Gonal-f is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program.

Gonal-f is indicated in men for the induction of spermatogenesis in men with primary and secondary hypogonadatropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.

The initial dose of Gonal-f is 75 units per day. The dose is increased as needed. The duration of treatment with Gonal-f should not exceed 35 days.

Gonal-f Pen is a disposable, prefilled drug delivery system intended for the subcutaneous injection of multiple and variable doses of liquid formulation of recombinant human follicle stimulating hormone.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Gonal-f Pen" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. These exercises were conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the names.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Gonal-f Pen. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns about the name with regard to promotional claims.

2. The Expert Panel identified potential for confusion with Gonal F and Penicillin. The product information is listed in Table 1 (See page 4), including the dosage forms available and usual dosage.

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[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

[3] The DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/main/trademarks.htm

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1. Potential Sound-Alike and/or Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose	Look-alike or Sound-alike
Gonal-f Pen	Follitropin Alfa Injection Disposable injection pens contain solution for injection 300 International Units 450 International Units 900 International Units	Initial dose is 75 units per day. Increase as needed. Treatment duration should not exceed 35 days.	
Gonal-f or Gonal-F	Follitropin Alfa for Injection Lyophilized form is reconstituted with 2 mL of bacteriostatic water for injection, USP. **Single dose vials**: 37.5 units/vial, 75 units/vial, 150 units/vial, **Multi-dose vial**: 1050 units/vial (formerly packaged as ampules)	Initial dose is 75 units per day. Increase as needed. Treatment duration should not exceed 35 days.	Look-alike and Sound-alike
Penicillin (various)	Potentially confused with the "Pen" portion of "Gonal-f Pen"		
*Frequently used, not all-inclusive.			

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

DMETS' Phonetic Orthographic Computer Analysis (POCA) database was unavailable to search at the time of this review.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

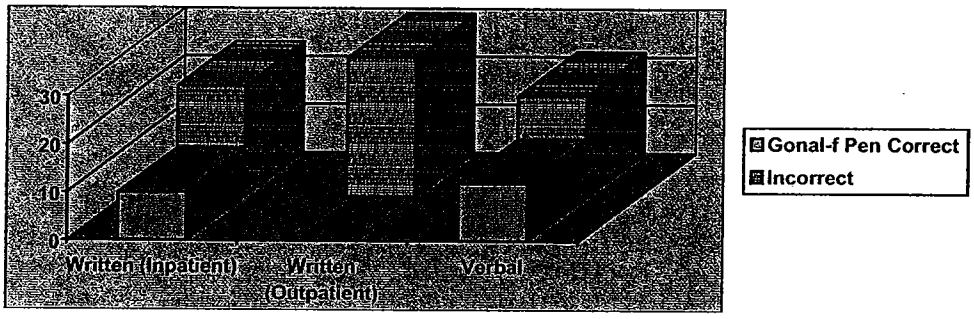
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Gonal-f Pen with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Gonal-f Pen. (See page 5). These prescriptions were optically scanned and one prescription was delivered to each of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to each of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS		VERBAL PRESCRIPTION
	Gonal F Pen	
Inpatient:	Genal F Pen 75 IU SC QD as dir #6	
Outpatient:	Genal F Pen 75 IU SC QD as dir #6	*Verbal:* "...her last prescription is for Gonal-f Pen. Seventy-five international units sub-Q every day as directed. Number six."

2. Results

Table 2. Results of the Prescription Analysis Studies

Study	# of Participants	# of Responses	"Gonal-f Pen" Response	Other Response
Written: Inpatient	43	33 (77%)	10 (30%)	23 (70%)
Written Outpatient	43	29 (67%)	0 (0%)	29 (100%)
Verbal:	43	33 (77%)	13 (39%)	20 (60%)
Total:	129	95 (74%)	23 (24%)	72 (76%)



Among participants in the written prescription studies, 52 of 62 respondents (84%) interpreted the name incorrectly. Thirteen of the incorrect responses were *Genal F Pen.*

Other misinterpretations of the written prescription studies included: *Genae F Pen, Fenal F P, Genal F Pe, Genal F Pin, Genal F Pr, Genal F Pu, Genal F Pir, Genal F Pen, Genal F P, Genal F, Gonal F, Genral F Pen, Genrl F Per, Genla F Pen, Geral F Pen, Ginal F Pen, Ginal F Pu, Ginal F Per, Gonal F Por, Gonal F PM, Gnal F Pa, Gonal F La* and *Gonal F P.* None of the interpretations are similar to a currently marketed drug product (excluding Gonal-F and Gonal-f).

Among participants in the verbal prescription studies, 20 of 33 (60%) interpreted the name incorrectly. However, some of the incorrect responses were phonetically equivalent to Gonal-f Pen. These included *Gonel F Pen, Gonol F-Pen,* and *Gonyl F Pen.*

Other misinterpretations of the verbal prescription studies included *Fagonal F Pen, Fergonal F Pen, Forgonal 75, Gonal F 10, Gonal FN, Pergonal F 10, Progonal FN,* and *Progonal F Pin.*

The response "*Pergonal F 10*" includes a product that is currently available in the US marketplace, Pergonal.

C. ADVERSE EVENT REPORTING SYSTEM (AERS)

Gonal-f Medication Error Reports

DMETS conducted a search of the FDA Adverse Event Reporting System (AERS) database for all post-marketing safety reports of medication errors reported for the active ingredient term "follitropin alfa%" and trade name "Gonal-F%", using the Meddra Preferred Terms, Medication Error and Accidental Overdose.

This query uncovered two (n=2) cases of medication errors with Gonal F. One of which was related to the similar appearance of the labeling and packaging of Gonal F to Fertinex (Urofollitropin) manufactured by Serono as well. The other report involved a patient who received Gonal-F and Buserelin at the same time. See attachment B for all report narratives.

D. SAFETY EVALUATOR RISK ASSESSMENT

1. Sound-alike and Look-alike Name Issues

   a. In reviewing the proprietary name, Gonal-f Pen, the primary concern raised was related to Gonal-f, which already exists in the U.S. marketplace. The probability of errors resulting from this confusion would more likely be the result of the inadvertent omission of the term "Pen" from a verbal or written order for Gonal-f Pen. In the event that Gonal-f is inadvertently dispensed rather than Gonal-f Pen, the patient would have the correct medication. However, there may confusion involving the instructions for use for the vial versus the pen formulation.

   b. One study participant misinterpreted the verbal prescription of Gonal-f Pen as "Pergonal F 10". It is likely that when this person heard the portion of the verbal order, "*her last prescription is **for Gonal**-f Pen*", the "for Gonal" became "***Pergonal***".

Pergonal has potential for sound-alike confusion with Gonal-f Pen. Pergonal is a combination of menotropins used with human chorionic gonadotropin (hCG) to induce ovulation and pregnancy or to stimulate spermatogenesis. Pergonal is administered as an intramuscular injection. The likelihood for confusion is increased because there is overlap in the patient population, prescribers, dosing and dosage strength similarities and both are manufactured by Serono. The risk for confusion is further increased if the practitioners interpreting a verbal do not hear the "Pen" portion of the name. Pergonal was approved in 1975 and Gonal-f was approved in 1997. Although, these products have co-existed in the marketplace for approximately 6 years, there are no medication error reports in our database that describe this type of confusion. Thus DMETS feels the potential for name confusion between Gonal-f Pen and Pergonal is minimal.

Table 3. Pergonal and Gonal-f Pen Information

Product Name	Established name; Dosage form(s)	Usual adult dose	Look-alike or Sound-alike
Gonal-f Pen	Follitropin Alfa Injection Disposable injection pens; contain solution for injection 300 International Units 450 International Units 900 International Units	Initial dose is 75 units per day. Increase as needed. Treatment duration should not exceed 35 days.	
Pergonal	Menotropins Lyophilized Powder or Pellet for Injection 75 units FSH activity and 75 units LH activity 150 units FSH activity and 150 units LH activity	Initial IM dose is 75 units FSH/75 units LH per day for 7 to 12 days	Sound-alike

c. The expert panel discussion noted some concern that the "pen" portion of the name could be confused with another "Pen" name. This was confirmed by the prescription analysis studies, where several participants misinterpreted the word, "Pen" as the word "ten." Additionally, "-pen-" is a common prefix or suffix for various products that contain penicillin as the active ingredient (e.g., Pfizerpen). Moreover, sponsors are introducing "Pen" injection devices to simplify the self-administration of medications by patients (e.g., Nutropin AQ Pen). However, the initial dose of Gon-f is 75 units. Therefore, if a prescription for Gonal-f Pen were misinterpreted as Gonal-f ten, the dose (i.e., 10 units) would need to be verified prior to dispensing or administration. Despite the potential for the modifier "Pen" to be misinterpreted as "ten", DMETS feels the risk of medication errors is minimal.

2. Gonal-f Pen Safety Concerns

a. When priming the device the user is instructed to "Check to make sure that the dose arrow is set at 37.5...

. The amount of liquid seen at the needle tip is part of the extra medicine from the pen. If no liquid appears the first time, repeat these steps until

i. When priming the device the user is instructed to "depress the injection button Is there an audible "click" or visual cue to help the user to know when the button is fully depressed?

ii. If the device is not successfully primed, then the patient is instructed to repeat the steps. However, the patient is not instructed to depress the injection button. Thus emitting any residual drug located in the needle hub, etc. Could any residual drug be potentially added to the patients' first dose?

b. DMETS is concerned with the steps required to verify that the dose selected on the Gonal-f Pen is loaded. Patients use the Dosage dial to select the correct dose and verify that the dose is loaded by pulling out the injection button. The Patient Information Leaflet Instruction #6 (August 29, 2003 submission) states " Pull out the injection button

the loaded dose is indicated by the last mark (flat arrow) on the dosage control scale that

i. The sample device, submitted for review, included an injection button that rotated freely. To verify that the correct dose was loaded, the injection knob had to be turned to the corresponding dose. However, the directions for use did not include information pertaining to rotation of the injection knob. Please comment.

ii. We note that patients are directed to "...pull out the injection button ...the last mark (flat arrow)..." However, the numbers are visible before patients see the flat arrow. Thus this step is error-prone because once the dosage dial is set to the correct amount, the user may not properly load the dose. Additionally, if the dose is not fully loaded, the user can "think" they injected the amount next

to the arrow on the dosage dial, when in reality they received less than that amount. Please comment.

iii. DMETS notes that the numbers and the flat arrow on the injection knob are extremely small, thus increasing the possibility of error. Consider use of color or some system to clarify the purpose of the scale on the injection button.

c. Eliminate unnecessary numbers on the dosage dial. For example, on the device for 300 international units, the scale should end with 300.

III. LABELING, PACKAGING and SAFETY RELATED ISSUES

A. GENERAL COMMENTS

1. Revise to read "mcg" rather than "µg" throughout labels and labeling. Postmarketing experience has demonstrated that "µg" is often misinterpreted as "mg". See Appendix B for a partial list of dangerous abbreviations from the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP).

2. DMETS does not recommend the use of "IU" as an expression of dosage strength. This abbreviation is dangerous and has been misinterpreted as IV. We recommend revising "IU" to read "International Units" on all labels and labeling. See Appendix C for Carton Labeling and Pen Cap Label of Gonal-f Pen.

3. The — is distracting and interferes with the readability of the proprietary name. We request — be deleted from the proprietary name. See Appendix C for Carton Labeling and Pen Cap Label of Gonal-f Pen.

4. The font style of the letter "f" is inconsistent among the labels and labeling. The letter "f" appears —
— , while on the container label it appears in a lower case font (see below). We recommend revising the labels and labeling so that the "f" appears uniform throughout the labels and labeling. See Appendix C for Carton Labeling and Pen Cap Label of Gonal-f Pen.

5. Ensure adequate differentiation of the Serono product line to minimize the potential for medication errors due to look-alike labeling and packaging. —
— See Appendix A for a medication error report of confusion between Fertinex and Gonal-F.

6. Manufacturers of insulin delivery devices have posted useful information on web sites. This information includes clear pictorials and in some cases, animated flash movies depicting every step of the insulin administration process. An example can be found for the FlexPen on the Novo Nordisk web site:

   http://www.novologmix70-30.com/patient/content_pa.asp?pn=010200

   We note that useful patient information appears on the sponsor's web site for Gonal-F: http://www.seronousa.com/fertility/gonal_injecting.html

   If the sponsor plans to provide web based patient information for the Gonal-f Pen, DMETS encourages the inclusion of clear pictorials and, if possible, animated instructions for proper use of the Gonal-f Pen device.

B. CARTRIDGE LABEL (Gonal-f Pen Device Label)

1. See General Comments A-1, A-2, A-4, and A-5.

2. Increase the differentiation of the dosage strengths by use of font style, highlighting or bolding to make this information more prominent and minimize the likelihood of confusion among the various dosage strengths of Gonal-f Pen.

3. Increase the prominence of the statement, "Use within 28 days of first injection."

4. Consider a space for "Date of first injection" or design a system (such as a sticker for the device itself or for a calendar) to assist patients in knowing when to discard the pen (28 days).

5. It is not clear if the sponsor plans to individually label the cartridge in addition to labeling the Device. If the sponsor plans to label the cartridge, DMETS notes that this label was not submitted for review. Please comment.

C. CARTON LABELING

1. See General Comments A-1 through A-5 and Comments B-2 and B-3.

2. Define the abbreviation "S.C." located on the back panel of the carton.

D. INSERT LABELING

1. See General Comments A-1 and A-2.

2. DOSAGE AND ADMINISTRATION

a. We note the strength is expressed in terms of international units as well as micrograms. However, the drug is dosed on international units alone. This dual presentation will be confusing to health care practitioners. Therefore, we recommend deleting the microgram equivalent from the expression of strength on all labels and labeling.

b. The information regarding usual injection sites should be consistent between the insert labeling and the patient information leaflet. Revise accordingly.

2. ADMINISTRATION INFORMATION FOR PATIENTS

This section should be consistent with the information presented in the Patient Information Leaflet. DMETS concurs with the Division of Surveillance, Research, and Communication Support's comments listed in their October 15, 2003 review. We also have the additional comments found in section D (Patient Information Leaflet).

E. PATIENT INFORMATION LEAFLET

1. See General Comments A-1 and A-2.

2. Under "**What is Gonal-f Pen?**" revise the sentence,

3. Under ' consider adding a sentence to identify any additional resources available, such as a video, website, etc.

IV. RECOMMENDATIONS

A. DMETS has no objection to the use of the proprietary name, Gonal-f Pen. However, DMETS has concerns with the design and labeling of the Pen (See Sections II and III of the review).

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

B. DMETS recommends implementation of the labeling revisions as outlined in Section III.

C. DDMAC did not have concerns about the name, Gonal-f Pen, with regard to promotional claims.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

_____

Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

_____

Denise Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPENDIX A – Medication Error Reports for Gonal-f

FDA receipt date Event Date Location Pt Age/Gender	AERS/DQRS/ USP Number	Patient Outcome	Abbreviated Narrative
June 2000 — 33 yr. Female	3507508-1	Error was caught prior to patient administration.	A prescription written for Fertinex was entered correctly but filled with Gonal-F. The products, look identical in size and shape and are available from the same manufacturer.
Nov. 2002 — 37 yr. female	4004188-6	Death	A 37-year-old female treated with Gonal-F for infertility treatment experienced cardiac arrest and died. The patient was treated with Gonal-F 225 IU for 2 days when she experienced a cardiac arrest, which resulted in death on —. In the morning of — she received the first Gonal-F injection at the hospital. At 11 PM on the same day, her husband injected her Gonal-F together with buserelin. At 11 PM on the same day, her husband injected her Gonal-F together with buserelin. It seemed that he got confused and administered both drugs together. At 11 PM, she received the third Gonal-F injection. A post mortem was performed on — however the results were inconclusive.

APPENDIX B – NCCMERP Safety Information

National Coordinating Council for Medication Error Reporting and Prevention

Taken from: Dangerous Abbreviations (http://www.nccmerp.org/council/council1996-09-04.html)

Abbreviation	Intended meaning	Common Error
U	Units	Mistaken as a zero or a four (4) resulting in overdose. Also mistaken for "cc" (cubic centimeters) when poorly written.
µg	Micrograms	Mistaken for "mg" (milligrams) resulting in an overdose.

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Denise Toyer
11/7/03 10:22:03 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/7/03 11:50:34 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
11/7/03 12:00:34 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your July 28, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f Pen ™ (follitropin alfa injection).

We are reviewing the Clinical Pharmacology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide Tables and Figures with mean and standard deviation as follows:
   a. Males and females (i.e., all completed subjects)
   b. Males only
   c. Females only

   Note that the submitted figures and tables for median data are not acceptable in PK/BE studies.

2. Note that all mean data should be reported as 'arithmetic means' rather than 'geometric means'. Provide replacement tables, as applicable.

3. Provide explanation on the significant difference in both Cmax and AUC between males and females.

4. Clarify the title of Figures 6 (reference) and 7 (test) for individual FSH serum concentration-time profiles in pages 58 and 59 (volume 1.7). Both figures indicate the data are for 22 subjects and after a dose of 250 μg. Our understanding is that 39 subjects have completed the study for both the reference and the test products. In addition, the dose was 20 μg (300 IU), not 250 μg.

5. In addition, the dose reported in the Pre-NDA meeting package dated November 12, 2003 for the same study was 22 μg (300 IU). This dose was reported in several locations of that pre-NDA package (e.g., in page 4 under objectives). Also, it was reported in the CMC section of the current NDA as 300 IU equivalent to 22 μg. Clarify the dose in the BE study, CMC section, and the label.

6. Provide all individual data for the studies conducted to ensure consistency in the delivery volumes between the standard syringe used in the BE study and the PEN injection device.

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

Sincerely,

{see appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
10/30/03 11:49:47 AM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

INFORMATION REQUEST LETTER

Serono, Inc.
Attention: Pamela Williamson Joyce, R.A.C.
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your July 28, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f Pen ™ (follitropin alfa injection).

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the current drug substance specification.

2. The drug product composition per cartridge tabulated in Section 3.2.P.1 is for the 0.5 g cartridge, 0.75 g cartridge, and 1.5 g cartridge. The actual fill weights per cartridge are —. Provide the composition tables to state the actual amounts of components per cartridge, , per CTD-Q guidelines.

3. Provide an explanation for the during the compatibility studies (page 30, Volume 1, Module 3).

4. Clarify whether testing will be performed by the drug product manufacturer on the drug substance. Per 21 CFR 211.84, the manufacturer must perform an identity test on the drug substance, at minimum, and validate the supplier's certificate of analysis. In addition, the manufacturer

5. Clarify whether tests per the drug product specification are performed on the filled cartridges before or after pen assembly.

6. Clarify the start of the expiration dating period of the drug product.

7. Add the process control (test and acceptance criteria) for

8. Confirm that procedure in the manufacture of the drug product.

9. Provide information (e.g., description, justification, validation results) on the controls of critical steps and intermediates in the manufacture of the drug product per ICH guidelines. One such control (test and acceptance criteria) would be for

10. Clarify whether testing will be performed by the drug product manufacturer on the excipients. Per 21 CFR 211.84, the manufacturer must perform an identity test on the excipient, at minimum, and validate the supplier's certificate of analysis.

11. In the drug product specifications, rename for accuracy.

12. Revise the post-approval stability protocol to incorporate the storage at room temperature for as follows: The revised protocol includes the storage of the stability samples at 25 °C/60% RH all tests per stability specification, are performed at or the samples stored at 5 °C; and all tests per stability specification, are performed at for the samples stored at 25 °C/60% RH.

13. Submit three copies of the Methods Validation package. See FDA guidance: Submitting Samples and Analytical Data for Methods Validation.

Labeling Comments:

1. The label on the body of the pen injector should include "IU", for example: 300 IU.

Cartridge Label:

2. Remove the statement '

3. Add the statement "Store at 2° – 8°C (36-46 F) until expiration date, or at 20° – 25°C (68-77 F) for up to one month or until expiration date, whichever occurs first."

4. Add the statement '

Carton Label:

5. Add the following statement to the side panel after the storage statement: "

Physician Insert:

6. The physician insert (How Supplied section) should be revised as follows:

After the first injection, the Gonal-f ™ Pen may be stored refrigerated (2°-8°C/36°-46°F) or at room temperature (20°-25°C/68°-77°F) , for up to 28 days. Protect from light. Discard unused material after 28 days.

Other labeling comments may be provided during the review of this NDA.

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

Sincerely,

{see appended electronic signature page}

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

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/s/

Moo-Jhong Rhee
10/24/03 10:20:06 AM

MEMORANDUM

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

DATE: October 15, 2003

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Achana Reddy, M.P.H., Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Gonal-F Pen
(follitropin alpha for injection), NDA 21-684

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Gonal-f Pen (follitropin alpha for injection), NDA 21-684. We have simplified the wording, made it consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on the draft prescribing information (PI) submitted by the sponsor on July 28, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

E

6 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
10/15/03 10:27:04 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/15/03 02:57:27 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-684

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f™ Pen (follitropin alfa injection).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Approvability of NDA 21-684 depends on the regulatory actions on NDA 20-378/S-015 and S-032.

2. This application may require a separate clinical study to determine the "ease of use" and comprehension of instructions for the Gonal-f™ Pen. This is a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also have the following requests:

1. Three copies of the Methods Validation package as required by 21 CFR 314.50 (see FDA Guidance: Submitting Samples and Analytical Data for Methods Validation) and as part of the 3.2.R Regional Information section of the Module 3 Quality of the NDA.

2. Additional samples of the Gonal-f™ pen-device and any additional patient instruction materials (i.e., video).

Please respond only to the above requests. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
10/9/03 05:22:53 PM
Chief, Project Management Staff

DHHS/PHS/FDA/CDRH
DIVISION OF ANESTHESIOLOGY,
GENERAL HOSPITAL, INFECTION CONTROL
AND DENTAL DEVICES
9200 CORPORATE BOULEVARD
HFZ-480
ROCKVILLE, MARYLAND 20850

DATE: _____

FROM: P. Cricenti

TO: A. Raddy

FAX #: _____

SUBJECT: _____

ADDITIONAL COMMENTS: _____

_____

_____

OF PAGES & COVER SHEET: 3

PHONE NO: (301) 443-8879
FAX NO: (301) 480-3002

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, Maryland 20850

Consultation Review

Date: September 16, 2003

To: CDER/Division of Reproductive and Urologic Drug Products (HFD-580)

From: Reviewer,
General Hospital Devices (HFZ-480)
CDRH P. Cavanaugh Chief 6 HDB

Document No: NDA 21-684
Company Name: Serono, Inc.
Product Name: Gonal-f Pen

I. Purpose

This is a New Drug Application for the Gonal-f Pen, a disposable, prefilled combination product for self-administration of Gonal-f (follistropin alfa injection). The Gonal-f Pen consists of a pen injector containing a manufacturer-inserted drug cartridge. Pen injectors are Class II devices, classification 880.5860, product code 80FMF.

II. Device Intended Use and Description:

The Gonal-f Pen is intended for the subcutaneous administration of multiple and variable doses of follitropin alfa injection, a liquid formulation of recombinant human follicle stimulating hormone. The Gonal-f Pen is a prescription product available in three different multidose presentations: Gonal-f Pen 300IU, Gonal-f Pen 450IU, and Gonal-f Pen 900IU.

The mechanical components of the Gonal-f Pen are manufactured by [redacted] and consists of: cartridge holder, main body (containing the dose dial, injection, and plunger piston), and a cap. The sponsor assembles the Gonal-f Pen by inserting a prefilled 3mL glass cartridge into the cartridge holder, snapping the cartridge holder and main body together, and adding the cap to the cartridge holder. Once connected, the cartridge holder and main body cannot be disassembled without damage. The Gonal-f Pen is discarded when the treatment regimen is complete or when the cartridge is empty.

The dose ranges of the Gonal-f pen injectors are 37.5IU to 300IU for the Gona-f Pen 300IU, and 37.5IU to 450IU in increments of 37.5IU for the Gonal-f Pen 450IU and Gonal-f Pen 900IU.

The sponsor compared the Gonal-f Pen to the Eli Lilly pen injectors cleared by the CDRH as K982842 and the Disetronic Injection Pen cleared as K982966. The sponsor provided a technical report from — to demonstrate that the Gonal-f Pen meets the requirements of ISO 11608-1:2000 "Pen Injectors for medical use-Requirements and test methods". Device testing included the specific dosing range and dose increments for Gonal-f.

The Gonal-f Pen is supplied with 29G — single-use pen needles —; additional needles are commercially available.

III. Recommendation

There are no objections to the device aspects of the Gonal-f Pen. Based upon the information provided in the submission, the mechanical/device components of the Gonal-f Pen are comparable to legally marketed pen injector devices for the subcutaneous administration of drug products and have no differences in intended use or technological characteristics that would raise any new questions of safety and effectiveness.

Von Nakayama

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/s/

Archana Reddy
10/8/03 12:59:40 PM
CSO

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: Center for Devices and Radiological Health
Division: ODE/DAGID
Mail Code: HF Z-480
Consulting Reviewer Name: Pat Cricenti
Building/Room #: Corporate Room 340D
Phone #: 4-1287 (EXT. 169)
Fax #: 480-3002
Email Address: cricenti@cder.fda.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: Center for Drug Evaluation and Research
Division: Division of Reproductive and Urologic Drug Products
Mail Code: HFD-580
Requesting Reviewer Name: Suong Tran, Ph.D.
Building/Room #: Parklawn Bldg., Rm. 18B-09
Phone#: 7-7515
Fax #: 7-4267
Email Address: trans@cder.fda.gov
RPM/CSO Name and Mail Code: Archana Reddy, M.P.H., HFD-5
Requesting Reviewer's Concurring Supervisor's Name: Moo-Jhong Rhee, Ph.D.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: August 9, 2003 **Requested Completion Date:** 9/30/03

Submission/Application Number: N 21-684 (Not Barcode Number)
Submission Type: NDA (510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: June 30, 2003 Official Submission Due Date: December 30, 2003

Name of Product: Gonal-f Pen Name of Firm: Serono, Inc.

Intended Use: Induction of ovulation and pregnancy in anovulatory infertile patients.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
Device Information in 510(k) Format

Documents to be returned to Requesting Reviewer? ☑ Yes ☐ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

CDRH Consult Review Request for NDA 21-684 (Gonal-f Pen)

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/s/

Archana Reddy
8/11/03 04:24:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-684

Serono, Inc.
Attention: Pamela Williamson Joyce
Vice President, U.S. Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Gonal-f™ Pen (follitropin alfa injection)
Review Priority Classification:	Standard
Date of Application:	July 28, 2003
Date of Receipt:	July 29, 2003
Our Reference Number:	NDA 21-684

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 26, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 28, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room, 8B-45
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
8/25/03 10:24:08 AM
Chief, Project Management Staff

18. USER FEE

As discussed with the Agency on December 11, 2002, for administration purposes, a New Drug Application (NDA) number will be assigned for this liquid formulation to avoid confusion with the lyophilized powder formulation approved for Gonal-f® (follitropin alfa for injecton) approved on September 29, 1997. A User Fee for this NDA will not be applied.

Please refer to the December 11, 2002 Meeting Minutes at the "FDA Letters" tab in Module 1.

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

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Serono, Inc.
One Technology Place
Rockland, MA 02370

2. TELEPHONE NUMBER *(Include Area Code)*

(781) 982-9000

3. PRODUCT NAME

Gonal-f Pen (follitropin alfa injection)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☑ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

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

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

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

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

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Vice President, Regulatory Affairs and Quality Assurance, North America	July 28, 2003

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-7454 EF

005

4/4/03

Teleconference Minutes

Date: December 11, 2002 **Time:** 3:00 – 4:00 PM **Location:** PKLN 17B-43

Drug: NDA 20-378 **Name:** Gonal-F ® (follitropin alfa for injection)

Sponsor: Serono, Inc.

Indication: Development of multiple follicles in ovulatory patients undergoing assisted reproductive technologies and stimulation of follicular development.

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

External Participant Lead: Pamela Williamson Joyce

Meeting Recorder: Archana Reddy, MPH

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Audrey Gassman, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, MPH, Project Manager, DRUDP (HFD-580)
David Lin, Ph.D., Chemistry Team Leader, DNDC II @ DRUDP (HFD-580)
Venkat Jarugula, Ph.D., Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Yvonne Yang, Chemistry Reviewer, Division of New Drug Chemistry II (DNDC II) @ Division of Metabolic and Endocrine Drug Products (HFD-510)
Duu-Gong Wu, Ph.D., Deputy Director, DNDC II (HFD-820)

External Participants:
Robert Bassett, Manfacturing Product Director
Celine Carlet-Alameda, Corporate Regulatory Affairs Manager
Michel Chrisen, Patients Care Technology
Reinoud Driebergen, Director, Center of Expertise, Quality Control Systems
Lisa S. Mills, Manager, US Regulatory Affairs
Isabelle Trinchard-Lugan, Head of Study Management, Serono Human Pharmacology Group
Pamela Williamson Joyce, Vice President, US Regulatory Affairs

Meeting Objectives: To discuss the pre-sNDA meeting Information Package dated November 12, 2002 containing a summary of the bioequivalence study, CMC information, device technical information, and submission format for the new liquid formulation of Gonal-F ® multidose presentations.

Background:
Serono is proposing to submit a sNDA for a new liquid formulation of Gonal-F. Gonal-F® is currently approved (NDA 20-378) as a freeze-dried powder available in glass vials.

Discussion:
- The Agency emphasized to the sponsor that this teleconference is a guidance meeting and that no final decisions will be reached.
- For administration purpose, a new NDA number may be assigned for this proposed new liquid formulation to avoid confusion with the currently approved lyophilized powder formulation for Gonal-F® (NDA 20-378).
- As described in the pre-sNDA Information Package, the proposed new liquid formulation is compared in a bioequivalence study with a new lyophilized powder formulation submitted in supplement SCF-015, which was found not to be bioequivalent to the currently approved lyophilized powder formulation. The reference used in bioequivalence comparison is considered invalid.
- It has been brought to the Agency's attention that an Approvable letter was sent to the firm, with regard to SCF-015, on Feb-28-2002 with the CMC deficiencies only, while the Clinical Pharmacology deficiency regarding the bioequivalence issues was not included in the Approvable letter.
- In the mean time, the firm has submitted a "complete response" addressing all of the CMC deficiencies listed in the Approvable letter, for supplement SCF-015.
- The Division is expected to send a letter to the firm with comments on the bioequivalence issue of the two lyophilized powder formulations in supplement SCF-015.
- The Agency asked the firm to conduct in-use stability testing and provide the results at the time of submission for the liquid formulation.
- The firm will provide in-use stability protocol for the Agency to review and comment before starting the stability study.
- The Agency asked the firm to perform

  and to provide the information for review.

Clinical Pharmacology
- Based on Clinical Pharmacology review of supplement SCF-015, the new lyophilized formulation was found bioinequivalent to the approved formulation.
- The Division will send a letter to the sponsor with comments on the issue of the two formulations being bioinequivalent as submitted in supplement SCF-015.

Microbiology
The following information needs to be provided in the CMC package:
- for all cartridge/pen components containing the drug product.
- The results of media fills using the new 3-ml cartridges.
- The results of testing on the drug product packaged in the new container system.

Questions

1. Serono has developed liquid formulations of Gonal-f® multidose presentations. A study was performed to confirm the bioequivalence of a subcutaneous dose of the lyophilized monodose (methionine-containing) formulation in its to-be-marketed container-closure system (i.e., vial) and a subcutaneous dose of the liquid multidose formulation in its to-be-marketed container-closure system (i.e., cartridge). Both formulations were administered as a subcutaneous injection with a needle and syringe. Does FDA concur that this bioequivalence study is acceptable to support approval (without additional clinical data)?
   DRUDP Response:
   This is dependent upon the previous bioequivalence studies. The sponsor is not using the appropriate reference product. The bioequivalence study would not support approval of the liquid formulation because the reference product used in this study is not an approved product and was previously found to be bioinequivalent to the approved product. The sponsor may request additional discussion with the Division about the bioequivalence study.

2. Technical information on the device (injection pen) will be submitted in the sNDA for consultation with CDRH. The device was not used in the bioequivalence study. Sufficient information will be included in the sNDA to demonstrate that a subcutaneous injection from the injection pen and a subcutaneous injection with a needle and syringe deliver the equivalent volume thereby delivering the same dose. Does FDA concur that this approach is acceptable to support approval of the liquid formulation with the injection pen?
   DRUDP Response:
   Acceptable. The sponsor should compare volume and assay for protein content.

3. Does the Agency agree that the proposed CMC package is adequate to support approval?
   DRUDP Response:
   This is adequate for filing; however the data need to be reviewed before a decision about the approvability can be reached.

4. Is the proposed Common Technical Document (CTD) submission format acceptable for filing and subsequent approval of the sNDA?
   DRUDP Response:
   Acceptable.

5. Are there any additional considerations that the Agency would recommend be incorporated into the submission?
   DRUDP Response:
   A consult to CDRH would be needed. The sponsor should provide a sample of the drug product and a sample injector.

Signature: Meeting Chair
Shelley Slaughter, M.D., Ph.D.
See appended electronic signature page

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Cc:
Arch
HFD-580/Division Files
HFD-580/Reddy/Lin/Slaughter/Jarugula/Gassman
HFD-510/Wu/Yang

Drafted by: Archana Reddy, March 24, 2003
Concurrence: yy/dgw/April 7, 2003, dtl/April 4, 2003, vj/April 11, 2003
Finalized: ar/April 11, 2003

Teleconference Minutes

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/s/

Theresa Van Der Vlugt
4/14/03 11:17:25 AM
I concur as Acting Team Leader.

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

Statistical Review of Carcinogencity Studies

A statistical review of carcinogencity studies was not required.

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

CAC/ECAC Report

This new drug application was not the subject of a CAC/ECAC report.

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Pre-Approval Safety Conference

This new drug application was not the subject of a pre-approval safety conference.

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Demographic Worksheet

This new drug application did not require a demographic worksheet, as this is not a new molecular entity.

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Drug: Gonal-f ® RFF Pen (follitropin alfa injection)
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Public Communications

The new drug application is not the subject of any Press Office notices.

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Sponsor: Serono, Inc.

Post-Marketing Commitments

The new drug application is not the subject of any Post-Marketing commitments.

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Methods Validation

Methods Validation will be requested at the time of NDA approval.

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User Fee Goal Dates

The user fee goal date is May 26, 2004 for this new drug application.

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Special Programs

This new drug application does not qualify for any special programs.

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Application Integrity Policy (AIP)

The new drug application is not the subject of the AIP.

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Controlled Substances Staff Review

This new drug application was not the subject of a Controlled Substances Staff review.

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Sponsor: Serono, Inc.

Advisory Committee Meeting

The new drug application is not the subject of any advisory committee meeting.

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

Federal Register Notices

The new drug application is not the subject of any Federal Register Notice.

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Facilities Inspection

The facilities inspection was found to be acceptable. See addendum to Chemistry review.

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Microbiology Efficacy

A microbiology efficacy review is not required for this new drug application.

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Safety Update Review

See Medical Officer's review.

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Non-clinical Inspection Review Summary

A non-clinical inspection was not required for this new drug application.

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Statistical Review

A statistical review of this new drug application was not required.