CENTER FOR DRUG EVALUATION AND RESEARCH

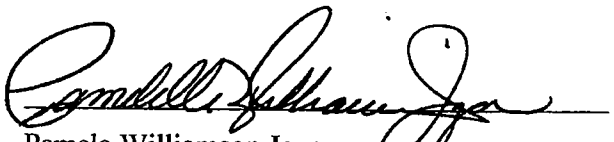
APPLICATION NUMBER:

21-765

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 female infertility.



Pamela Williamson Joyce
Vice President, Regulatory Affairs

25 Feb 03
Date

EXCLUSIVITY SUMMARY for NDA # 21-765 **SUPPL #** N/A

Trade Name N/A
Generic Name follitropin alfa for injection
Applicant Name Serono, Inc. **HFD-** 580
Approval Date March 26, 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 /_X__/ NO /__/

      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.

      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. 3/29/04

Signature of Preparer Date
Title: Regulatory Project Manager

Daniel Shames, M.D. 3/29/04

Signature of Office or Division Director Date

cc:
Archival NDA 21-765
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

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

Rosann J. Reinhart
Executive Director, Regulatory Affairs

12-Feb-03

Date

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA : 21-765	Efficacy Supplement Type SE-	Supplement Number :	
Drug: (follitropin alfa for injection)		Applicant: Serono, Inc.	
RPM: Archana Reddy, M.P.H.		HFD- 580	Phone # 7-7514
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 20-378/Gonal-f	

❖ Application Classifications:	
• Review priority	(X Standard ( ) Priority
• Chem class (NDAs only)	3s
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	March 26, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X)Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(X Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
General Information	
❖ Actions	
• Proposed action	(X AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	X (December 11, 2002)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (Division Director, Medical Team Leader, 3.25.04)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X (3.25.04)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (Medical Officer's Review)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X (3.17.04)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (3.25.04)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (1.16.04)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X (3.25.04)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (3.25.04)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report) See memo from Dr. Chen (Chemistry Review)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested **(X)** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (3.25.04)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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

/s/

Archana Reddy
3/29/04 11:46:24 AM

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type): 21-765, Tradename (follitropin alfa for injection)

Applicant: Serono, Inc.

Date of Application: May 23, 2004

Date of Receipt: May 27, 2004

Date of Filing Meeting: July 15, 2003

Filing Date: July 25, 2003

Indication(s) requested: Ovulation induction and Assisted Reproductive Technologies

Type of Application: Full NDA __X_____ Supplement _____
(b)(1) _____X____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S__X____ P_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.)___3s___
Other (orphan, OTC, etc.)____N/A_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain. No, this new drug application is on the AIP list.

User Fee Status: Paid ____X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES__X_____ NO_____
User Fee ID#_____4540_____
Clinical data? YES __X_____ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: __March 26, 2004____

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES NO

- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Technical Document, does it follow the guidance? YES NO NA

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES; If yes, _____years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:
  Waiver granted for pediatric studies
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: 38,172

End-of-Phase 2 Meeting? Date_____ NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) 12/11/2002 NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO NA

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO
If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 15, 2003

BACKGROUND:

This new drug application provides for a new formulation (fill-by-mass) for Gonal-f®.

Women:

Gonal-f® (follitropin alfa for injection) is indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-F® is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program.

The original new drug application for the new Gonal-f® formulation contained two pharmacokinetic studies (IMP 21859 and IMP 22596) to determine bioequivalence. This NDA was approved on September 29, 1997. The sponsor has submitted an efficacy supplement (SE8-032) on May 23, 2003 to provide for a new lyophilized formulation, filled by mass. This application also provides for changes to the Gonal-f® package insert based on these recently conducted clinical studies. The Biopharmaceutics Division reviewed studies IMP 21859 and 22596. The Biopharmaceutics reviewer determined that the new Gonal-f® formulation was not bioequivalent to the approved Gonal-f® formulation (review date November 30, 2001).

The conclusions of the Division were not relayed to the sponsor until a teleconference on December 11, 2002. The sponsor had been initially prepared to discuss a new liquid formulation of Gonal-f® for the December 2002 meeting. The sponsor requested an additional meeting with the Division to discuss the lack of bioequivalence between the new Gonal-f® formulation (r-hFSH) and the approved Gonal-f® formulation. The meeting with the Division was held on December 5, 2003. At the meeting, the sponsor proposed submission of two completed clinical studies to evaluate bio-equivalence of the new formulation (vials filled by mass) to the currently approved formulation of Gonal-f®. Bioequivalence of the new formulation of Gonal-f® would be demonstrated using clinical endpoints. The Division agreed to evaluate the two phase III clinical studies (Studies 21884 and 22240) and the studies were submitted electronically on 28, 2003. Study 21884 was originally submitted March 17, 2000 (IND 38,712 – serial number 083). Study 22240 was originally submitted February 20, 2001 (IND 38,712 – serial number 094).

ATTENDEES:
Sonia Castillo, Ph.D., Statistical Reviewer
Shelley Slaughter, M.D., Ph.D., Medical Team Leader
Audrey Gassman, M.D., Medical Officer
Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader
D.J. Chatterjee, Ph.D., Clinical Pharmacology Reviewer
Archana Reddy, M.P.H., Regulatory Project Manager

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Audrey Gassman, M.D.
Secondary Medical:	Shelley Slaughter, M.D., Ph.D.
Statistical:	Sonia Castillo, Ph.D.
Pharmacology:	Lynnda Reid, Ph.D.
Statistical Pharmacology:	N/A
Chemist:	Yvonne Yang, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	D.J. Chatterjee, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Roy Blay, Ph.D.
Project Manager:	Archana Reddy, M.P.H.
Other Consults:	Archana Reddy, M.P.H.

Per reviewers, all parts in English, or English translation? YES__X__ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES___X_____ NO_____

MICROBIOLOGY CLINICAL – File____N/A____ Refuse to file_____

STATISTICAL – File ___X_____ Refuse to file _____

BIOPHARMACEUTICS – File ____X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ____X_____

PHARMACOLOGY – File ____N/A_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X___NO_____ File_____ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

___X____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

_Archana Reddy, M.P.H._____
Regulatory Project Manager, HFD-580

A

5 Page(s) Withheld

✓ Trade Secret / Confidential

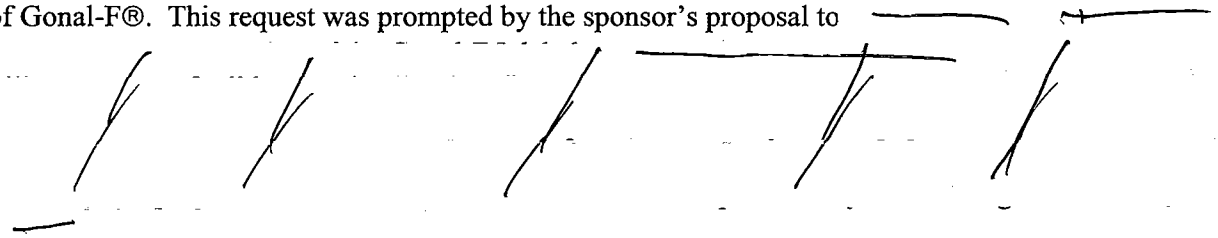
_____ Draft Labeling

_____ Deliberative Process

DEPARTMENT OF HEALTH AND HUMANSERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	ODS POSTMARKETING SAFETY REVIEW	
TO: Audrey Gassman, M.D., Medical Officer Division of Reproductive and Urologic Drug Products (DRUDP) HFD-580	**FROM:** Evelyn R. Farinas, RPh, MGA Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430	**ODS PID # DO40029**
DATE REQUESTED: January 20, 2004 **DATE RECEIVED:** January 20, 2004	**REQUESTOR/Phone #:** Archana Reedy, Project Manager HFD-580	
DRUG (Est): Follitropin alpha for injection)	**NDA # 20-378**	**SPONSOR:** Serono
DRUG NAME (Trade): Gonal-F®	**THERAPEUTIC CLASSIFICATION:** infertility drugs	
EVENT: Hypersensitivity reactions		

Executive Summary:

ODS received a request from HFD-580 for a search in the AERS database of reports listing hypersensitivity reactions, such as erythema, rash, facial swelling, and allergic or anaphylactic reactions in association with the use of Gonal-F®. This request was prompted by the sponsor's proposal to



AERS was searched for all events associated with Gonal-F®, and specifically for any hypersensitivity reported events. The search identified 70 cases with Gonal-F® as suspect drug; this raw count includes duplicates. Ten of the total 70 listed a hypersensitivity event. All ten unduplicated cases were retrieved for hands-on analysis. Two of the reports were excluded from further review because in one the adverse event was described as hepatocellular jaundice, and in the other, the reported identified injection site welts associated with injecting a mixture of Gonal-F® with Pergonal. In the remaining eight cases, half of the reports listed a serious outcome such as hospitalization in three and disability in one. The adverse events were described as allergic reaction (3), anaphylactic/oid reaction (2), rash (2) and asthma aggravated (1). Most of the cases indicated that the adverse events occurred after repeated dosing, such as after two or more doses or during the second or subsequent cycles. Most of the women were from the US with an average age of 34.7. The appearance or worsening of allergic reactions in all of the cases after two or more injections suggests a Type I hypersensitivity reaction.

A literature search uncovered eight articles that showed how the use of human DNA recombinant follicle stimulating hormone (rFSH) or highly purified follicle stimulating hormone eliminated the allergic reactions seen in women following previous therapy with human urine follicle stimulating products (FSH). In general the authors suggest the use of the recombinant products to avoid the allergic reactions caused by prior use of FSH. No articles were found showing hypersensitivity reactions following the use of r-FSH.

It must be remembered that the main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, when considering these figures, it should be realized that accumulated case reports cannot be used to calculate incidence or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Thus from the AERS data we can't provide incidence data nor an approximate frequency of occurrence in the general population for any of the allergic reactions of interest.

The labels of six currently marketed infertility drug products were reviewed to identify if the existing language specifically mentioned postmarketing adverse events or

The Clomid and Cetrotide labels have language that indicated that events have been reported postmarketing. None of the labels used language

From the AERS reports it appears that patients may experience rash, urticaria, allergic and anaphylactic reactions following the recommended doses, often after an uneventful first dose or cycle, and in some cases worsening upon subsequent doses. Thus we recommend that the label for Gonal-F

Reason for Request/Review: The Division is asking for feedback and comments supported by the AERS database regarding the sponsor's proposal (SE8-032 submission, dated January 4, 2004) for

Relevant Product Labeling

Usage Information:
Drug utilization data has been requested, and will be submitted when available.

Search Date: February 11, 2004	**Search Type(s):** x AERS x Literature Other

Search Criteria:

AERS Search:

Drug Names: Gonal-F® was searched using follitropin alfa as the active drug term and Gonal-F as trade name and verbatim terms.

MedDRA terms: In the first search no MedDRA terms were entered to capture the raw counts of all adverse events reported to provide the adverse event profile of Gonal-F®. In the second search, two High Level Group Terms (HLGT) were selected (Allergic Conditions and Epidermal and Dermal Conditions) to capture hypersensitivity/allergic and anaphylactic/anaphylactoid reactions reports.

Literature Search: PubMed was searched using two combinations of index terms: follicle stimulating hormone and allergic reactions, and recombinant follicle stimulating hormone and allergic reactions. The search was limited to articles in English involving human adult female subjects only.

Search Results:

AERS Search:

The AERS search for all events listing Gonal-F® as suspect drug identified 70 cases, which includes duplicate reporting. The list below shows counts of most frequently reported events from the line listings in descending order of occurrence (terms reported with a frequency of two or less are not included). The majority of these adverse events were mentioned in the label, as indicated by the asterisk following the frequency of events.

Dyspnea	(7) *
Ovarian Hyperstimulation Syndrome	(7) *
Drug Effect Decreased	(5)
Dysphagia	(5)
Hypersensitivity	(4)
Asthenia	(3) * (described as fatigue in the labeling)
Back Pain	(3) *
Cerebrovascular Accident	(3) *
Goitre	(3)
Injections Site Reaction	(3) *
Speech Disorder	(3)

The AERS search for cases of allergic or hypersensitivity reactions identified a total of 10 unduplicated cases. Two cases were excluded from further review. The first one, from France, was excluded because it listed jaundice and elevated transaminases, without any other dermal or allergic symptoms. This patient did not have any biliary disorders nor portal or suprahepatic obstruction. Viral serologies for hepatitis A, B, C and E were negative. The second case, from the US, was excluded because the patient reported injection site wheals following the injection of a mixture of Pergonal and Gonal-F®. Previous individual injections of each medication had not elicited an adverse skin reaction. The remaining eight cases are further described in the attached table.

Demographics/characteristics of the eight cases are:

# of unduplicated cases: 8

Origin: US (6), GBR (1), France (1)

Age: range 28-41, median 36, average 34.7

Gender: Female (8)

Reported adverse events: allergic reaction (3), anaphylactic/oid reaction (2), rash (2), asthma aggravated (1)

Onset of adverse events: AEs starting on/after second cycle (4); AEs worsening on/after second cycle (2); AEs manifesting after two or more injections (2)

History of allergies/asthma: asthma history (2); hayfever (1); amoxicillin allergy (1)

Concomitant products: two cases listed concomitant products associated with hypersensitivity reactions: Repronex (1) and Lupron (1)

Literature Search:

Of the 12 articles uncovered in Pub Med using either FSH or rFSH and allergic reactions as index terms, eight specifically addressed hypersensitivity or allergic reactions through case presentations. These cases described the lack of or the successful management of hypersensitivity reactions in women re-treated with rFSH or highly purified FSH. These women had experienced allergic reactions following previous therapy with injections of FSH or menotropins. The allergic reactions were described as itching, redness, swelling or generalized systemic allergic reactions. After recombinant therapy, the women remained free of allergy reactions. The lack of hypersensitivity reactions was attributed to the higher degree of purification of the recombinant follicle stimulating hormone products. No citations were found describing cases where individuals experienced hypersensitivity reactions following the use of human DNA r-FSH products.

Discussion:

The review of the eight cases showed that allergic reactions, ranging from rash to more severe cases of anaphylactic reactions, could be associated with the use of Gonal-F® despite the findings stated in the literature. These literature articles point out to the greater purity of the rFSH products, and suggest the use of rFSH to avoid adverse reactions caused by prior use of urine-derived gonadotrophins. Nevertheless, the AERS cases suggest that the reported hypersensitivity reactions could be IgE mediated because in the majority of the cases (6/8) the hypersensitivity reaction was manifested subsequent to a previous exposure of Gonal-F®. The development of urticaria or rash after the first dose in two additional cases may indicate that this drug product could also have a non-immunogenic hypersensitivity provoking mechanism. This dual action has been reported for vancomycin.

Some of the cases indicate the presence of allergenic concomitant drugs, a history of atopic conditions, and the use of high doses which could be interpreted as potential confounders. In two cases there was concomitant use of drugs associated with anaphylaxis and hypersensitivity (Repronex in one case and Lupron in the other). However, in each case the reporters listed only Gonal-F as suspect drug. Four of the cases, including the one listing Lupron as concomitant drug, indicated that the patients had a history of asthma, drug allergy or hay fever. While the presence of atopy, such as asthma, does not predispose to a higher risk of reactions to small molecules, there may be a higher rate of allergic reactions to protein drugs in atopic individuals. Three reports stated that the patients received large doses of Gonal-F, either at or above the upper limits of the recommended dose.

It must be remembered that the main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, it should be realized that accumulated case reports cannot be used to calculate incidence or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process and underreporting exists. Further, because of the multiple factors which influence reporting, comparisons of drug safety cannot be made from this data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions.

The labels for several of the other currently marketed infertility products (i.e., Follistim, Repronex, Antagon and Ovidrel) were examined to identify if the existing language specifically mentioned postmarketing adverse events or [redacted] While none of these labels specifically stated that a reported event occurred during post-marketing experience [redacted] ll provided a caveat regarding the causality of some of the events reported. In general, the caveat indicated that a causal attribution could not be made.

Two additional products, Clomid and Cetrotide, had statements indicating the reporting of some events post-marketing. The Clomid label has a Postmarketing Adverse Events section, which includes these sentences: 'The following adverse experiences were reported spontaneously with CLOMID. The cause and effect relationship of the listed events to the administration of CLOMID is not known." The Cetrotide label provided the following language: "During post-marketing surveillance, rare cases of hypersensitivity reactions including anaphylactoid reactions have been reported."

Conclusion:

From the AERS reports it appears that patients may experience rash, urticaria, allergic and anaphylactic reactions following the recommended doses, often after an uneventful first dose or cycle, and in some cases worsening upon subsequent doses. Thus we recommend

Reviewer's Signature / Date:	**Team Leader's Signature / Date:**
Division Director Signature / Date:	**Office Director Signature / Date:**
Attachments:	
Cc: NDA 20-378 **HFD-430 Avigan/Truffa/Farinas/Birdsong/Gonal F®** **HFD580 Griebel/Gassman/Reedy**	

Summary of Unduplicated Allergic Reactions Cases in AERS listing Gonal-F® as suspect drug					
Case # Age/weight Dose Year of event Country	AE	Time to onset	Conc. drugs	Out.	Comments
Foreign Cases					
3971555 28/NS 75u/day; 37.5/day; 2003 France	Asthma exacerbation	After second and third cycle	None	H	No adverse events followed the first cycle, dosed at 75 u/day for 7 days. Asthma was exacerbated on second cycle of same dosing regimen. She required salbutamol, prednisolone, eformoterol, beclomethasone and montelukast therapy. After the patient respiratory status was satisfactory, a third cycle was started at half the previous dose (i.e., 37.5 u/day). After the second injection in this cycle, she experienced a severe asthma attack requiring hospitalization. She received parenteral corticosteroids. Her pulmonary function studies were normalized. The patient had a history of controlled allergic asthma and no known allergy to any drug.
3714696 29/69 Kg 150 u/day 2001 GBR	Urticaria around her body Anaphylactoid reaction (swollen lips, breathing difficulties, rash)	After first treatment, and then after fourth injection of second cycle	None	H	Recurrent urticarial patches associated with first cycle therapy, treated with Zyrtec. She developed anaphylactic shock symptoms after 4th injection of new cycle. She was hospitalized, and treated with hydrocortisone and adrenalin. Patient had a history of mild asthma for which she did not receive regular treatment.
US cases					
3420974 34/103 lbs 300-450 u/day 1998 USA	Allergic reaction (hives on torso and back)	After the 5th dose of the second cycle	None	Not serious	Patient developed hives in torso and back after the 5th injection of the second cycle. She was treated with Benadryl. There had been no adverse events noted after the first cycle. The patient has no known allergies.
3511413	Rash on arms and legs	After each	None at	Not	For the first 5 days of the cycle,

Summary of Unduplicated Allergic Reactions Cases in AERS listing Gonal-F® as suspect drug					
Case # Age/weight Dose Year of event Country	AE	Time to onset	Conc. drugs	Out.	Comments
36/125 lbs 75 u/month 1999 USA		of several cycles	time of Gonal F therapy; but Clomiphene during the first 5 days of the cycle	serious	the patient received Clomiphene, followed on day 9 with 75 u of Gonal F. The patient developed a severe rash on her arms and legs which worsened during each subsequent cycle. The event did not require therapy. She completed four cycles. The patient has a history of endometriosis and allergy to Amoxicillin. Patient was started on Repronex, without any adverse events.
3511414 36/NS 150 u/day 2000 USA	Allergic reaction (chest tightness, shortness of breath, hot flashes, left shoulder to fingertips numbness)	After 5th dose	Repronex	Not serious	Patient received 150 units of Gonal F from Feb. 2 through Feb. 6, at which time she developed symptoms. She treated these with Vicoprophen and heat. The symptoms resolved slowly. The patient administered another dose on Feb. 7 without further complaints. She was also using Repronex during the same time interval (Feb 2 through Feb 6).
3420954 39/NS 300-450 u/day 1998 USA	Rash	After second dose	None	Not serious	Patient had completed two days of Gonal F therapy, when she developed a rash. The patient took Benadryl and the event subsided.
3734996 3639868 41/155 lbs 600 u/day 2000 USA	Hypersensitivity reaction (bilateral hemorrhagic cysts with intense feeling of heat, inflammation throughout the body, dizziness, abdominal pain, chills, cough, feverish symptoms, headache, malaise, menstrual irregularities, musculoskeletal pain, pelvic pain, pharyngitis,	During third cycle	Prenatal vitamins Iron Fish oil Progesterone Gonadotrophin Lithium Lupron	Disab.	Patient was treated daily with 600 units for 10 days (9/23 through 10/2). Nine days later (10/11) symptoms developed. Symptoms subsided. The patient indicated that she tried acupuncture therapy for 5 months to alleviate the symptoms. Patient had received two prior cycles of Gonal F with no adverse events. She has a history of bipolar disorder and hayfever.

Summary of Unduplicated Allergic Reactions Cases in AERS listing Gonal-F® as suspect drug					
Case # Age/weight Dose Year of event Country	AE	Time to onset	Conc. drugs	Out.	Comments
	sinusitis, weakness)				
3987862 NS/NS NS 2003 ? USA	Anaphylactic reaction (rash, flushing, difficulty breathing)	Fifth injection of third cycle	None	H	Patient developed symptoms after fifth injection of the third cycle. She was treated with Benadryl, without remission of symptoms. "She had epinephrine and other treatments but was then admitted to the ICU."

Bibliography:

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Battaglia C, Salvatori M, Regnani G, Primavera MR, Benazzani AR, ARtini PG, Volpe A. Allergic reaction to a highly purified urinary follicle stimulatin hormone preparation in controlled ovarian hyperstimulation for in vitro fertilization. Gynecol Endocrinol. 2000 June; 14(3): 158-161.

Bernstein IL et al. annals of Allergy, Asthma and Immunology 1999: 83 (6): 655-700.

Harrison S, Wolf T, Abuzeid MI. Administration of recombinant follicle stimulation hormone in a woman with allergic reactin to menotropin: a case report. Gyneco Endocrinol. 2000 Jun; 14(3): 149-52.

Lee CE. Consultation regarding allergic reactions noted in clinical trials conducted to gain marketing approval of abarelix (Plenaxis — FDA document. April 20, 2001.

Li TC, Hindle JE. Adverse local reaction to intramuscular injections of urinary-derived gonadotrophins. Hum Reprod. 1993 Nov; 8(11): 1835-6.

Phipps WR, Holden D, Sheehan RK. Use of recombinant human follicle-stimulating hormone for in vitro fertilization-embryo transfer after severe systemic immunoglobulin E-mediated reaction to urofollitropin. Fertil Steril 1995 ul; 66(1): 148-50.

Redfearn A, Hughes EG, O"Connor M, Dolovich J. Delayed type hypersensitivity to human gonadotropin: case report. Fertil Steril 1995 Oct; 64(4): 855-6.

Whitman-Elia GF, Banks K, O'Dea LS. Recombinant follicle-stimulating hormone in a patient hypersensitive to urinary-derived gonadotropins. Gynecol Endocrinol. 1998 Jun; 12(3): 209-12

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/s/

Evelyn Farinas
2/25/04 12:21:59 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
2/25/04 04:44:20 PM
DRUG SAFETY OFFICE REVIEWER

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

DATE RECEIVED:	**DUE DATE:** October 30, 2003	**ODS CONSULT #:**
August 18, 2003	**PDUFA DATE:** March 27, 2004	03-0234

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

CC: Archana Reddy, MPH
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:**
Gonal-f (Follitropin Alfa for Injection) 37.5 International Units, 75 International Units, and 150 International Units (Single Dose Vials) 450 International Units and 1050 International Unites (Multi-dose Vials) **NDA #:** 20-378/S-032	Serono, Inc.

SAFETY EVALUATOR: Denise P. Toyer, PharmD

DMETS RECOMMENDATION:

1. DMETS recommends implementation of the labeling revisions for the Insert Labeling (including the Patient Instructions) as outlined in Section III.

2. DMETS notes that the acceptability of the proposed name Gonal-f Pen (NDA# 21-684 and DMETS consult #03-0156) is dependent upon the approval of Supplements #015 and #032. If, the Division determines that the aforementioned supplements cannot be approved, then the sponsor must submit another name to DMETS for review.

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
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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

LABEL AND LABELING REVIEW

DATE OF REVIEW: January 4, 2004

NDA: 20-378/SE-032

NAME OF DRUG: Gonal-f
(Follitropin Alfa Injection)
37.5, 75 and 150 International Units (Single Dose Vials)
450 and 1050 International Units (Multi-dose Vials)

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 insert labeling which contains the Patient Instructions for Use for Gonal-f Single Dose and Multi-dose vials. Currently Gonal-f is marketed as single-dose ampules (37.5, 75, and 150 International Units) and a multi-dose vial (1050 International Units).

The sponsor submitted Supplement #015, which provides for a new lyophilized formulation of Gonal-f in vials that are filled by mass. The sponsor also submitted Supplement #016, which provides for a new strength of Gonal-f multi-dose vials (600 international units total strength/450 international units to be delivered).

Supplement #032 was submitted to demonstrate clinical equivalence (using two clinical trials) between the currently marketed formulation and the new lyophilized formulation, filled by mass.

The sponsor proposed changing the capital letter "F" to appear as a lowercase letter "f" in the proprietary name. DMETS reviewed this change and had no objections as long as the lowercase letter 'f' was consistent throughout the labels and labeling.

DMETS also reviewed the proposed proprietary name Gonal-f Pen (see DMETS consult 03-0156 dated October 6, 2003) for the new drug application (NDA # 21-684). DMETS had no objections to the use of the name Gonal-f Pen. The Gonal-f Pen NDA received a 'not approvable' action on November 25, 2003. One of the two main deficiencies listed in the action letter involved the use of a non-approved drug product as Serono's reference product in Study 23572. Serono used the unapproved lyophilized formulation of Gonal-f (filled by mass) as the reference product for the studies involving Gonal-f Pen.

PRODUCT INFORMATION

The NDA for Gonal-f ampules and multidose vials was approved on September 29, 1997. 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.

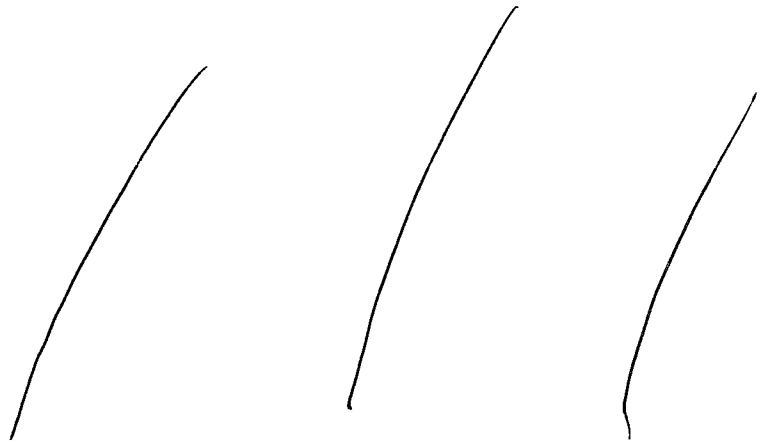
The initial dose of Gonal-f ranges from 75 units per day to 150 units per day depending upon the indication of use.

II. RISK ASSESSMENT

Since Gonal-f has been marketed for more than six years, 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, Accidental Overdose, Overdose, Treatment Noncompliance, and Pharmaceutical Product Complaint.

This query uncovered two 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) which is also manufactured by Serono. The other report involved a patient who received Gonal-f and Buserelin at the same time. Neither of these two reports involved errors relating to the reconstitution or use of the multidose vials or ampules. DMETS addressed the potential for look-alike labels and labeling with the Serono product line in DMETS consult 03-0156.

III. INSERT LABELING AND SAFETY RELATED ISSUES (Including the Patient Instructions for Use)



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✓ Draft Labeling

_____ Deliberative Process

IV. RECOMMENDATIONS

1. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review.

2. DMETS notes that the acceptability of the proposed name Gonal-f Pen (NDA# 21-684 and DMETS consult #03-0156) is dependent upon the approval of Supplements #015 and #032. If, the Division determines that the aforementioned supplements cannot be approved, then the sponsor must submit another name to DMETS for review.

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.

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

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/s/

Denise Toyer
2/18/04 08:28:15 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/18/04 08:42:39 AM
DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: January 16, 2003

TO: Archana Reddy, Regulatory Project Manager, HFD-580
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

FROM: Roy Blay, Ph.D.,
Director Regulatory Review Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-378

APPLICANT: Serono, Inc

DRUG: r-hFSH (new formulation)

STUDY(s): Protocol #21884 entitled, "A phase III, multicenter, multinational, randomized, assessor-blind study to compare the safety and efficacy of a new formulation of recombinant human FSH (r-hFSH) versus Fertinex versus Gonal-F in stimulating multiple follicular development prior to ART in patients treated with GnRH-agonist" and Protocol #22240 entitled, "A phase 3, prospective, randomized, assessor blind, multicenter, multinational, comparative trial of a new formulation of r-hFSH versus Fertinex® versus Gonal-F® in oligoanovulatory infertile women undergoing ovulation induction"

THERAPEUTIC CLASSIFICATION: 1(S)

INDICATION:

DSI GOAL DATE: February 27, 2004
REVIEW DIVISION GOAL DATE: March 26, 2004
ACTION GOAL DATE (PDUFA Date): March 26, 2004

I. BACKGROUND:

Protocol #22240 was relatively complex in its objectives of (1) determining whether the newly formulated r-hFSH was clinically equivalent to Gonal-F® in terms of ovulation rates and cumulative dose of FSH administered, and (2) The primary endpoint for this study is the ovulation rate; i.e., the number of patients who ovulate divided by the number of subjects treated.

Protocol #21884 is similar to protocol # 22240 in that a comparison is being made between the test article and Fertinex® and Gonal-F®; however, the primary endpoint is the total number of fertilized oocytes. This study is intended to demonstrate ile the secondary objective is to assess the equivalence of the test article to Gonal-F® in ART.

The clinical sites of Drs. Bayer, Neuspiller, Carizza, and Sueldo submitted data that were essential to the approval of this submission; thus, they were selected for inspection. The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and Federal regulations. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events.

II. RESULTS (by site):

NAME	CITY, COUNTRY	ASSIGNED DATE	INSPECTION DATES	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Stephen Bayer, M.D.	Waltham, MA	6 Aug 03	8-23 Sep 03	9 Oct 03	NAI/011011
Carlos Carizza, M.D.	Rosario, Argentina	5 Aug 03	3-5 Nov 03	15 Dec 03	NAI/011077
N. Neuspiller, M.D.	Buenos Aires, Argentina	7 Aug 03	7-14 Nov 03	15 Dec 03	NAI/011076
Carlos Sueldo, M.D.	Buenos Aires, Argentina	7 Aug 03	27-31 Oct 03	15 Dec 03	NAI/011075

Site #1
Stephen Bayer, M.D.
40 Second Avenue, Suite 300
The Waltham Center
Waltham, Massachusetts 02451
See **Assessment and Recommendations**, below

a. 74 subjects were enrolled in the study with 57 subjects progressing to completion (embryo transfer). Consent forms for all subjects were reviewed and the records for 8 subjects were reviewed in depth.

b. There were no limitations on the inspection.

c. A Form 483 was not issued.

Site #2
Carlos Carizza, M.D.
Medical Director
Centro para La Fertilidad de La Pareja (CEFEP), BV
Orono 1520 (2000)
Santa Fe, Rosario
Argentina
See **Assessment and Recommendations**, below

a. Ten subjects were enrolled in the study, and all ten subjects completed the study. The records of all ten subjects were reviewed with source documentation being compared to the CRFs and the sponsor-generated data listings.

b. There were no limitations on the inspection.

c. A Form 483 was not issued.

Site #3
Nicolas Neuspiller, M.D.
Medical Director
Instituto Medico Integral de Fertilidad (FECUNDITAS)
Larrea 790 (1030)
Buenos Aires
Argentina
See **Assessment and Recommendations**, below

a. 44 subjects were enrolled in study protocol #21884 and 34 subjects completed the study. 9 subjects were enrolled in protocol #22240 and six subjects completed the study. The records of eleven subjects in protocol # 21884 and nine subjects in protocol # 22240 were reviewed in depth with source documentation being compared to the CRFs and the sponsor-generated data listings.

b. There were no limitations on the inspection.

c. A Form 483 was not issued.

Site #4
Carlos Sueldo, M.D.
Instituto de Ginecologica y Fertilidad (IFER)
Marcelo T de Alvear 2259
7 Piso (C1122AA1)
Buenos Aires
Argentina
See **Assessment and Recommendations**, below

a. 26 subjects were enrolled in study protocol #21884 and 24 subjects completed the study. 9 subjects were enrolled in protocol #22240 and six subjects completed the study. The records of seven subjects in protocol # 21884 and eight subjects in protocol # 22240 were reviewed in depth with source documentation being compared to the CRFs and the sponsor-generated data listings.

b. There were no limitations on the inspection.

c. A Form 483 was not issued.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this NDA by Drs. Bayer, Carizza, Neuspiller, and Sueldo appear acceptable.

Roy Blay, Ph.D.,
DSI/GCPBI

CONCURRENCE:

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 2085

DISTRIBUTION:

NDA 20-378
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-580/Project Manager/Reddy
HFD-46/Blay
HFD-46/CIB File #s 011011, 011077, 011076, and 011075
HFD-46/Reading File

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/s/

Michele Lackner
1/20/04 03:11:37 PM
TECHNICAL
Please disregard previous DFS submission. The wrong attachment was included.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-378/S-032

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 May 23, 2003 supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f ® (follitropin alfa for injection).

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

Study #21884:

1. For study 21884, resubmit SAS dataset SCLR1.XPT and include an additional variable to identify the visit at which the bloodwork was drawn for each bloodwork value (for example, VISIT_CD).

2. Submit case report forms for the following patients:
   005-0012
   005-0015
   023-0011
   031-0001
   031-0017
   031-0032

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

APPEARS THIS WAY
ON ORIGINAL

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/s/

Margaret Kober
12/30/03 02:07:18 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-378/S-032

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 May 23, 2003 supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f ®
(follitropin alfa for injection).

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

Study #21884:

1. Please confirm whether patient(s):
   - Had more than three embryos or two blastocysts transferred and were included in the efficacy analysis. (i.e. patients 218840040018, 218840050042, 218840050038).
   - Had a hydrosalpinx present during stimulation (i.e. patients 218840040017, 218840090023, and 21884026001).
   - Did not achieve down-regulation by estradiol criteria (patients 218840110015, 218840110016, 218840260004, 218840050043, 218840090007, 218840110007, 218840110013, 218840110016, 218840170020, 218840240004, 218840250007, 218840270007, 218840170007, 218840170019, 218840240002, 218840260004).
   - Had mixed inseminations (patients 218840130007, 218840010025, 218840020001, 218840020005, 218840020013, 218840020022, 218840030013, 218840030019, 218840030027, 218840030028, 218840030036, 218840030042, 218840030047, 218840030049, 218840030062, 218840030070, 218840030075, 218840240020, 218840270002, 218840010016, 218840010027, 218840020019, 218840030005, 218840030012, 218840030029, 218840030032, 218840030069, 218840050005, 218840130007, 218840340025). Verify that these patients were not included in the efficacy analysis. Also, include any additional patients that had mixed inseminations that were not included in this list.
   - Did not have a hysteroscopy or hysterosalpingogram (as per protocol) (patient 218840320012).

- Received Puregon ® instead of the study medication and was included in the efficacy analysis (patient 218840330016).

2. Send the case report forms for patient 218840130006 who had a seizure during retrieval.
3. Confirm whether there is a variable in data set 21884 that would allow the reviewers to determine the screening serum estradiol levels (not the down-regulated serum estradiol level). If not, please submit this data as a SAS transport file. The submitted information should include subject number, treatment group, center number, and country.
4. Provide a list of patients whose FSH dose was greater than 6 ampules per day and verify that they were not included in the efficacy analysis. (i.e. patients 218840040023 and 218840010010).
5. In data set COMMET.xpt, the variable VALUE for patient 218840040012 (observation 2258) states that the "actual amount of FSH administered was 8.5 ampules." Verify if this amount is the overall total or a daily total.
6. Provide the case report forms for all patients who had ovarian hyperstimulation syndrome in study 21884.
7. Confirm whether patient 218840040025 had ovarian hyperstimulation syndrome. This patient was not listed in the serious adverse events Table (Table 142).

Study #22240:

1. Provide the sign-off page (with signatures and dates) for the Documentation of Statistical Methods section in Appendix 16.1.9.
2. Provide the date of the first cycle of treatment data available for analysis for all patients in this study.
3. Provide the date of the last patient's first cycle completion.
4. Provide the case report forms for all patients that had ovarian hyperstimulation syndrome in study 22240.

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
10/30/03 12:08:39 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-378/S-032

INFORMATION REQUEST LETTER

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

Dear Ms. Williamson Joyce:

Please refer to your May 23, 2003 supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f ® (follitropin alfa for injection).

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

Information requests for studies 22240:

1. Confirm whether patients 22240-4060016 and 22240-5250007:
   - Had an ultrasound that demonstrated fetal sac(s) without heartbeat(s)
   - Subsequently delivered a liveborn baby

2. Confirm if there is a variable in data set 22240 that would allow the reviewers to determine if a patient was administered human chorionic gonadotropin (hCG) or not. If not, submit this data as a SAS transport file. The submitted information should include the subject number, treatment group, country, and whether the patient received hCG or not.

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
9/12/03 03:00:19 PM
Chief, Project Management Staff

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Director, DDMAC
HFD-42

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

DATE: August 18, 2003	IND NO.	NDA NO. 20-378/SE-8/032	TYPE OF DOCUMENT: Efficacy Supplement	DATE OF DOCUMENT: May 23, 2003
NAME OF DRUG: Gonal-f	PRIORITY CONSIDERATION: Priority		CLASSIFICATION OF DRUG: Gonadotropins	DESIRED COMPLETION DATE: Ocotber 30, 2003

NAME OF FIRM: Serono, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Request for review of labeling. The updated labeling is available electronically on the EDR. \\Cdsesub1\n20378\S_032\2003-08-12\labeling

Archana

PDUFA DATE: MARCH 27, 2004
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival NDA: 20-378
HFD-580/Division File
HFD-580/Reddy
HFD-580/Shames/Kober/Slaughter/Gassman/Tran/Rhee/Raheja/Thornton/Chatterjee/Parekh

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Screening of New NDA for Statistical Filing
Division of Biometrics II

NDA #: 20-378

Applicant: Serono, Inc.

Trade/Generic Name: Gonal-f (follitropin alfa for injection)

Indication: Treatment of infertile female patients

Date of Submission: May 23, 2003

Filing Date: July 25, 2003

User Fee Goal Date: March 27, 2004

Project Manager: Archana Reddy

Medical Reviewer: Audrey Gassman, M.D.

Comments: This NDA is fileable from a statistical perspective.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	EDR data present
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	NA

Reviewer: S. Castillo

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/s/

Sonia Castillo
7/29/03 03:05:45 PM
BIOMETRICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-378/S-032

INFORMATION REQUEST LETTER

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

Dear Ms. Williamson Joyce:

Please refer to your May 23, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f® (follitropin alfa for injection).

We are reviewing the Clinical and Statistical sections 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.

A. Information requests for studies 21884 and 22240:

1. Please supply the date of data lock for both studies.

2. Supply the date of data unblinding for both studies.

3. Provide a separate data set for the two studies (21884 and 22240) with the patient's ID, the type of gonadotropin treatment, the type of insemination received, the duration of treatment in days, and the total dose as a numerical value (international units (IU) or micrograms (mcg) per patient per cycle. Please note for study 22240, an additional column should indicate which treatment cycle the patient was in.

4. Use all numeric values for variables in the requested datasets except for clinical pregnancy, fetal sac, and heartbeat. The variables for clinical pregnancy, fetal sac, and heartbeat can be yes/no or 1 / 2. Provide the definitions for any codes used.

B. Information requests for study 21884:

1. Provide a breakdown by obstetrical history (gravid and para)– previous ART pregnancy in a separate data table.

2. Describe the criteria used to determine normal morphology for a patient's semen analysis (by Kruger's criteria or WHO criteria). In addition, please verify whether that the decision on

sperm morphology was made by the principal investigator at the site or by the sponsor. Please provide this information as a SAS dataset.

3. Provide an additional data table for study 21884 with the number of baseline follicles <11 mm and ≥ 11 mm and stratify the table by patient ID, age, and type of insemination received. Please provide this information as a SAS dataset.

4. Verify whether patients in study 21884 who had assisted reproductive technology procedures and used donor oocytes were included in the efficacy or safety analysis.

5. One patient (4004007) in study 21884 is listed as having a value for dose calculated based on an equivalence of Puregon and rFSH 75IU. Did this patient receive gonadotropin medication that was not supplied by the sponsor?

6. One patient (502010) had a weight gain of 49 lbs post treatment. Verify this and recheck pre and post study weights and also resubmit weight of patients in kilograms.

7. One patient (4480006) had a hematocrit of 53.9 % in treatment cycle 3. Verify that this was normal post-study.

8. Verify that patients from study 21884 who that were converted from assisted reproductive technology procedures (IVF or ICSI) to intrauterine insemination (IUI) were excluded from the efficacy and safety analysis.

9. Verify that two patients in study 21884 who were listed as having hydrosalpinx (218840130007 and 21884002008) were excluded from analysis.

10. The dataset for study 21884 contains table ARHI1. In table ARHI1 there is a column designated INSTY_CD. In your submission you state the regular IVF is coded as 1 and ICSI is coded as 2. Please explain why these numbers appear to be reversed compared to the column named INSEMINA.

11. Additionally, in table ARHI1, there are two columns (OOCFE_NB and OOCRC_NB) these columns are labeled as total number of oocytes fertilized and total number of oocytes recovered. Please verify why are these numbers for OOCFE_NB and OOCRC_NB different in than the efficacy dataset variables (N-2PN and N-RET).

12. Your submission for study 21884 stated that "*The primary efficacy endpoint of this study is the total number of fertilized oocytes. The "number of fertilized oocytes" is the total number of 2 PN oocytes observed on the day of fertilization (one day after OPU). This number will be calculated per patient using the variable stage_cd, which is found in the "OPU, insemination*

and embryo/blastocyst development" page of the e-CRF. All patients treated for whom ovum pickup will be performed and for whom fertilization will be assessed on day 1 after OPU will be considered for this parameter." Verify that the data for total oocytes was derived from raw data and not derived data.

13. In order to review the dataset for study 21884, we request a line listing for the following data for the treatment cycle:
    a. Total oocytes per patient
    b. Total metaphase oocytes per patient
    c. Total fertilized oocytes (2PN) per patient
    d. Embryos per patient
    e. Serum estradiol level at the time of screening and hCG (pg/mL)
    f. Clinical pregnancy (Yes/No)
    g. Fetal Sac (Yes/No)
    h. Heartbeat (Yes/no)
    i. Total dose of gonadotropin (in international units (IU) or micrograms (mcg) for the cycle for each individual patient
    j. Pregnancy clinical outcome (miscarriage, ectopic, live birth, singletons, twins, triplets, other)
    k. Serum estradiol level after down-regulation (pg/mL)
    l. Local tolerance data (INJECT) by treatment group

    Include in the dataset the following variables for each line listed: Patient ID, Age, Center Number, Country (U.S. or Argentina), Initial Type of Insemination Patient was Randomized to (IVF or ICSI) and Type of Insemination Patient Actually Received (IVF, ISCI or mixed), Gonadotropin Treatment Patient was Randomized to, and measurement units for hormone levels.

14. The data sets STIM1, OPUI, and ULSC have missing values for the variable TREATME1 for some subjects. Please check the rest of the data sets in the submitted database to make sure that the variable TREATME1 has a value. Provide a reason for the missing information and resubmit a revised complete database for this study.

15. One patient in study 21884 was listed as having convulsions in the new Gonal-f® formulation treatment group. Send the Division more detailed information on this adverse event.

C. Information requests for study 22240:

1. There were two protocol amendments listed for study 22240 dated 06 Aug 2001 and 22 Oct 2001. The review team would like to know if these two Amendments were submitted to the Division. In addition, if the Amendments were submitted, provide both the submission dates and which file the Amendments would be located in (IND 38,712 or to NDA 20-378)?

2. Describe the criteria that were used to determine an acceptable semen analysis, concentration, motility or just a report from an investigator at the each site?

3. Provide a separate data set with a line listing for the following data for treatment cycle one only:
   a. Cycle serum progesterone levels (ng/dL)
   b. Estradiol level at time of screening and hCG (pg/mL)
   c. Clinical pregnancy (Yes/No)
   d. Heartbeat (Yes/No)
   e. Fetal Sac (Yes/No)
   f. Total dose of gonadotropin in international units (IU) or micrograms (mcg) for the cycle for each patient

   Also, include in the dataset the following variables: Patient ID, Age, Center Number, Country, and measurement units for hormone levels. In addition, please indicate for each progesterone level the day of cycle that the serum progesterone was drawn.

D. For the above requests and comments, address the following comments:

1. Provide all datasets and variable documentation for the above comments.
2. The Division requests that all datasets be conveyed in a SAS transport file.
3. The Division also recommends that you recheck and reanalyze the datsets for merging errors before sending the SAS transport files.

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
7/11/03 03:36:10 PM
Chief, Project Management Staff

DSI CONSULT: Request for Clinical Inspections

Date: June 13, 2003

To: Antoine El-Hage, Ph.D., Associate Director, DSI
Khin Maung U, M.D. Branch Chief, GCPI, DSI

Through: Joanne Rhoads, M.D., M.P.H.
Director
Division of Scientific Investigations, HFD-45

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

From: Nita Crisostomo, R.N., Regulatory Health Project Manager, HFD-580
Division of Reproductive and Urologic Drug Products, HFD-580

Subject: Request for Clinical Inspections
NDA 20-378/SE8-032
Sponsor: Serono, Inc.
Drug: Gonal-f® (follitropin alfa for injection)

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This submission provides for the following:

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Assisted Reproductive Technologies	Study 21884	Site ID #3 Steven Bayer, MD Boston IVF – The Woburn Center 23 Warren Avenue Woburn, MA 01801	N = 74 patients
Assisted Reproductive Technologies/ Ovulation Induction	Studies 21884/ 22240	Site ID #30/383 Nicolas Neuspiller, M.D. FECUNDITAS Larrea 790 (1030) Buenos Aires, Argentina	n= 23 for study 21884 n=8 for study 22240

Assisted Reproductive Technologies/ Ovulation Induction	Studies 21884/ 22240	Site ID #33/356 Carlos Sueldo, MD IFER Marcelo T. De Alvea 2259 7 Piso (1122) Buenos Aires, Argentina	n= 16 for study 21884 n=11 for study 22240
Ovulation Induction	Study 22240	Site ID #448 Carlos Carizza, MD Centro para la Fertilidad de la Pareja-CEFEP Bv. Orono 1520 (2000) Rosario, Argentina	N=10 treated patients

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Five or more Inspection Sites:

We have requested these sites for inspections (international and/or domestic) because of the following reasons. The sites are listed in order of priority.

International Inspections:

We have requested inspections because (please check appropriate statements):

____ There are insufficient domestic data

____ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

__X__ Other: The rationale for these inspections are:

The new formulation of Gonal-f® was originally submitted with two pharmacokinetic studies (IMP Studies IMP 21859 and IMP 22596) only. The pharmacokinetic studies showed a lack of bioequivalence between the approved Gonal-f® product and the new Gonal-f® formulation. The sponsor subsequently submitted two additional clinical studies (21884 and 22240) to demonstrate equivalent clinical outcomes. The original design of these studies 21884 and 22240 ___ The Division is concerned that studies 21884 and 22240 are being used for a different purpose then the sponsor intended. Therefore, because of the change in study objectives that will base the approval of the new proposed Gonal-f® formulation on these two clinical studies, we request DSI inspections.

The rationale for the United States Inspection:

1. Center #003 contributed the largest number of patients to study 21884.
2. Center #003 had a significant number of patients that did not receive embryo transfer and therefore did not complete treatment (approximately 17%).

The rationale for International Inspections:

1. The three sites in Argentina (#30/383, #33/356 and #448) were chosen because they enrolled a considerable number of subjects in the two clinical trials. The total enrollment of patients from Argentina compromises 23% of patients in study 21884 and 28% of patients in study 22240. Argentina has not been used routinely for these types of assisted reproductive technology studies.
2. Four of the Argentinian sites are used in both clinical studies 21884 and 22240.

In conclusion, the Division is uncomfortable evaluating data from these sites for ART indications without additional DSI inspection.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **October 13, 2003**. We intend to issue an action letter on this application by (action goal date) **March 26, 2004**.

Should you require any additional information, please contact Nita Crisostomo or Archana Reddy at 301-827-7260.

Concurrence: (if necessary)

Shelley Slaughter, M.D., Ph.D., Medical Team Leader
Audrey Gassman, M.D., Medical Reviewer

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/s/

Shelley Slaughter
6/23/03 05:13:27 PM
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-378\S-032

INFORMATION REQUEST LETTER

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

Dear Ms. Joyce:

Please refer to your May 23, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-f (follitropin alfa for injection).

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

Please refer to Studies #22240 and #21884 sites located in Argentina. One of these sites (#33/356) is listed as:

Carlos Sueldo, MD
IFER
Marcelo T. De Alvea 2259 7 Piso
(1122) Buenos Aires, Argentina

Please confirm whether this site:

- Has been accredited by the Latin American Network of Assisted Reproduction
- Is listed in the Latin American Registry.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober
Chief, Project Management Staff
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/

Margaret Kober
6/17/03 08:42:08 AM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-378/S-032

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

Dear Ms. Williamson Joyce:

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

Name of Drug Product:	Gonal-f® (follitropin alfa for injection)
NDA Number:	20-378
Supplement number:	032
Review Priority Classification:	Standard (S)
Date of supplement:	May 23, 2003
Date of receipt:	May 27, 2003

This supplemental application contains two clinical studies (one for ovulation induction and one for Assisted Reproductive Technologies) to support the approval of S-015 and S-016 by demonstrating clinical equivalence between the currently marketed formulation and the new lyophilized formulation, filled by mass. In addition, this supplement also provides for changes to the package insert based on these two studies.

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 July 25, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 26, 2004.

All communications concerning this supplement should be addressed as follows:

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

If you have any question, please 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
6/16/03 07:57:12 AM
Chief, Project Management Staff

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 19, 2003

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: Meeting minutes from 5/05/03 industry meeting for Gonal-f.

Total no. of pages including cover: 7

Comments:

Pamela,

Attached are meeting minutes from the 5/05/03 industry meeting for Gonal-f.

Archana Reddy

Project Manager/DRUDP

Document to be mailed: ☐ YES ☑ NO

MEETING MINUTES

Date: May 5, 2003 **Time:** 3:00 – 4:00 PM **Location:** Conf. Rm. K

NDA: 20-378

Drug: Gonal-F ® (follitropin alfa for injection)

Sponsor: Serono, Inc.

Type of Meeting: Type A (Stalled Programs)

Indications:

Women:

Gonal-F® (follitropin alfa for injection) is indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-F® is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program.

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

Meeting Recorder: Archana Reddy, MPH

External Participant Lead: Pamela Williamson Joyce

FDA Attendees:
Shelley R. Slaughter, M.D. Ph.D., Medical Team Leader, DRUDP, HFD-580
Audrey Gassman, M.D., Medical Officer, DRUDP, HFD-580
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP, HFD-580
Ameeta Parkeh, Ph.D., Clinical Pharmacology Team Leader, DRUDP, HFD-580
D.J. Chatterjee, Ph.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP, HFD-580
David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP, HFD-580
Yvonne Yang, Ph.D., Chemistry Reviewer, DNDC II @ DMEDP, HFD-510

External Participants
Lisa Mills, Manager, Regulatory Affairs
Pamela Williamson Joyce, Vice President, Regulatory Affairs and Quality Assurance

North America
Paul Lammers, M.D., Chief Medical Officer and Acting Head of Reproductive Health, Clinical Development Unit
Donald Tredway, M.D., Ph.D., Medical Director, Reproductive Health Clinical Development Unit

Background:
A supplemental new drug application (sNDA) S-015 providing for a new formulation of Gonal-F in vials filled by mass was submitted on August 3, 2001, and an Agency approvable letter was sent with a letter date of February 28, 2002. A complete response to the approvable letter was submitted on August 30, 2002. A supplemental new drug application S-016 providing for a new dosage strength, Gonal-F Multidose 450 IU was submitted on August 22, 2001, and an Agency approvable letter for S-016 was sent with a letter date of December 21, 2001. A complete response to the December 21, 2001 approvable letter was submitted on September 24, 2002. On November 12, 2002, an information package was submitted for a December 11, 2002 teleconference with the Agency to discuss the new liquid formulation of r-hFSH. An Agency letter dated March 26, 2003 provided comments on the bioequivalence studies from S-015.

Discussion:

Clinical Question #1:
In the absence of a positive determination on the matter of bioequivalence and considering the significant amount of time that has elapsed since the original sNDA submission and the additional work that Serono has already undertaken (including the development of the liquid r-hFSH product), Serono requests that the Agency consider the following alternatives for approving the new formulation of Gonal-f filled by mass:

Proposal 1: Serono will formally submit the study synopsis for ART Study 21884 and OI Study 22240. Clinical data from these studies confirm that the FbM formulation and the currently marketed formulation are clinically equivalent. These synopses (including the datasets as SAS transport files) would be submitted as an Amendment to the Pending sNDA (S-015). In view of FDA's comments regarding the bio-inequivalence of these two formulations, Serono respectfully requests a prompt review of these clinical summary data in support of approving S-015, the new formulation of r-hFSH in vials filled by mass.

DRUDP Response:
• No, the Division will not accept study synopses as an amendment to S-015.

Clinical Question #2:

Does the Agency agree that the study synopses (and clinical datasets as SAS transport) could determine clinical equivalence and, therefore, support the approval of S-015, the new formulation of r-hFSH in vials filled by mass?

Proposal 2: Alternatively, Serono would submit the full study report for ART Study 21884. Clinical data from this study confirms that the FbM formulation and the currently marketed formulation are clinically equivalent. The report (including the datasets as SAS transport files) would be submitted as an Amendment to the pending sNDA (S-015). In view of FDA's comments regarding the bio-inequivalence of these two formulations, Serono respectfully requests a prompt review of these clinical data in support of approving the new formulation of r-hFSH in vials filled by mass.

DRUDP Response:
• No, the Division will not accept Study 21884, by itself, as an amendment to S-015. The Division requests that both studies 21884 and 22240 be submitted in full study reports. These study reports should be submitted as an efficacy supplement with a ten-month review clock.

Clinical Question #3:
If the Agency does not agree with Proposal 1, will the Agency agree to an expedited review of the full study report for ART Study 21884 to determine clinical equivalence and, therefore, to support the approval of S-015, the new formulation of r-hFSH in vials filled by mass?
DRUDP Response:
• See response to question 2.

Sponsor Comments:
- Serono then asked that the Division consider a review clock shorter than the standard 10-month clock for an efficacy supplement. The company states that they have lost considerable time in product development because of the FDA's late notification of the finding of bio-inequivalence between the FBM formulation and the currently marketed formulation.

DRUDP Response
- There is no regulatory provision for a six-month review of an efficacy supplement. Priority reviews are reserved for drug products that have potential for providing some therapeutic advance. The Division has a high workload and does not have the personnel to devote to expedited reviews of standard applications. However, the Division agreed to have further internal discussion of Serono's request for a six month review time and to notify the company as soon as possible as to the outcome of this discussion.

Clinical Question #4:
Does the FDA agree to accept for filing and concurrent review the NDA for the liquid formulation while the clinical equivalency for the FBM formulation and currently marketed formulation (amendment to pending S-015) are being assessed in order to regain lost time and impact on the product improvement programs?

DRUDP Response:
• Serono may submit both applications concurrently. Comments will be determined at the time of filing and during the review process. A risk exists that submission of the second application may fail pending the outcome of the first submission for the fill-by-mass product.

Clinical Comments:
• The Division had four clinical comments that will be review issues:
1. The Division's position is that in vitro fertilization and intra-cytoplasmic injection procedures are not identical in outcomes. Therefore the data from Study 21884 will need to be re-analyzed for these groups separately.
2. The Division's position is that for tests of non-inferiority, a one-sided 97.5% confidence interval or a two-sided 95% confidence interval will be used for analysis.
3. The Division's position is that the ovulation rate will be determined by serum progesterone levels of greater than 10 ng/mL. Patients with "chemical" pregnancies will not be included in the success rate.
4. Provide the following information on patients with ovarian hyperstimulation syndrome:
    - Please provide the scoring system used for ovarian hyperstimulation syndrome in both clinical trials.
    - Please provide case reports for all patients in trials 21884 and 22240 who developed severe ovarian hyperstimulation syndrome or were hospitalized for ovarian hyperstimulation syndrome.

Clinical Pharmacology Question:
In view of the Agency's determination that the new formulation filled-by-mass and the currently marketed formulation are not bioequivalent, is there any additional information or supplemental data that the clinical pharmacologist would consider adequate to provide support for approving the new Gonal-F formulation?

DRUDP Response:
No, there are no additional requests for the sponsor at this time in order to prove bioequivalence of approved Gonal-F to the new fill-by-mass formulation.

Chemistry Comments:
- Regarding the bio-inequivalence of the two formulations (fill-by-IU and fill-by-mass): the Agency inquired about whether the protein content of the two formulations

were checked immediately before the start of the two bioequivalence studies to ensure that the patients receive the same amount of protein. The firm is not sure whether that was done.

- The Agency inquired about whether the firm has any explanations for the observation of the bio-inequivalence of the two formulations. The firm answered that they have re-examined and re-evaluated all pieces of information; however, no obvious reason stands out as the cause for the bio-inequivalence.

- The Agency inquired about the lack of consistency in the Gonal-F® labeling, the firm agreed to look into it.
- The Agency emphasized the significance of reassurance of receiving the same amount of protein by the patients in studies with formulation change. The firm stated that the protein content has been checked before the start of their recent studies.

Decision Reached:
The sponsor can submit a new NDA for the liquid formulation and an efficacy sNDA for the clinical equivalency for the fill-by-mass formulation and currently marketed formulation concurrently, but this is at the sponsor's risk. DRUDP will discuss the possibility of a six month review cycle internally and get back to the sponsor about the decision.

Action Items:
1. The Project Manager will fax the meeting minutes to the sponsor within 30 days.

Meeting Chair	Meeting Recorder
Shelley R. Slaughter, M.D., Ph.D.	Archana Reddy, M.P.H.

Note to sponsor: Please note that these minutes are considered the official meeting minutes. Any discrepancies or differences should be reported to the Division as soon as possible.

Cc:
Original NDA 20-378
HFD-580/Division Files
HFD-580/Slaughter/Reddy/Lin/Parekh/Gassman
HFD-805/Hussong
HFD-510/Yang/Wu

Created by: Archana Reddy/5.06.03
Concurrence: yy, dtl/5.12.03, ss/, ag/5.06.03, ap/djc,5.06 .03, ss/5.19.03
Finalized: ar/5.19.03

Teleconference Minutes

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/s/

Shelley Slaughter
5/20/03 10:34:34 AM
I concur.

MEMORANDUM OF TELECON

DATE: May 6, 2003

APPLICATION NUMBER: NDA 20-378, Gonal-f

BETWEEN:

Name: Pamela Williamson Joyce, Vice President, Regulatory Affairs and Quality Assurance, North America
Phone: 781-681-2298
Representing: Serono, Inc.

AND

Name: Daniel Shames, M.D., Division Director
Shelley Slaughter, M.D., Ph.D., Medical Team Leader
Archana Reddy, M.P.H., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: To discuss the possibility of a six month review clock for sponsor's anticipated NDA submission for the formulation of Gonal-f filled by mass.

DISCUSSION:
There is no regulatory mechanism to allow for a six-month review of the sponsor's anticipated NDA submission for the formulation for Gonal-f filled by mass. However, internally the Division will make an effort to review this NDA submission within 6 months. This informal agreement is contingent upon finding no significant issues during the review of this supplement that would delay the action. It also assumes that the Division does not receive priority NDA or have other emergency issues that compete for the time of the reviewing personnel. The sponsor will receive a 74 Day Filing Issues Review letter once the initial 60 day filing period is complete upon submission of the NDA. The sponsor will submit the final study report electronically to the Electronic Document Room (EDR). A Pre-NDA meeting will not be requested by the sponsor for this new formulation.

_____

Daniel Shames, M.D.
Division Director

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

/s/

Daniel A. Shames
5/14/03 09:46:21 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

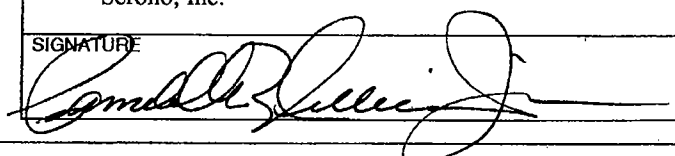
Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	see attached list of investigators	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Pamela Williamson Joyce, RAC	Vice President, Regulatory Affairs and Quality Assurance, North America
FIRM/ORGANIZATION	
Serono, Inc.	
SIGNATURE	**DATE**
	March 28, 2003

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (6/02)

Created by: PSC Media Arts (301) 443-2454 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

Name of

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☑ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Pamela Williamson Joyce, RAC	Vice President, Regulatory Affairs and Quality Assurance, North America
FIRM/ORGANIZATION: Serono, Inc.	
SIGNATURE	DATE: March 28, 2003

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Dr. [redacted] Boston IVF [redacted]. Dr. [redacted] site enrolled [redacted] patients. Serono, Inc. has provided an ongoing consultation fee totaling more than the $25,000 limit defined in 21 CFR 54.2.

In view of the above, a separate statistical analysis of the primary efficacy endpoint in Study [redacted] was conducted, which excluded all patients from Site [redacted]

Excluding the [redacted] patients did not affect the power to detect non-inferiority, and the results of this analysis confirmed that, even without the data from site [redacted] the new formulation of r-hFSH is non-inferior (equivalent) to the currently approved formulation of Gonal-F.

APPEARS THIS WAY
ON ORIGINAL

Serono, Inc.
One Technology Place
Rockland, MA 02370
Tel: 781-982-9000
Fax: 781-681-2924
www.seronousa.com

March 19, 2004

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

Dear Sir/Madam:

Enclosed please find a check in the amount of $266,700 which represents the balance of User Fees for New Drug Application (NDA) 21-765 which was submitted on May 23, 2003 to the Center for Drug Evaluation and Research, US Food and Drug Administration pursuant to Section 314 of the Code of Federal Regulations.

User Fees (No. 4540) in the amount of $266,700 were paid on May 22, 2003 for a Supplemental New Drug Application (SNDA) containing clinical data (NDA 20-378/S-032). This SNDA has been re-classified as a New Drug Application, NDA 21-765. As discussed with Michael Jones, Special Assistant (ORP), the balance of the FY2003 fees for a NDA in the amount of $266,700 has been applied to NDA 21-765.

1.	**Company Name and Address:**	Serono, Inc. One Technology Place Rockland, MA 02370
2.	**Contact Person and Phone Number:**	Pamela Williamson Joyce Tel: (781) 982-9000
3.	**Application:**	NDA 21-765 for Gonal-f® (follitropin alfa for injection)
4.	**User Fee Number:**	4540

This original NDA contains clinical data generated to support a new formulation of Gonal-f®.

Sincerely,

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

Cc (cover letter only):

Michael Jones
Special Assistant
Office of Regulatory Policy, HFD-005
Center for Drug Evaluation and Research
Food and Drug Administration
Rockwall-2, Room 1118
5515 Security Lane
Rockville, MD 20852

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Fishers Document Room
5600 Fishers Lane, Room 8 B 45
Rockville, MD 20857

18. USER FEE

Serono, Inc. has made a payment of $266,700 for the review of this Supplemental New Drug Application requiring clinical data.

Please refer to the attached User Fee Cover Sheet, cover letter, and photocopy of the check sent to the US Food and Drug Administration's lockbox at the Mellon Bank located in Pittsburgh, PA.

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 (follitropin alfa for injection)

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

NDA 20-378

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

4540

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)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President, Regulatory Affairs and Quality Assurance, North America	May 23, 2003

CONFIDENTIAL

Serono, Inc.
One Technology Place
Rockland, MA 02370
Tel: 781-982-9000
Fax: 781-681-2924
www.seronousa.com

May 22, 2003

Food and Drug Administration (360909)
Mellon Client Service Center RM 670
500 Ross Street
Pittsburgh, PA 15262-0001

Dear Sir/Madam:

Please find enclosed herewith a check in the amount of $266,700.00 for User Fees related to the following Supplemental New Drug Application (SNDA) which will be submitted to the Division of Urologic and Reproductive Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration.

1.	**Company Name and Address:**	Serono, Inc. One Technology Place Rockland, MA 02370
2.	**Contact Person and Phone Number:**	Pamela Williamson Joyce, RAC Vice President, Regulatory Affairs and Quality Assurance, North America Tel: (781) 982-9000
3.	**Application:**	Labeling SNDA containing clinical study reports to update the package insert for Gonal-f® (follitropin alfa for injection) NDA 20-378
4.	**User Fee Number:**	4540

Sincerely,

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

Standard Register ®

serono Serono Inc.
One Technology Place, Rockland, MA 02370
(800) 283-8088

CHECK NO. 74889
DATE 15-MAY-03

INVOICE	DATE	DESCRIPTION	AMOUNT
USER FEE SNDA	14-MAY-03	ID #4540	266,700.00
VENDOR	FOOD & DRUG ADMINISTRATION	TOTAL >>>	266,700.00

FORM B11284 PRINTED BY STANDARD REGISTER U.S.A.

VERIFY THE AUTHENTICITY OF THIS MULTI-TONE SECURITY DOCUMENT. CHECK BACKGROUND AREA CHANGES COLOR GRADUALLY FROM TOP TO BOTTOM.

serono Serono Inc.
One Technology Place, Rockland, MA 02370
(800) 283-8088

BankBoston Maine, N.A.
South Portland, ME

52-153
112

User Fee #4540

CHECK NO.	74889
DATE	15-MAY-03
AMOUNT	****$266,700.00

PAY ⇨⇨⇨ PAY ONLY 266700 00 CTS

TO THE ORDER OF
FOOD & DRUG ADMINISTRATION
MELLON CLIENT SVC CENTER
ROOM 670
500 ROSS STREET
PITTSBURGH, PA 15262-0001

AUTHORIZED SIGNATURE

Monica Elliott
AUTHORIZED SIGNATURE

⑈074889⑈ ⑆011201539⑆ 80 024 730⑈

FOLD

serono Serono Inc.
One Technology Place, Rockland, MA 02370
(800) 283-8088

IMAGE SEAL® 5,427,851 85C11Z08 (REV. 3-98)

FOOD & DRUG ADMINISTRATION
MELLON CLIENT SVC CENTER
ROOM 670
500 ROSS STREET
PITTSBURGH, PA 15262-0001

C

13 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Teleconference minutes

Date: 7/19/01

Recorded by: Duu-Gong Wu, Ph.D, ChemistrTeam Leader

Subject: Supplement proposal, NDA 20-378, Gonal-F (Serono)

Background:

Serono sent to the reviewer directly a proposal for an incoming supplement submission and requested a feedback. A teleconference was held on 7/19/2001 between the reviewer and Pamela Williamson Joyce of Serono to discuss the proposal. In the faxed proposal, reference is made to the meeting with FDA of January 13, 2000 regarding the proposal to change the manufacturing process from filling the vials by international units to filling the vials by mass(mcg). The rationale was that filling the vials by mass (mcg) will provide a more consistent product in term of dosing as compared with the vials filled based on less precise biological activity. During the meetings, the amount of stability data to be submitted in support of two manufacturing sites and three dosage strengths was discuss and agreed. However, the current proposal includes three manufacturing sites (instead of two) and a total of 5 dosage strengths. In addition, the formulation for the lower strength is also changed to include methionine — and — Tween 20. The formulation for two multidose vials remains unchanged.

In addition to the vial filling, other changes included in this proposal are summarized below:

1. The manufacturing formulation has been modified to include a — and methionine for three single dose vials including 37.5 IU, 75 IU, and 150 IU.
2. For the multiple dose vials, a new strength of 450 IU is also added.
3. Instead of two manufacturing sites as proposed in the meetings for monodose strengths, a total of three manufacturing sites are proposed, including ' —
4. Stability bracket is also proposed for the three sites as listed below.

Masa/IU	No of lots with — stability data at the time of submission	Stability commitment	Annual lots
— mcg/37.5IU			
— mcg/75IU			
— mcg/150 IU			
— mcg/450 IU			

After reviewing the proposal that the also include a stability bracketing scheme, the following recommendations were communicated to the applicant during the teleconference:

1. The changes included in the proposal should be divided into two separate supplements because the types of changes. The first supplement should include only the changes of formulation and manufacturing site for lower strengths of IU, 75 IU, and 150 IU. The second supplement will be for the two multi-dose vials for which the formulation and manufacturing site are not changed. The addition of a new strength and the vial filling by mass are the subjects for a review.

2. As a result of formulation and manufacturing changes, the test and acceptance criteria for the drug substance (including , manufacturing process, stability protocol, and labeling will need to be revised accordingly. Also, microbiology and biopharm review may be needed.

3. The proposed stability bracket described above is not acceptable. Because it involves in changes in formulation and additional sites. The modified testing scheme as listed in the table below should be followed.

Masa/IU	No of lots witl . stability data at the time of submission	Stability commitment	Annual lots
mcg/37.5IU			
ncg/75IU			
mcg/150 IU			
ncg/450 IU			

Stability data should be provided for the new strength of 450IU, since it is a new strength.

4. I also informed her that in addition to historical data, the data from the vials filled by mass should be validated to establish the correlation of mass (mcg) to biological activity, if there was a greater variation regarding the protein content for historical lots (filled by IU).

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/s/

Duu-gong Wu
9/4/01 01:06:57 PM
CHEMIST

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9 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

NDA: 21-765
Drug: Tradename (follitropin alfa for injection)
Sponsor: Serono, Inc.

CAC/ECAC

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

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Statistical Review of Carcinogenicity Studies

This new drug application does not require a statistical review of carcinogenicity studies.

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Methods Validation

This will be reviewed after NDA approval

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Controlled Substances Staff

This new drug application does not require review by the Controlled Substances staff.

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Microbiology Efficacy

This new drug application did not require a microbiology efficacy review.

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Safety Update Review

See Medical Officer's review.

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Environmental Assessment

A categorical exclusion was granted for this new drug application.

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Advisory Committee Meeting

This new drug application was not the subject of any advisory committee meeting.

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Federal Register Notice

This new drug application was not the subject of any Federal Register Notice.

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Financial Disclosure

See Medical Officer's review.

NDA: 21-765
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Press Office

This new drug application was not the subject of any Press Office releases.

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Application Classifications

This is a new drug application for the fill-by-mass formulation of Gonal-f (follitropin alfa for injection), which was originally approved on September 27, 1997. This was originally submitted as NDA 20-378/S-032, but it was decided during the review cycle that a new NDA number would be assigned to this efficacy supplement.

NDA: 21-765
Drug: (follitropin alfa for injection)
Sponsor: Serono, Inc.

User Fee Goal Date

This new drug application has a user fee goal date of March 26, 2004.

NDA: 21-765
Drug: Tradename (follitropin alfa for injection)
Sponsor: Serono, Inc.

Special Programs

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

NDA: 21-765
Drug: Tradename (follitropin alfa for injection)
Sponsor: Serono, Inc.

Application Integrity Policy

This new drug application is not on the AIP list.