CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-684

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM TO CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Dhruba J. Chatterjee, Ph.D.

NDA:	21-684
Category:	3S
Generic Name:	Follitropin Alfa injection (r-hFSH)
Brand Name:	**Gonal-F Pen**
Indication:	Ovulation induction
Sponsor:	Serono, Inc., Rockland, MA
Submission Dates:	July 28, 2003, November 4, 2003.

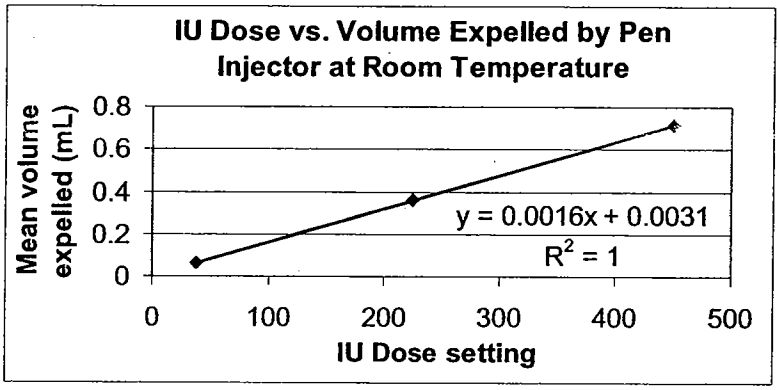
In this ADDENDUM, reference will be made to the following 3 formulations:
(i) Formulation A (fill-by-IU recombinant FSH sterile powder that is **approved**),
(ii) Formulation B (fill-by-mass recombinant FSH sterile powder that is **not-approved and not bioequivalent, or BE, to A)** and
(iii) Formulation C (sterile solution of recombinant FSH that is the subject of this NDA).
[Note: Formulation C has 2 relevant aspects: i) formulation itself as delivered by a syringe in the BE study and ii) formulation C as delivered by a Pen Injector device (the to-be-marketed product]

The current NDA determines whether Formulation C (test, as Pen Injector) is BE to B (reference). However, as noted in (ii) above, formulation B is an unapproved reference, which is not BE to A. Currently, a review is ongoing for NDA# 20-378, S-032 to determine whether Formulation B is equivalent to Formulation A based on clinical efficacy/safety itself, since BE could not be established. Note that formulation B may end up as an approved stand-alone formulation based on its efficacy from this 'non-inferiority' study which is focusing on ovulation induction indication alone.

In this current NDA, formulation C ***was bioequivalent*** to formulation B (albeit, C was administered via a syringe), however decision on marketability of formulation C may not be granted until review of NDA# 20-378 S-032 is completed and formulation B is found as an acceptable reference.

In the current NDA, the sponsor conducted BE study (# 23572) to compare systemic exposure to FSH following injection of similar doses of formulation B and C. Specific injection volumes were used in syringes for dosing – 1 mL of formulation B (containing 21.93μg of r-FSH) vs. **0.480 mL** of formulation C (containing 20.08 μg of r-FSH) – both equivalent to 300 IU of r-FSH. Note that formulation B was 8% higher in dose as compared to formulation C (as per sponsor's correction provided on 11/4/03). The intended commercial mode of administration is via pen-injectors, **a device that was not used in the BE study as noted above.**

Hence, an essential component of the equivalence is to establish that similar volumes that were used for formulation C in the BE study could be reproduced by the 'to-be-marketed' pen-injectors (all other components of the formulations remain same). The sponsor conducted an *in vitro* study in which they measured expelled volumes from the injector pens at different temperatures. They used 37.5, 225 and 450 IU dose settings for determining the performance of the expelled volumes. The injectors were weighed before and after each injection, and density of the expelled placebo solution (all components other than the drug) was used to convert the weight to the volume. The following graph represents the sponsor's findings at room temperature.



All volumes were within the specification range (ranging ±17% for the 37.5 IU dose and ±5% for the higher doses). Using the above graph, one can compute that the volume expelled by the injector when set to 300 IU would be 0.483 mL (note: this was similar to the target volume injected in the BE study with syringes of 0.48 mL – most of the values injected in the BE study were between 0.481 – 0.495 mL). Similar results were also obtained (as above graph) when the study was repeated at other temperature conditions. The results show that the pen-injector is consistent in its ability to expel the intended volume.

Hence, the sponsor has provided adequate evidence to prove that the pen-injector can predictably, accurately and reproducibly inject target volumes of the drug solution from different device settings and different temperatures. The volume injected from the 300 IU setting is the same as that injected as formulation C from the syringe in the BE study .

Conclusion: Formulation C Pen Injector (solution of r-FSH – subject of the current submission) is deemed bioequivalent to Formulation B (fill-by-mass r-FSH sterile powder) from an OCPB perspective. However, as mentioned above, marketability of formulation C may not be granted until review of NDA# 20-378 S-032 is completed and formulation B is found as an acceptable reference.

Contingency of Bioequivalence: This being a key "bridging" BE study (there is no clinical information on formulation C other than limited safety information from this BE study) an inspection has been requested for this BE Study (# 23572) with DSI. The above conclusion is, therefore, contingent upon the finding of this inspection.

Additional Safety Issue

Based on the Medical Officer's concern involving the limited data available on QT prolongation in the BE study, a review of the data was performed. The sponsor reported single determination of pre-dose, during treatment and post-dose ECG findings. Based on the data reported, a significant number of patients were observed to show change in QTc values of over 10 msec from either treatments (formulation B and C). About 8 or 44 patients showed outliers > 30 msec in QTc changes.

Details on the conduct of the ECG determinations were not available (eg. when and how the ECGs were determined). Hence, based on this initial review, a conclusive determination could not be made whether the ECG findings were of concern. Therefore, the sponsor is requested to submit information on details of the conduct of these ECG determinations, submit electronic data files on the ECGs and report the QTc values using both Bazette and Fridericia correction methods.

Comments to Sponsor

Please submit the following information involving the ECG findings from the BE study:

- All relevant protocol details on how the ECG determinations were conducted (eg. when were they read with respect to time of day, treatment, meals etc).
- Employ both Bazette *and* Fridericia correction methods for determining QT corrections (QTc values).
- Electronic data sets reporting all individual ECG findings.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB) REVIEW (DFS/Final Version November 18, 2003)

NDAs: 21-684
Category: 3S

Submission Date:
July 28, 2003
November 4, 2003

Generic Name	Follitropin Alfa injection (r-hFSH)
Brand Name:	**Gonal-F Pen**
Formulations:	Liquid formulation of injection
Route of Administration:	Subcutaneous (SC)
Indication:	Ovulation induction
Sponsor:	Serono, Inc., Rockland, MA
Type of Submission:	NDA
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.
Dates of Review:	
	Received for Review: August 21, 2002
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	Briefing Draft: November 3, 2003
	DFS/FinalVersion: November 18, 2003

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Synopsis:

Gonal-(follitropin alfa) is human follicle stimulating hormone preparation of recombinant DNA origin (r-hFSH). It is indicated for ovulation induction and pregnancy in infertile women and for the development of multiple follicles in the ovulatory patients participating in an Assisted Reproductive Technology (ART) program.

Gonal-f was approved in September 29, 1997 as freeze-dried sterile powder (formulation A). However, as part of Phase IV commitment, the sponsor was requested to ensure the stability of the drug products. Therefore, the sponsor modified the approved formulation by adding methionine and polysorbate 20 (formulation B). The formulation was also manufactured using filled by mass technology. To link the two formulations, the sponsor conducted a bioequivalence (BE) study in 2001. However, this study did not show bioequivalency between the modified formulation B and the marketed formulation A. Therefore, the sponsor submitted information on additional clinical/efficacy study (not BE study) with formulations A and B. This study is currently under review by the Division (NDA# 20-378, S-032). The goal action date for this supplement is in March 26, 2004.

The current NDA is with four months review clock with a goal date of November 28, 2003. This is for a new multidose liquid formulation packaged in a cartridge as part of a PEN injector device (formulation C). This new formulation is slightly different from formulation B in which m-cresol was added and polysorbate 20 was substituted with poloxamer 188 Therefore, the sponsor conducted a BE study to establish equivalency between formulation B, which is currently under review (NDA 20-378, S-032) and the new multidose liquid formulation (i.e., formulation B versus C). Thus, the sponsor used a formulation B which is not bioequivalent to the currently marketed formulation A, unless the efficacy study proves otherwise.

The BE study was conducted following a single dose of 300 IU (20 μg) of r-hFSH in 44 subjects (22 males and 22 females). The dose was administered using a regular syringe with 29 G needle rather than PEN/Device injector. The data show that the two formulations are bioequivalent (i.e., formulation B is equivalent to formulation C). The 90% CI was 0.8855, 0.9505 for Cmax and 0.9222, 0.9810 for AUClast. In this study, the expelled dose as measured by r-hFSH protein content in the reference formulation was 8% higher than the test formulation. It should be noted that in this BE study, both the formulations were injected using a 1 mL syringe. The 'to-be-marketed' formulation C is to be injected using a pen-injector device (NOT used in the current BE study).

Although the current BE study shows that the two formulations are bioequivalent, the approval of the new multidose formulation C (PEN) is contingent to the approval of formulation B submitted in NDA 20-378 (S-032), which was used as a reference. The reason for this is that formulation B is not bioequivalent to formulation A (the currently marketed formulation).

I. Executive Summary

The NDA is for Gonal-f (follitropin alfa) containing a DNA recombinant human Follicle Stimulating Hormone (r-hFSH). Gonal-f was approved in September 29, 1997 for ovulation induction and pregnancy in infertile women and for the development of multiple follicles in the ovulatory patients participating in an Assisted Reproductive Technology (ART) program.

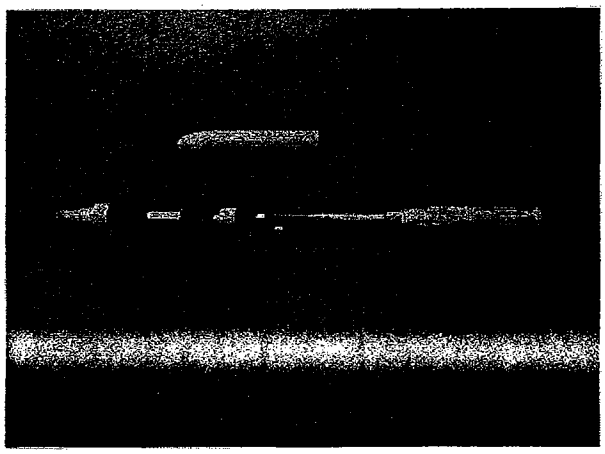
Gonal-f was approved under NDA # 20-378. However, the current submission is under a new NDA number (21-684). This strategy for a new NDA number was agreed upon at the pre-NDA meeting held with the sponsor on December 11, 2002. The reason for assigning a new NDA number for the current submission was to avoid confusion between other supplements that have been submitted for gonal-f post-approval. It was also agreed that this NDA would be considered as an "administrative supplemental NDA" with 4 months review clock.

Originally, the drug was approved as freeze-dried sterile powder (formulation A) with Phase IV commitment to ensure the stability of the drug product. Therefore, the sponsor modified the approved formulation A by adding nethionine and polysorbate 20 (formulation B). To link the two formulations, the sponsor conducted a BE study in 2001. Upon review, these two formulations were not found to be bioequivalent. The sponsor was then conducted a clinical/efficacy study (not BE study) with formulations A and B which is currently under review by the Division under the original NDA# 20-378 (S-032).

The current NDA is for a new multidose liquid formulation packaged in a cartridge placed within a PEN injector device and attached with 29 G needle (formulation C). In terms of composition, the new formulation C (test) differs from formulation A (currently marketed formulation) with the introduction of Methionine Poloxamer 188 and replacement of benzyl alcohol with m-cresol Therefore, the new multidose formulation differs from formulation B (freeze-dried filled by mass i.e., reference) by the addition of m-cresol and in the substitution of polysorbate 20 by Poloxamer 188.

The new multidose formulation will be supplied as an aqueous solution for SC injection in three different strengths: 300 IU/0.5 mL (22 µg/0.5 mL), 450 IU/0.75 mL (33 µg/0.75 mL), and 900 IU/1.5 mL (66 µg/1.5 mL). These strengths will be supplied in cartridges placed in PEN injection device attached with 29 gauge needle for self-injection and dose adjustment as shown in the following Diagram (**Figure A**):

Figure A: Pen and Injection Device Diagrams



Pen

1 injection button
2 dosage control scale
3 dosage dial
4 dose arrow
5 reservoir holder (cartridge)
6 plunger piston
7 reservoir scale
8 ribbed tip
9 pen cap

Needle

10 removable needle
11 needle shield
12 needle container
13 protective peel tab

For the approval of this multidose formulation/device, the sponsor conducted a BE study to establish equivalency between the reference formulation B (freeze-dried lyophilized powder filled by mass), which is currently under review (NDA 20-378, S-032) and the new multidose liquid formulation C (test). Note that formulation B (reference) is not bioequivalent to the currently marketed formulation A.

In this submission, the sponsor conducted a BE study following a single dose of 300 IU (20 μg) of r-hFSH for both the reference and the test formulations. Note again that formulation B (the reference) is not bioequivalent to the currently marketed formulation A. The study was conducted in 44 subjects comprised of 22 males and 22 females. The total number of subjects completed the study was 39. The data show that the two formulations are bioequivalent (i.e., formulation B and formulation C). **Figure B** and **Table A** show the summary of the data. The PEN injector device (to be marketed) was *not* used to inject formulation C in this BE study (a 1 mL syringe was used). In addition, the sponsor conducted an *in vitro* determination to find out the exact expelled dose for the test and reference formulations. The expelled dose, as expressed by r-hFSH protein content, was 8% lower in the test formulation as compared to the reference formulation (20.08 μg/dose for the test and 21.93 μ/dose for the reference).

Figure B. Mean (±SD) Serum FSH Concentration-Time Profiles Following Monodose Freeze-Dried (FD) and Multidose Liquid Formulation (PEN) in 39 subjects.

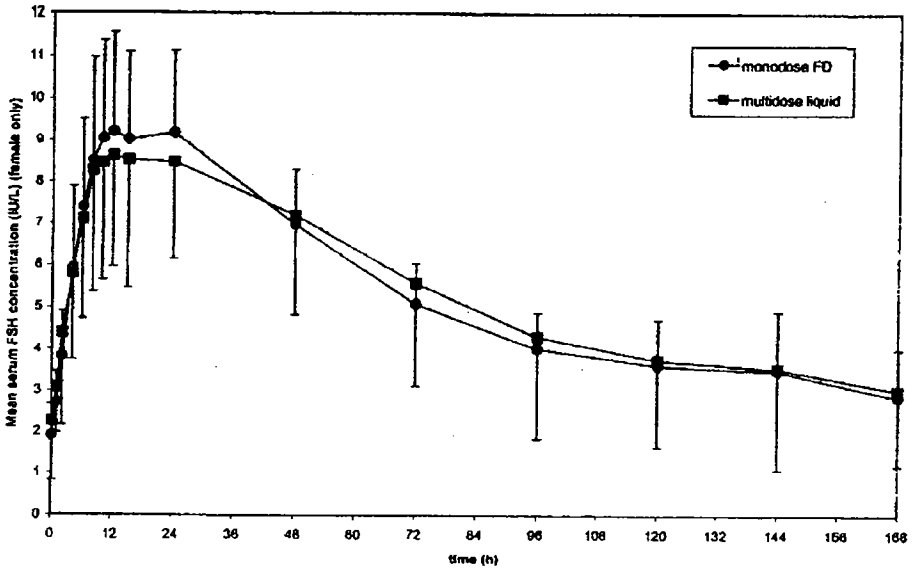
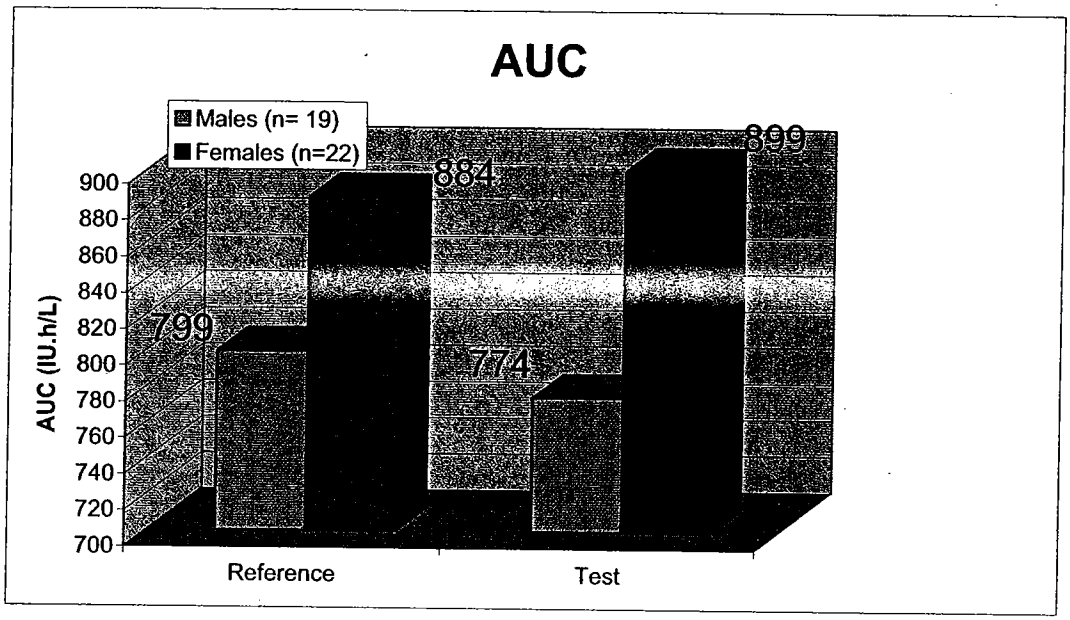


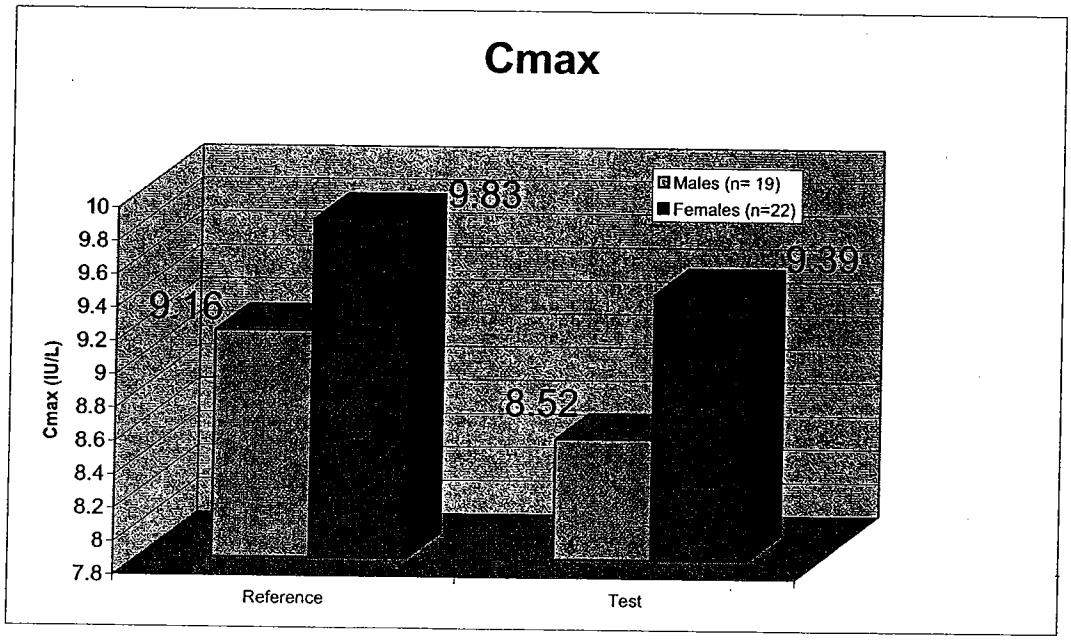
Table A. Summary of PK/BE Data for Monodose Freeze-Dried (FD) Formulation and Multidose Liquid Formulation (PEN) in 39 subjects.

Average Bioequivalence corrected for baseline r-hFSH					
Response	Estimated Ratio	Intravolunteer CV(%)	90% C.I.	Decision Rule	Bioequivalent?
C_{max}	0.9175	9.21	0.8855, 0.9505	Inclusion in (0.8,1.25)	YES
AUC_{last}	0.9512	8.03	0.9222, 0.9810		YES
Average Bioequivalence					
Response	Estimated Ratio	Intravolunteer CV(%)	90% C.I.	Decision Rule	Bioequivalent?
C_{max}	0.9261	10.68	0.8892, 0.9646	Inclusion In (0.8,1.25)	YES
AUC_{last}	0.9568	8.68	0.9257, 0.9890		YES

There was a gender difference in Cmax and AUC. In females the Cmax and AUC were much higher than males (**Figure C and D**). The reason for this difference is unknown.

Figure C. Gender Differences in Cmax and AUClast





Conclusions:

Although, the two formulations are bioequivalent, the approval of the new mutidose formulation (PEN/device) may not be granted at this time. The approval of this current NDA is contingent upon the regulatory action on NDA # 20-378 supplement # S-032 with a 10 months clock (action expected in March 2004).

1.1 RECOMMENDATION:

The two formulations are bioequivalent. However, the approval of the new multiodose liquid formulation (PEN) is contingent to the approval of monodose formulation of the freeze-dried powered that is currently under review within the Division (NDA 20-378, S-032).

1.2 LABELING RECOMMENDATIONS

Labeling comments are pending the approval of the freeze-dried formulation, which is currently under review (NDA 20-378, S-032).

1.3 COMMENTS TO THE SPONSOR

The following comments were conveyed to the sponsor in a form of "information request" letter dated October 30, 2003.

1. Please provide Tables and Figures with mean and standard deviation as follows:

    a) Males and females (i.e., all completed subjects)
    b) Males only
    c) Females only

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

2. Please note that all mean data should be reported as 'arithmetic means' rather than 'geometric means'. Please provide replacement tables, as applicable.
3. Please provide explanation on the significant difference in both Cmax and AUC between males and females.
4. Please clarify the title of Figures 6 (reference) and 7 (test) for individual FSH serum concentration-time profiles in pages 58 and 59 (volume 1.7). Both figures indicate the data are for 22 subjects and after a dose of 250 μg. To our understanding is that 39 subjects have completed the study for both the reference and the test products. In addition, the dose was 20 μg (300 IU) not 250 μg.
5. In addition, the dose reported in the Pre-NDA meeting package dated November 12, 2002 for the same study was 22 μg (300 IU). This dose was reported in several

locations of that pre-NDA package (e.g., in page 4 under objectives). Also, it was reported in the CMC section of the current NDA as 300 IU equivalent to 22 µg. Please clarify the dose in the BE study, CMC section, and the label.

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

1.4 Summary of Sponsor's Response:

On November 4, 2003 the sponsor submitted a response that satisfactorily addressed all the issues above. The following is the summary of the sponsor's responses:

- The sponsor submitted new figures and Tables for the mean ± SD for FSH serum profiles and data in all subjects, males only, and females only.
- The sponsor provided clarification on the dose used in the BE study and the number of subjects. The sponsor apologized for the error in the dose and number of subjects.
- The dose was rounded to the nearest number. In terms of weight, the dose that was used in the BE study was 22 µg which is equivalent to 300 IU.
- The mean data for the protein content in the *in vitro* study was inverted. In the original submission, the expelled dose as measured by r-hFSH protein content in the test was 8% higher than that of the reference. The sponsor clarified that this was inadvertently inverted (i.e., the test is 8% lower than the reference).

1.5 DSI Inspection Request

The reviewer recommends DSI inspection of the BE study (Study #23572) and all relevant supporting information.

1.6 Safety Related Issues

Please refer to the addendum in reference to QTc prolongation (page 3).

2.0
Clinical Pharmacology and Biopharmaceutics Review (Question Based Review)

2.1 Background

Administrative Note (Why a New NDA #?):

This is an "administrative supplemental NDA" with 4 months review clock per the discussion with the Division held on December 11, 2002. In addition, the sponsor was requested at that meeting to open a new NDA in order to avoid confusion with the original NDA 20-378 and other post-approval supplements.

How Gonal-f is Currently Supplied?

Table 1 shows a summary of all submitted and approved formulations. Gonal-f is currently marketed in following strengths:

A) Single-dose Ampules (Formulation A)

- 37.5 IU (3 μg) lyophilized powder and 1 ml ampule of water for injection
- 75 IU (6 μg) and lyophilized powder and 1 ml ampule of water for injection
- 150 IU (12 μg) and lyophilized powder and 1 ml ampule of water for injection

B) Multi-dose vials (formulation A, exactly the same as above)

- 1200 IU lyophilized powder and 2 ml pre-filled syringe with bacteriostatic water for injection (0.9% benzyl alcohol). This would deliver approximately 1050 IU FSH activity after reconstitution with diluent.

Table 1. History of Formulation Composition of Gonal-f (from the Chemistry review).

Note: Formulation A (approved, NDA 20-378 and S-016)
Formulation B (S-015 and S-016 not approved and S-032 currently under review, NDA 20-378)
Formulation C (Current NDA, 21-684)

SUMMARY OF GONAL-F FORMULATIONS

		NDA 20-378 Approved, original submission				NDA 20-378 S-016	NDA 20-378 S-015	NDA 21-684 Under review, original submission		
		Single-dose powder For reconstitution in sterile water for injection				Multi-dose powder For reconstitution in bacteriostatic water for injection	Single-dose powder For reconstitution in sterile water for injection	Multi-dose solution		
Ingredient	Function	37.5 IU	75 IU	150 IU	1200 IU	1200 IU	75 IU	300 IU	450 IU	900 IU
Follitropin alfa	Active ingredient	37.5 IU	75 IU	150 IU	1200 IU	1200 IU	6 µg	22.[illegible]	33.[illegible]	66.[illegible]
Polysorbate 20							0.05 mg	0.05 mg	0.075 mg	0.15 mg
Poloxamer 188								0.05 mg	0.075 mg	0.15 mg
L-Met							0.1 mg	1.50 mg	2.25 mg	4.5 mg
m-Cresol								30 mg	45 mg	90 mg
Sucrose		30 mg	30 mg	30 mg	30 mg	30 mg	30 mg			
Na2HPO4 2H2O		1.11 mg	1.11 mg	1.11 mg	1.11 mg	1.11 mg	1.11 mg			
NaH2PO4 H2O		0.45 mg	0.45 mg	0.45 mg	0.45 mg	0.45 mg	0.45 mg			
o-Phosphoric acid		qs	qs	qs	qs	qs	qs	qs	qs	qs
Sodium hydroxide	pH adjusting agent	qs	qs	qs	qs	qs	qs	qs	qs	qs
Water for Injection	Solvent	qs	qs	qs	qs	qs	qs			

qs: quantity sufficient; trace amount

What is the Historical Background of Gonal-f Relative to Formulation?

There are three formulations for gonal-f as they are summarized in **Table 1.** Gonal-f was approved in September 29, 1997 (formulation A). There is another Supplemental NDA (NDA # 20-378, S-032) submitted on May 23, 2003 and is currently under review for ovulation induction and Assisted Reproductive Technology (ART). In the latter NDA a clinical study was conducted (not BE study) to establish clinical/eficacy equivalency between a new lyophilized formulation (formulation B), filled-by-mass (NDA 20-378 for S-015 and S-016) to the currently marketed formulation (A).

Supplement 015 (S-015) was submitted in August 3, 2001 for — — 75, — IU. The formulation — differs from the marketed formulation by the addition of polysorbate 20 and methionine (**Table 1**). These were not found bioequivalent to the approved formulation (see OCPB review, **Appendix I**). —

/

The current NDA is for a BE study to establish equivalency between the formulation that is currently under review (formulation B, NDA 20-378, S-032) and the new multi dose liquid formulation C (i.e., formulation B versus C). The only difference between formulation B and C is that formulation C contains m-cresol instead of benzyl alcohol — and poloxamer-188 — instead of polysorbate 20 present in formulation B. Additionally, the to-be-marketed formulation is designed to be injected using a PEN injector device.

Why the sponsor Used Incorrect Reference (i.e., Formulation B):

In 2001, the sponsor submitted two BE studies with formulation A and B (see below and OCPB review in **Appendix I**). Both studies showed that the two formulations were not bioequivalent. However, the sponsor believed that the two formulation were bio-equivalent based on their population analysis of the data. Therefore, an amendment to the review was made to confirm that the two formulation were not bioequivalent, even with the use of the population BE approach. In addition, the population BE approach is not currently acceptable by the Agency. The sponsor was informed of the Agency's decision.

What Studies were submitted in this NDA?

Study # 23572 was the only study that was submitted in this NDA to establish the bioequivalence (BE) between the test and reference formulation.

What is the Rationale for the Current Bioequivalence Study?

The formulation used in the clinical study (formulation B) that is currently under review in NDA# 20-378, S-032) are the same formulation that were not found to be

bioequivalent to the marketed formulation-A (**Appendix I**, OCPB reviews in February 2003 and in December 2001). In the original review the sponsor conducted two studies (#21859 and 22596). These two studies were conducted as part of a Phase IV commitment to ensure the stability of the drug products. Therefore, the sponsor modified the approved formulation (formulation A) by adding [redacted] methionine and polysorbate 20 as [redacted] (formulation B).

In both BE studies, a single dose of Gonal-F was administered using either a single dose vial (study 21859) or multidose vial (study #22596) of formulation (A) and new single dose of formulation B (vials filled by mass). Both studies showed that the two formulations were not bioequivalent. The second study (#22596) was for a single dose using a multidose vial of formulation (A) and new single dose vial of formulation B.

Therefore, the sponsor submitted this new NDA using formulation B (filled by mass) as a reference, which is also used in the clinical study (S-032), and the new multi-dose liquid formulation-PEN (formulation C). In this case the reference used (i.e., formulation B) is not a correct reference since it was not found to be bioequivalent to the approved formulation (A), unless the clinical data from S-032 (NDA 20-378) prove the contrary.

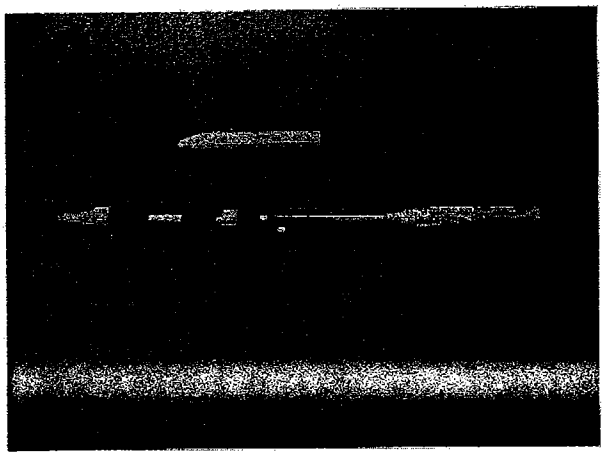
What is the Rational for the New Formulation?

The sponsor is developing a new multidose liquid r-hFSH formulation with the purpose to provide the patients and clinicians with an-easy-to-use formulation that simplifies the preparation of the injection.

The new multidose formulation will ultimately be available in cartridge as 3 different strengths achieved by different fill volumes coming from the same mother preparation. The following strengths will be available: 300 IU/0.5 mL (22 µg/0.5 mL), 450 IU/0.75 mL (33 µg/0.75 mL), and 900 IU/1.5 mL (66 µg/mL). All strengths will be available in a pre-filled glass cartridge that differ only in the filling volume, so the same concentration of both active ingredient and excipients is present in the 0.5, 0.75, and 1.5 ml.

This new formulation will ultimately be delivered with a pen device with 29G needle, from which the dose could be dialled directly as appropriate by the patient. **Figure 1** shows the diagram of the cartridge, PEN, and the injection device.

Figure 1: Pen and Injection Device Diagrams



Pen

1 injection button
2 dosage control scale
3 dosage dial
4 dose arrow
5 reservoir holder (cartridge)
6 plunger piston
7 reservoir scale
8 ribbed tip
9 pen cap

Needle

10 removable needle
11 needle shield
12 needle container
13 protective peel tab

What are the Compositions of Each Formulation:

The product has three dosage strengths: 300 IU (22 µg in 0.5 mL), 450 IU (33 µg in 0.75 mL), and 900 IU (66 µg in 1.5 mL). All three strengths have the same concentration of 625 IU/mL and are differentiated by fill volumes (for details, please see chemistry review and **Tables 1 and 2**).

A) Reference (Monodose freeze-dried formulation)

One vial is filled to deliver 10 µg (or 150 IU) of lyophilized powder of r-hFSH and also contains:

Sucrose	30 mg
Na_2HPO_4 2H2O	1.11
NaH_2PO_4 1H2O	0.45 mg
Methionine	0.1 mg

Diluent: 1 ml water for injection in either vials or pre-filled syringes (PFS). This is for reconstitution of the powder. For details see **Table 2.** Two vials were used to deliver 20 µg (300 IU) of the reference formulation (freeze-dried).

B) Test (Liquid Formulation)

One cartridge is filled to deliver 12 doses of 5 µg in 120 µl and also contains:

r-hFSH	66 —
Sucrose	90 mg
Na_2HPO_4 2H2O	1.66 mg
NaH_2PO_4 1H2O	0.675 mg
—	0.15 mg
Methionine	0.15 mg
m-Cresol	4.5 mg

This r-hFSH multidose was supplied in a liquid form of 3 ml cartridge (type I glass).

Table 2. Composition of Drug Product per Cartridge (from Chemistry review)

Component	Quality	Function	300 IU Amount per 0.5 g content	450 IU Amount per 0.75 g content	900 IU Amount per 1.5 g content
Follitropin alfa		Active ingredient	22	33	66
Poloxamer 188	USP		0.05 mg	0.075 mg	0.15 mg
Sucrose	USP		30 mg	45 mg	90 mg
-Met	USP		0.05 mg	0.075 mg	0.15 mg
Na2HPO4 2H2O	USP				
NaH2PO4 H2O	USP				
m-Cresol	USP		1.50 mg	2.25 mg	4.5 mg
o-Phosphoric acid	USP	pH adjusting agent	qs	qs	qs
Sodium hydroxide	USP	pH adjusting agent	qs	qs	qs

qs: quantity sufficient

What is the Objective of the BE Study (Study #23572)?

- The primary objective of the study is to compare the relative bioavailability of r-hFSH following a single SC dose as 1 ml from the monodose freez-dried formulation (formulation B) and 0.48 ml from the mutidose liquid formulation.
- The secondary objective of the study is to assess the local and systemic tolerability of both formulations.

How was the Study Designed?

Briefly, this was a crossover study in 44 male and premenopausal females subjects (n=22 in each gender). Two SC 300 IU (20 μg) injections were give of r-hFSH as either 1 ml of the reconstituted freeze dried monodose formulation (formulation B, reference) or 0.48 ml of new liquid multidose formulation (formulation C, test). One-week washout period was allowed between each treatment. Note that Formulation C was injected with a 1 mL syringe, but the intended commercial mode is a PEN injector device.

The volumes of 0.48 and 1ml were injected via plastic syringe with 29 gauge needle. Liquid form was supplied in 3 ml glass cartridge. Blood samples were collected at the following time points after each administration: 0 (pre-dose), 1, 2, 4, 6, 8, 10, 12, 15, 24, 48, 72, 96, 120, 144, and 168 h for measurement of r-hFSH serum concentrations. **Figures 2 and 3** show details of study flow chart and monitoring schedules (see also Medical Officer's Review for details).

Figure 2. Study Flow Chart

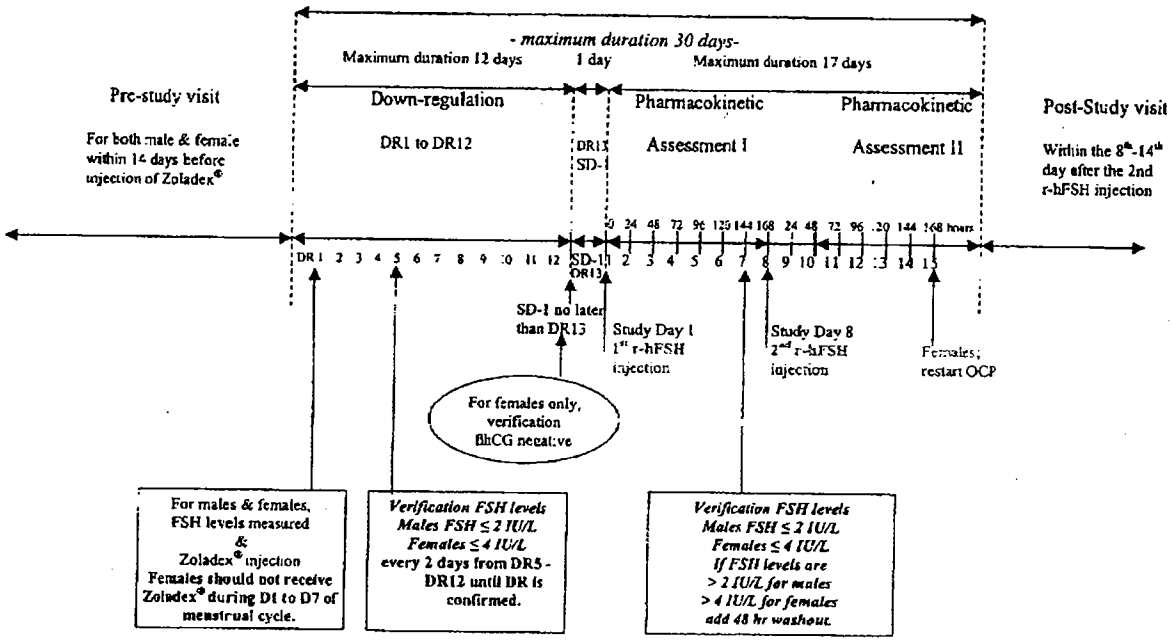


Figure 3. Scheduled Tests and evaluation

	Study day-1[1]	Pre-dose	1 h	2 h	4 h	6 h	8 h	10 h	12 h	15 h	24 h	48 h	72 h	96 h	120 h	144 h	168 h[4]
Residency																	
Randomisation	X																
Health assessment	X																
Blood Pregnancy test (females)	X																
ECG		X															
Blood pressure, Heart rate		X		X			X		X	X	X						
Oral body temperature		X		X			X		X	X	X						
Local tolerability[2]		X		X			X		X	X	X						
PK sample (FSH)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE observation																	
Volume of blood (mL)[3]	4.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5

➢ When measurements are coincident, the order of performance is: blood sample collection, local tolerability (VAS before clinical tolerability assessment) and vital signs.

1) only for the first injection.
2) the assessment of the pain was performed only 5 minutes after each injection.
3) total blood volume of approximately 300 mL.
4) 168 h after the first injection correspond to day of the second injection.

PK: pharmacokinetics

How Subjects Were Down Regulated:

All subjects were down regulated with a single SC dose of 3.6 mg Zoladex (Goserelin), an GnRH analog on Day 1 which is about 13 days prior to first FSH injection (**Figure 3**). Zoladex is commercially available in 3.6 mg pre-filled syringe. The purpose of Zoladex

administration is to produce pituitary down-regulation in order to suppress the production of endogenous FSH secretion prior to dosing with exogenous FSH (the test and the reference drugs).

What Other Concomitant Drugs Were Allowed During the Study?

A) 1% Lidocaine

Subjects were also given the option to receive 1% SC lidocaine as a local anesthetics prior to the administration of Zoladex.

B) Oral Contraceptives;

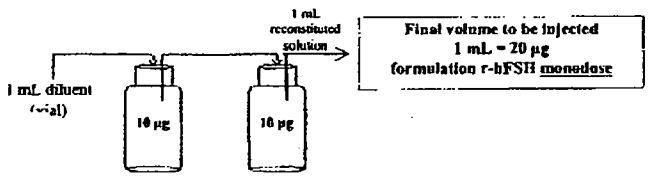
All females were taking the oral contraceptives (OC) pills upon entry into the study. They continued taking their OC until the sevenths day after the administration of Zoladex, and then stopped for the duration of the study. All females resumed taking their OC after the last PK blood samples was collected at 168 hour.

How Each Solution was Prepared and Injected?

Using a 1 ml plastic syringe, I ml, of water for injection was transferred into one vial of formulation r-hFSH monodose (**Figure 3 B**). The solution was mixed gently to avoid foaming. Using the same syringe, the reconstituted solution (1 mL) was transferred into a second vial of formulation r-hFSH monodose. This solution was mixed gently to avoid foaming. The final concentration was equivalent to 20 μg/ml of FSH. Using 1 ml plastic syringe, all of the reconstituted solution (i.e., 1 ml or 20 μg FSH) was withdrawn and injected SC using 29 gauge needle.

The second injection was 0.48 ml of the new multidose liquid formulation. The dose was also equivalent to 20 μg of FSH. Since the formulation is already in the liquid form in 3 ml cartridges, no preparation was necessary. Therefore, using a 1 mL plastic syringe, 0.48 ml of the solution was withdrawn and injected subcutaneously, also using a 29 gauge needle.

Figure 3 B. Steps of Solution Preparation for the Freeze-Dried formulation (reference)



Using a 1 mL syringe, transfer the 1 mL of water for injection into one vial of new formulation r-hFSH monodose. Mix gently to avoid foaming. Using the same syringe, transfer the reconstituted solution (1 mL) into a second vial of new formulation r-hFSH monodose. Mix gently to avoid foaming.

Using a 1 mL syringe, withdraw all of the reconstituted solution which is equivalent to 20 µg new formulation r-hFSH monodose.

The solution (20 µg in 1 mL) will be injected subcutaneously using a 29 gauge needle.
The preparation will be labelled according to the information provided in the section 8.3.

The syringe will be weighed before and after injection and results reported in the CRF.

How the Delivered Dose was Confirmed for the Test and Reference Formulations?

The sponsor conducted two studies to determine the expelled volume and protein content for both formulations in terms of r-hFSH protein content. Study 1 was conducted using 900 IU (66 µg) strength of the new liquid formulation (test) and 150 IU (11 µg) of Gonal-f freeze-dried (reference). The batches used in this study are shown in **Table 3**. Study 2, however, was conducted using two batches of 300 IU (22 µg) and 900 IU (66 µg) of the new liquid formulation as shown in **Table 4**. The second study was submitted as part of the CMC section (see also chemistry review).

Table 3. Batches Used in Expelled and Protein Content Test (Test 1)

Product	Batch number	Manufacturing site	Strength	Manufacturing date
Gonal-f, solution for injection (test)	GGC 101		900 IU (66 µg)	20 Dec 2001
Gonal-f, freeze-dried (reference)	19801030		150 IU (11 µg)	28 Mar 2000

Table 4. Batches Used in Expelled and Protein Content Test (Test 2)

Batch number	Manufacturing site	Strength	Manufacturing date	Drug Substance batch used
GFC 101		300 IU (22 µg)	20 Dec 2001	BFDA 01517
GFC 102		300 IU (22 µg)	24 Jan 2002	BFDA 01522
				BFDA 01523
GGC 101		900 IU (66 µg)	20 Dec 2001	BFDA 01517
GGC 102		900 IU (66 µg)	24 Jan 2002	BFDA 01522
				BFDA 01523

Study Procedure:

In study 1, the expelled volume and protein content (r-hFSH content) of the drug solution for the test and reference formulation (freeze-dried) were assessed based on the injection volumes as described earlier (i.e., 1 ml for the reference and 0.48 ml for the test).

The reference product was reconstituting per usual instructions. The test solution was removed from the vial using the administration syringe. The syringe and drug was then weighed (A). The drug was then expelled into an empty container. The weight of the empty syringe was recorded (B). The protein concentration was estimated using the SE-HPLC assay.

In study 2, the expelled volume and protein content (r-hFSH) of the drug solution was assessed based upon a dosage setting of 75 IU on the pen. The study was done on each of the batches, in triplicate, by using three separate pens each with the appropriate installed cartridge.

Calculation:

The expelled weight was converted to volume using the following equation:

Expelled weight = A - B

Expelled Volume = (A - B)/density

The expelled dose in protein content (r-hFSH content) was calculated as follows:

Expelled dose (µg) = (A-B)/density X r-hFSH concentration (µg/ml)

The expelled dose acceptance criteria for study 2 is shown in **Table 5.**

Table 5. Expelled Dose Study Acceptance Criteria for Study 2.

Expelled dose study parameter	Analytical procedure	Acceptance criteria for 75 IU dosage	Quantitation limit
Volume of solution	Weighing	/	N/A
Assay (r-hFSH content)	SE-HPLC		N/A

N/A. represents Not Applicable

Results:

Tables 6 and 7 show the summary of the data for both studies:

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Table 6. Protein Content in Both Test and Reference Formulations (Study 1)

Batch GGC 101 (test) Replicate	Protein Content (mcg/dose)
Mean	20.08
%CV	0.8
n	8
Batch 19801030 (reference) Replicate	**Protein Content (mcg/dose)**
Mean	21.93
	0.8
	8

Table 7. Expelled Dose and protein Content Data for PEN Injector (Study 2)

Batch GGC 101	Protein Content			Expelled Volume		
	Pen 1	Pen 2	Pen 3	Pen 1	Pen 2	Pen 3
Mean	5.14	5.14	5.07	0.120	0.120	0.118
%CV	2.25	1.74	0.81	2.12	1.77	0.61
n	12	12	12	12	12	12
Batch GGC 102	**Protein Content**			**Expelled Volume**		
	Pen 1	Pen 2	Pen 3	Pen 1	Pen 2	Pen 3
Mean	5.47	5.49	5.52	0.119	0.119	0.120
%CV	1.66	2.75	2.17	1.25	1.62	1.18
n	12	12	12	12	12	12
Batch GFC 101	**Protein Content**			**Expelled Volume**		
	Pen 1	Pen 2	Pen 3	Pen 1	Pen 2	Pen 3
Mean	4.96	5.07	5.08	0.119	0.120	0.121
%CV	1.97	3.07	1.54	1.87	2.99	1.59
n	4	4	4	4	4	4
Batch GFC 102	**Protein Content**			**Expelled Volume**		
	Pen 1	Pen 2	Pen 3	Pen 1	Pen 2	Pen 3
Mean	5.55	5.33	5.51	0.123	0.118	0.122
%CV	4.18	0.72	0.65	4.23	0.49	0.79
n	4	4	4	4	4	4
Overall Mean	**Protein Content**			**Expelled Volume**		
GGC 101	5.12			0.119		
GGC 102	5.49			0.119		
GFC 101	5.04			0.120		
GFC 102	5.46			0.121		

Comments:

In study 1, there was 8% difference between the test and the reference in terms of expelled dose as measured by r-hFSH protein content. This difference could be of limited clinical significance (see Medical Officer's Review). In study 2, the expelled dose for both strengths is within the specification set for these products for both the volume [redacted] and protein content [redacted]

Conclusion:

7

Both studies confirm consistency in volume delivery for both the test and the reference formulations.

How Accurate Was the Dose?

The dose accuracy of Gonal-f Pen has been tested in accordance with the dose accuracy specifications (see also chemistry and CDRH reviews). The specification limits for dose accuracy of pen injector with single-compartment cartridge are shown in **Table 8**. The corresponding lower limit (LSL), upper specification limit (USL) and test results are

shown in **Table 9**. The data show high consistency in the volume delivery using the pen device.

Table 8. Specification for Dose Accuracy of Pen Injector

Absolute error of pre-set dose - for pre-set dose < 0.2 ml -	Relative error of pre-set dose - for pre-set dose ≥0.2 ml

Table 9. Lower (LSL) and Upper (USL) Specification Limits of the Pen Injector

pre-set dose (IU FSH)	pre-set dose (ml)	LSL (ml)	USL (ml)	[X-(K*s)] (ml) - at room temp. -	[X+(K*s)] (ml) - at room temp. -

Is there any Safety Concern Related to the PEN Injection Device?

There was no safety related issues with the injection device. The safety of the injection device was reviewed by CDRH (see **appendix II**). The sponsor compared the Gonal-f pen to two similar pen injectors approved by CDRH. The device was tested for specific dosing range and dose increments for Gonal-f. According to CDRH report, the pen injector is acceptable.

What Assay was used for the Determination of FSH Serum Level?

This was a commercially available assay . This was a validated assay with a lower limit of quantification of , and the limit of detection was .

How the Data were Analyzed?

A) PK and BE Parameters:

- Data were assessed using noncompartmental analysis.
- AUC was determined from 0 to the last measurable concentration (AUC_{last}).

B) Statistical Analysis:

- AUC_{last} and Cmax were log-transformed and analyzed using ANOVA.
- Treatment by gender, sequence, and period were tested.

C) Serum Concentrations:

- Individual and median concentrations were presented graphically.
- Values below the Lower Limit of Quantification (LLOQ) before the first measurable concentration were set to zero.
- Values below the LLOQ after the last measurable concentration were regarded as missing data.
- For calculation of the median curves below the LLOQ were set to zero. However if there was more than 50% below the LLOQ for certain time-points, no median value was reported or graphically displayed.

How Many Subjects Completed the Study?
Was there any Drop-Out?

Out of 44 subjects enrolled, 39 successfully completed the study. Therefore, 5 subjects did not complete the study as follows:

- Two (2) subjects withdraw from the study without receiving the study medication.
- One (1) subject received only the reference formulation.
- Two (2) subjects received only the test formulation in period 1.

Was There Any Safety Related Issues in this Study?

Most of the side effects in this study were mild to moderate in terms of severity. They include headache, flushes, and rashes. See the Medical Officer's review for detail.

Results:

- The data are shown in **Figures 4-19** and **Tables 10-14.**
- The mean profiles for the two formulations are very comparable as shown in **Figure 4**. The monodose seems to produce slightly higher Cmax. The mean Cmax for the monodose was 9.51 ± 2.30 IU/L and for the multidose liquid was 8.99 ± 3.43 IU/L **(Table 10)**.
- There was some variability in the study as shown from the individual profiles **(Figures 5 and 6)**. Also, there was one clear outlier for serum FSH concentration-time profile **(Figure 6)**.
- There was a noticeable difference in Tmax between the two formulations. The mean Tmax following monodose was 15.8 ± 8.24 h and 18.8 ±10.6 h for multidose liquid **(Table 10)**. The variability is also high for Tmax (CV >50%). The reason (s) for this difference has not been explained by the sponsor.
- The 90% CI for both Cmax and AUClast fall within the 80%-125%. After baseline correction, the 90% CI for Cmax was 0.8855,0.9505 and for AUClast was 9.9222,0.9810 **(Table 11)**. It should be acknowledged that the 90% CI data for both Cmax and AUClast are very tight (i.e., between 0.88 to 0.98). As shown in **Figure 7**

for the individual 90% CI for all subjects, none of the subjects had a value greater than 1.0. Therefore, from this data it can be concluded that the two formulations are bioequivalent.

- Interestingly, the exposure in females was higher than in males as shown for both Cmax and AUC (**Tables 7 B & C, and Figures 8 A, B, and C**). The reason for this difference is unknown.
- Also, the boxplots show that the monodose exhibits a higher Cmax and AUC (**Figure 9**).
- Overall, FSH level was slightly higher in period 2 than in period 1 (**Figures 10 and 11**). This suggests that there was some carry over effect from the first treatment period. However, it is believed that this effect could be attributed to the incomplete suppression of endogenous FSH in period 2.
- The sponsor acknowledged that the suppression of the endogenous FSH production was incomplete. Therefore, the sponsor was unable to calculate the half-life of FSH nor AUC value to infinity, which requires extrapolation of the terminal portion of the serum profiles.
- There was no noticeable subject treatment interaction in this study for both Cmax (**Figure 12**) or AUC (**Figure 13**). Also **Tables 12** and **13** show the ANOVA analysis for the treatment, sequence and gender interactions.
- In terms of pharmacodynamic responses, there was some difference between the two formulations in vital signs during the study. For the new liquid formulation there was a consistently higher readings for both systolic (**Figure 14**) and diastolic (**Figure 15**) blood pressure, pulse rate (**Figure 16**), and oral temperature (**Figure 17**) than after the freeze-dried formulation.
- **Figure 18** shows the individual serum FSH concentration-time profiles and **Table 14** shows individual PK parameters (Cmax, Tmax, and AUC) for both formulations..

General Comments:

- The study shows that the two formulations are bioequivalent. However, the approval of the new liquid formulation (i.e., PEN) will remain contingent upon the approval of the freeze-dried formulation used as a reference in this NDA. The freeze-dried formulation is currently under review within the Division (NDA 20-378, S-032).
- It is not clear as to why female subjects consistently show higher FSH levels than male subjects.
- It is not clear as to why the new formulation consistently produces higher vital signs than the freeze-dried formulation.
- Based on the *in vitro* supportive study, the injector PEN was shown to deliver consistent volume of drug solution and protein content. In addition, there was 8% difference in expelled volume (or protein content) between the new liquid formulation (PEN) and the constituted freeze-dried formulation (reference). The clinical significance of this could be small (see Medical Officer's review).

Figure 4. Mean (± SD) r-hFSH Serum Profiles Following Test and Reference Formulations

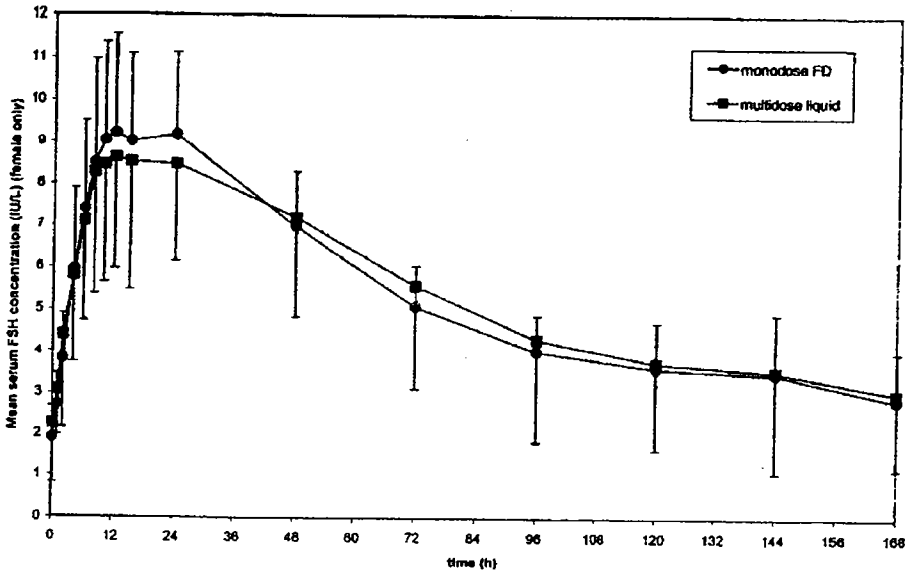

Figure 5. r-hFSH Serum Concentration-Time Profiles Following the Reference Formulation

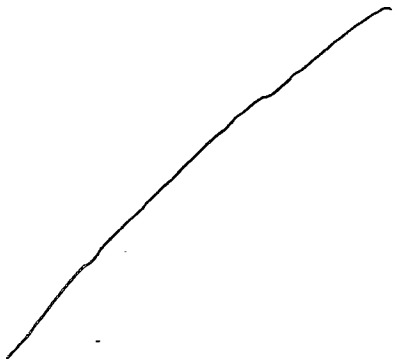

Figure 6. r-hFSH Serum Concentration-Time Profiles Following The Test Formulations

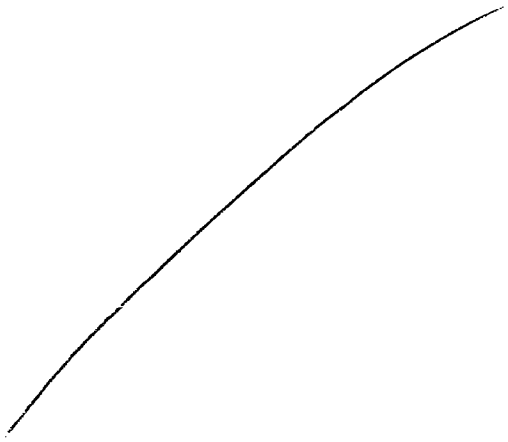

Table 10. Descriptive Statistics of the data

TREATMENT		AUC_{last} (IU·h/L)	C_{max} (IU/L)	T_{max} (h)
monodose FD (R)	N	40	40	40
	Mean	844	9.51	15.8
	SD	181	2.30	8.24
	Min		—	
	Median	840	9.40	12.0
	Max		—	
	Geometric Mean	824	9.23	14.1
	CV% Geometric Mean	22.8	26.1	51.3
multidose liquid (T)	N	41	41	41
	Mean	841	8.99	18.8
	SD	279	2.43	10.6
	Min		—	
	Median	808	8.90	15.0
	Max		—	
	Geometric Mean	811	8.69	16.4
	CV% Geometric Mean	26.0	26.5	56.2

Table 11. Summary of Average Bioequivalence Data

Average Bioequivalence corrected for baseline r-hFSH					
Response	Estimated Ratio	Intravolunteer CV(%)	90% C.I.	Decision Rule	Bioequivalent?
C_{max}	0.9175	9.21	0.8855, 0.9505	Inclusion in (0.8,1.25)	YES
AUC_{last}	0.9512	8.03	0.9222, 0.9810		YES
Average Bioequivalence					
Response	Estimated Ratio	Intravolunteer CV(%)	90% C.I.	Decision Rule	Biocquivalent?
C_{max}	0.9261	10.68	0.8892, 0.9646	Inclusion In (0.8,1.25)	YES
AUC_{last}	0.9568	8.68	0.9257, 0.9890		YES

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Figure 7. Individual 90% CI intervals for Cmax and AUClast in all subjects (n=39), except one outlier

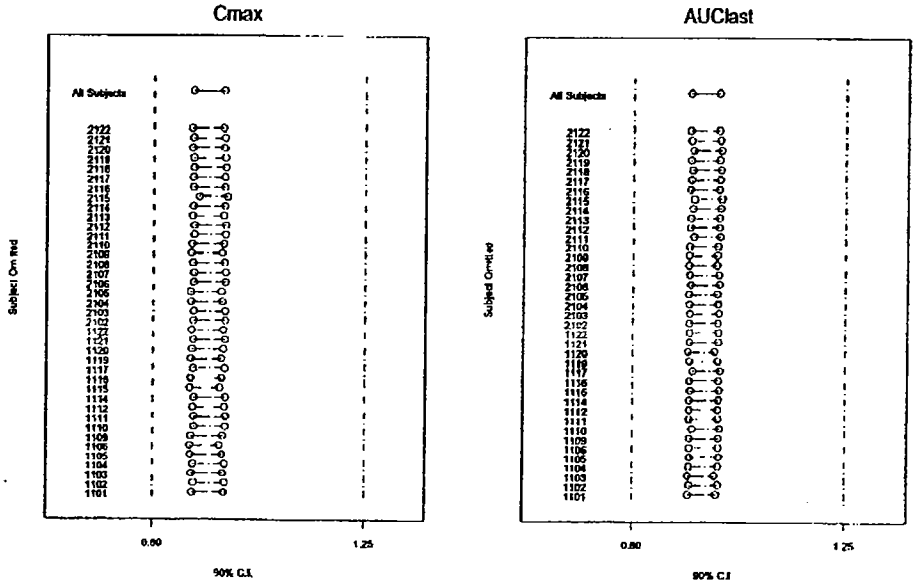

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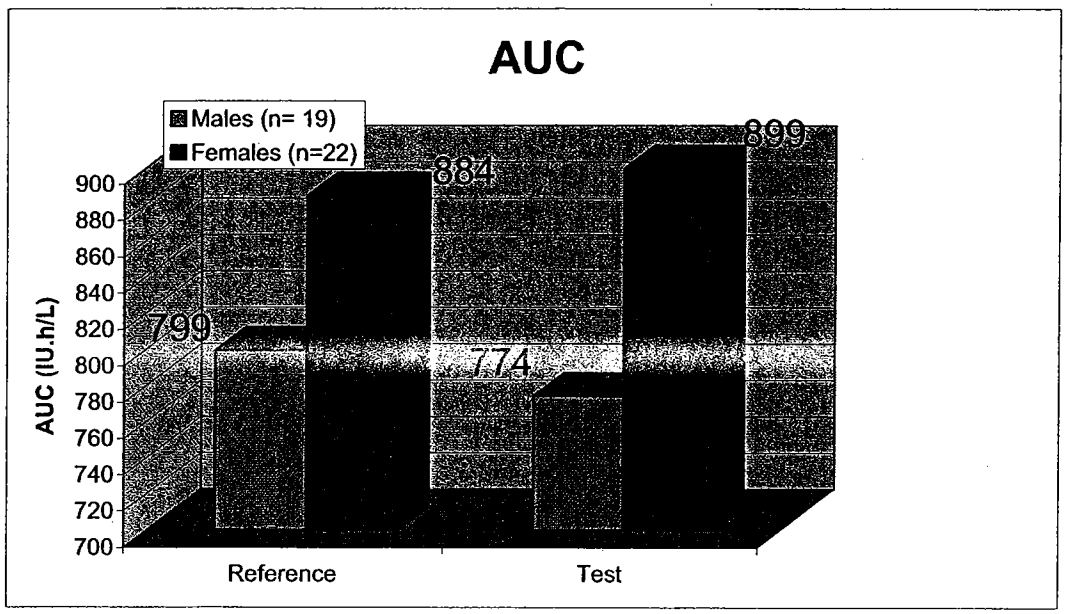
Table 7 B: PK Data for Females Only

TREATMENT	female only	AUClast (IU·h/L)	Cmax (IU/L)	Tmax (h)
monodose FD (R)	n	21	21	21
	Arithmetic Mean	884	9.83	15.5
	SD	179	2.26	6.65
	Min			
	Median	859	9.80	12.0
	Max			
multidose liquid (T)	n	22	22	22
	Arithmetic Mean	899	9.39	19.8
	SD	350	2.95	11.1
	Min			
	Median	833	8.90	19.5
	Max			

Table 7 C: PK Data for Males Only

TREATMENT	male only	AUClast (IU·h/L)	Cmax (IU/L)	Tmax (h)
monodose FD (R)	n	19	19	19
	Arithmetic Mean	799	9.16	16.2
	SD	177	2.36	9.89
	Min			
	Median	723	9.00	12.0
	Max			
multidose liquid (T)	n	19	19	19
	Arithmetic Mean	774	8.52	17.6
	SD	146	1.58	10.0
	Min			
	Median	796	8.60	15.0
	Max			

Figure 8A. Effect of Gender on Cmax and AUC



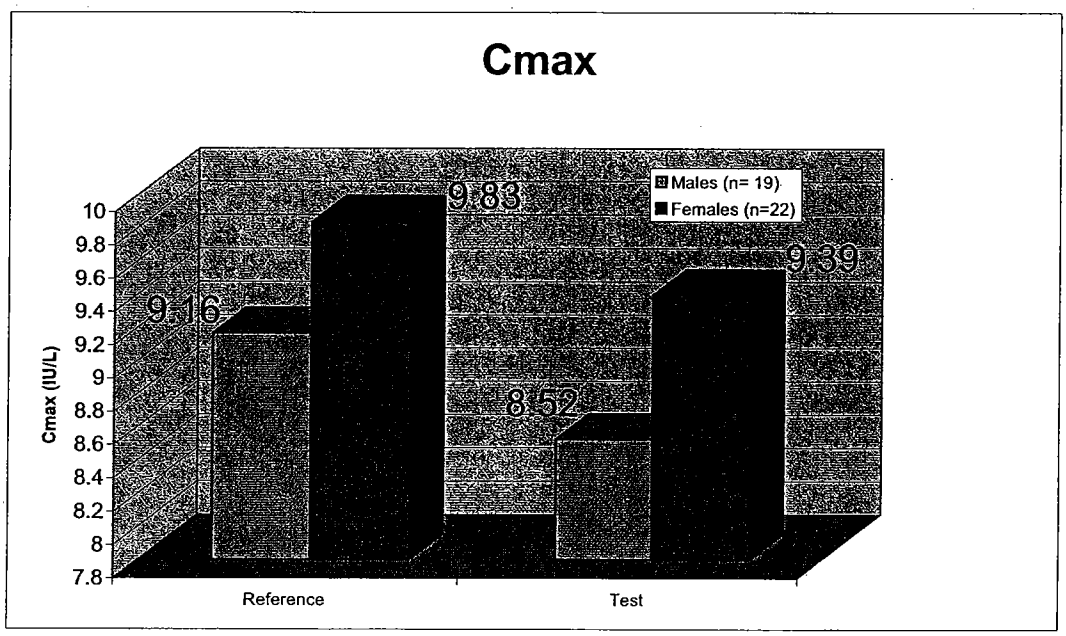
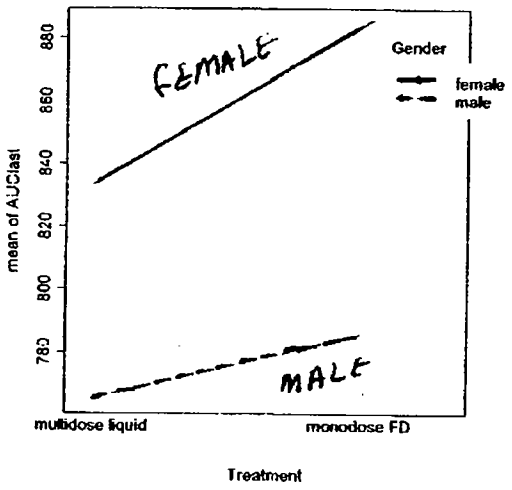


Figure 8B. Effect of Gender on Cmax and AUC

AUC



Cmax

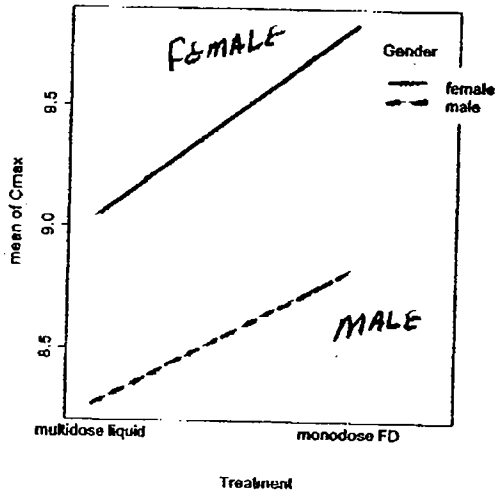


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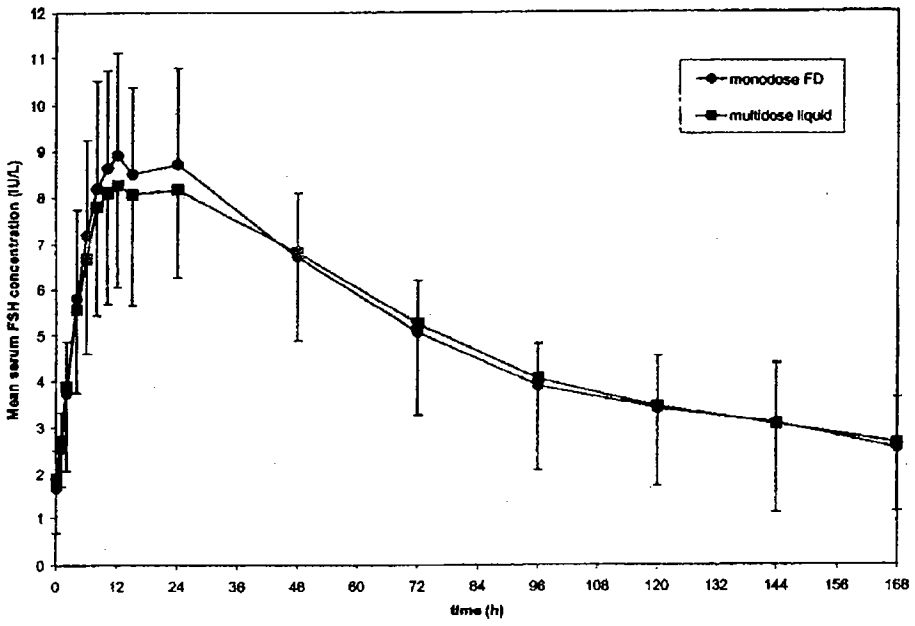
Figure 8C. Mean (± SD) r-hFSH Serum Profiles in Females only (top) and males only (bottom) for the Test and Reference Formulations

Females



Males

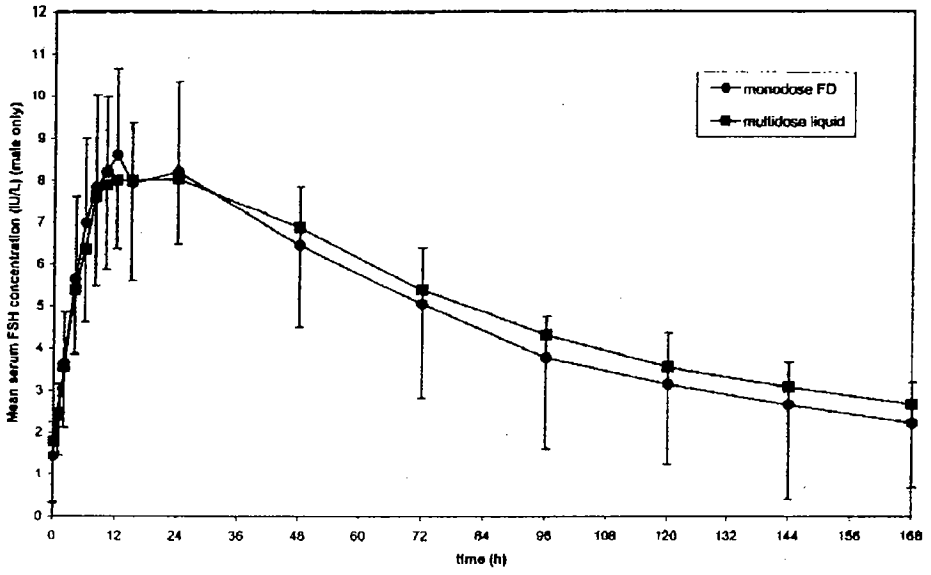


Figure 9. Effect of treatment on Cmax (left) and AUC_{last} (right) for the Test and Reference Formulations

Cmax **AUC**

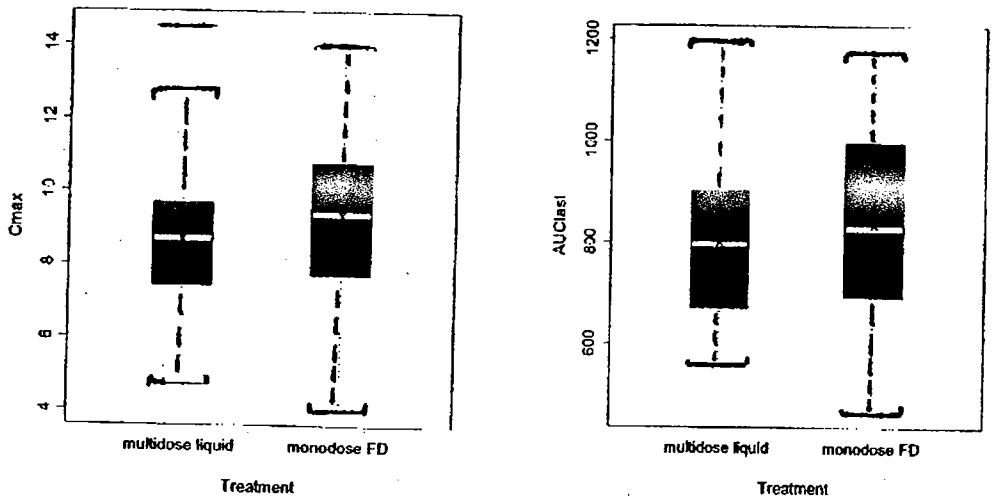


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Figure 10. Test Period (sequence) Effect on Cmax for the Test and Reference Formulations

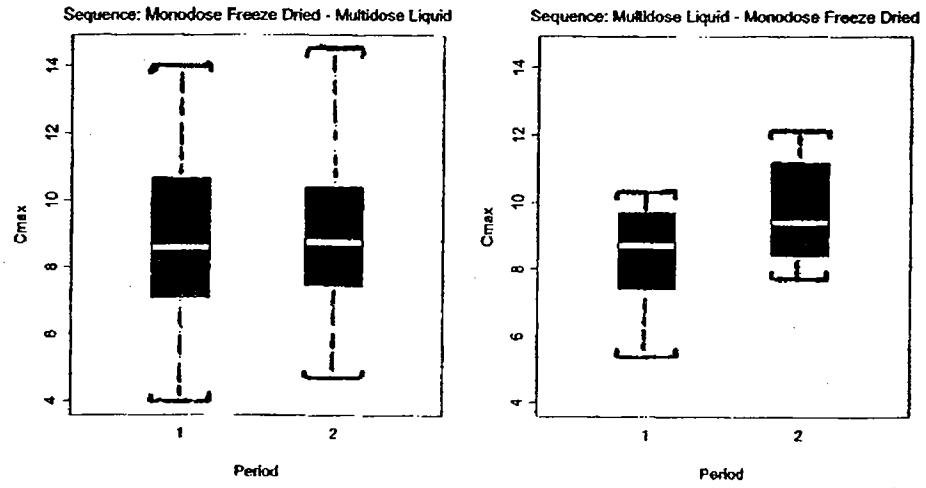

Figure 11. Test Period (sequence) Effect on AUClast for the Test and Reference Formulations

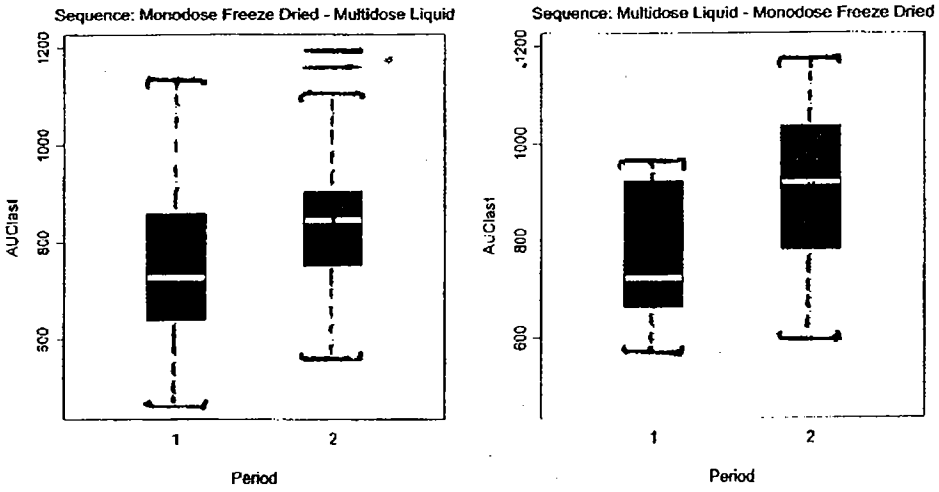

Figure 12. Subjects treatment Interaction Plots for Cmax

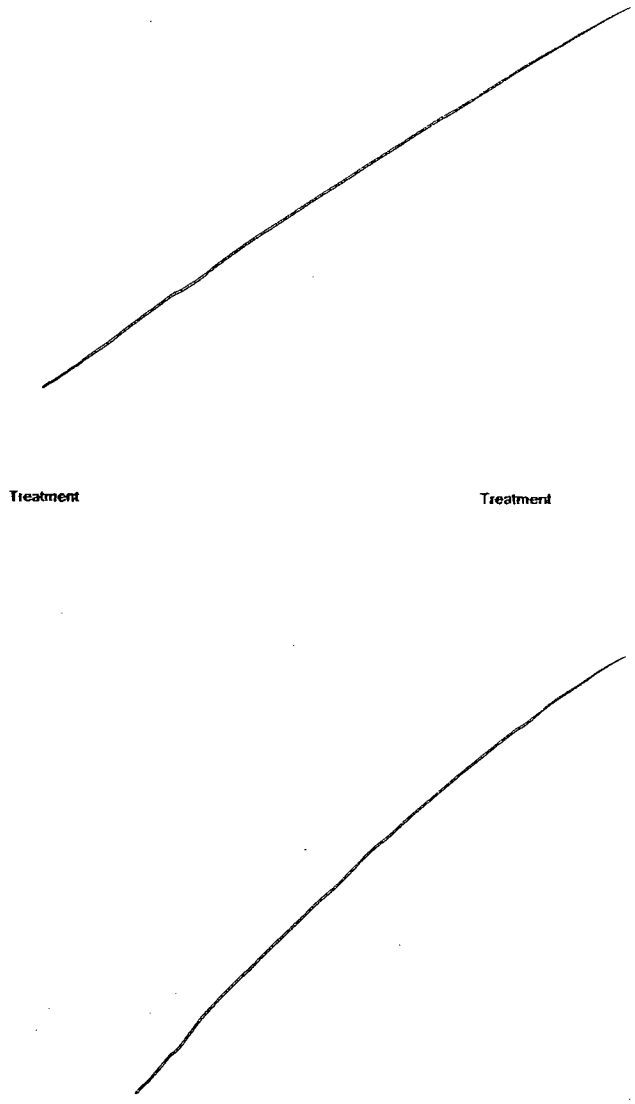

Figure 13. Subjects Treatment Interaction Plots for AUClast

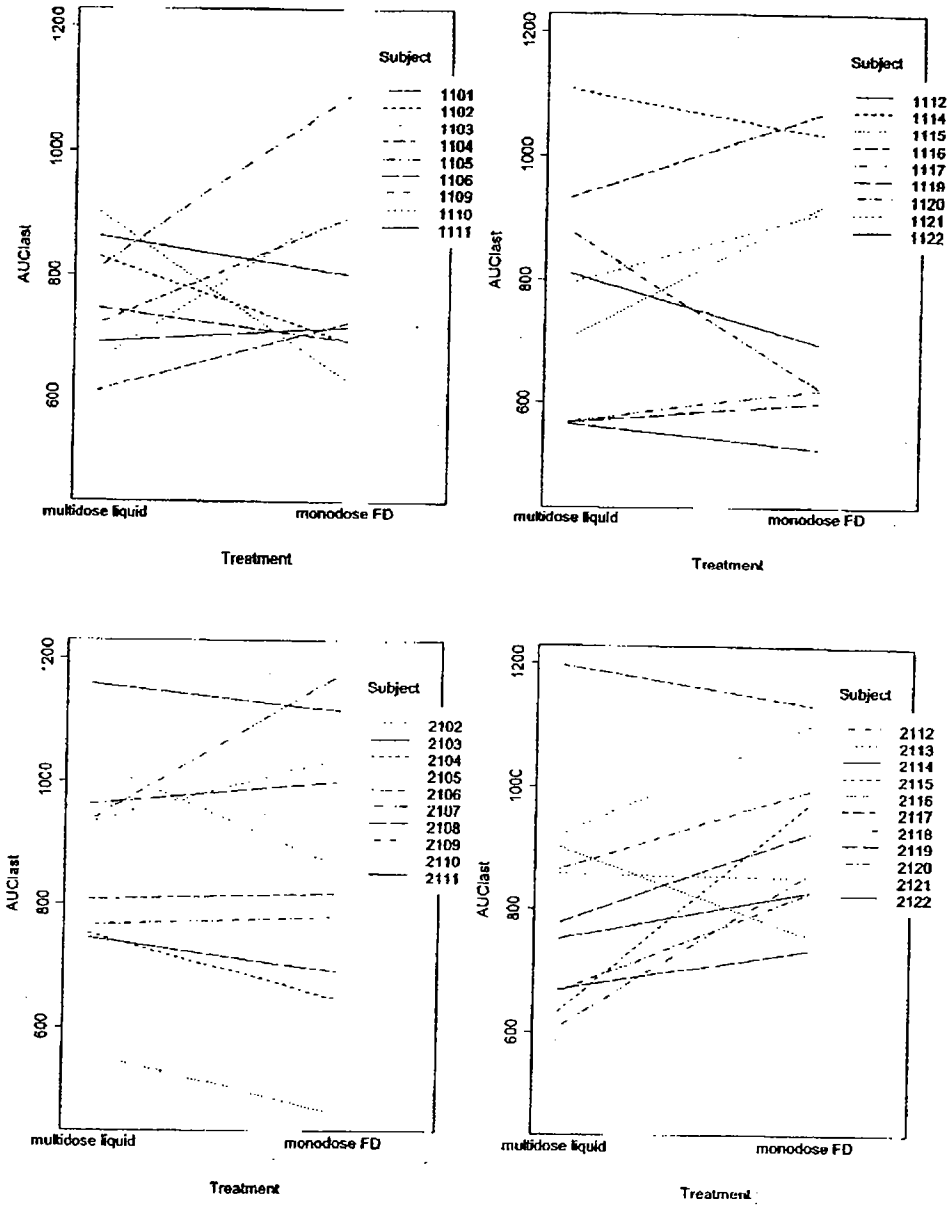

Table 12.ANOVA Model on Cmax Treatment and Gender Interaction

12.5.2.1 ANOVA table for model on C_{max} (including treatment gender interaction)

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Sequence	1	0.013151	0.0131509	0.12833	0.7222595
Volunteer %in% Sequence	36	3.689101	0.1024750	8.96999	0.0000000
Period	1	0.171821	0.1718214	15.04012	0.0004295
Treatment	1	0.109446	0.1094465	9.58022	0.0037947
Treatment : Gender	1	0.008304	0.0083044	0.72692	0.3995214
Residuals	36	0.411271	0.0114242		

12.5.2.2 ANOVA table for model on C_{max} (excluding the baseline)

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Sequence	1	0.011289	0.0112893	0.10946	0.7426219
Volunteer %in% Sequence	37	3.815906	0.1031326	9.09467	0.0000000
Period	1	0.170128	0.1701280	15.00262	0.0004226
Treatment	1	0.114765	0.1147647	10.12045	0.0029655
Residuals	37	0.419576	0.0113399		

12.5.2.3 ANCOVA table for final model on C_{max}

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Sequence	1	0.000304	0.0003036	0.00377	0.9513999
Volunteer %in% Sequence	37	2.983329	0.0806305	9.54205	0.0000000
Period	1	0.000000	0.0000001	0.00001	0.9974949
Treatment	1	0.142498	0.1424984	16.86367	0.0002207
Baseline	1	0.115375	0.1153751	13.65382	0.0007263
Residuals	36	0.304201	0.0084500		

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Table 13.ANOVA Model on Cmax Treatment and Gender Interaction

12.5.2.4 ANOVA table for model on AUC_{last} (including treatment gender interaction)

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Sequence	1	0.027452	0.0274520	0.38852	0.5370072
Volunteer %in% Sequence	36	2.543678	0.0706577	9.47256	0.0000000
Period	1	0.368451	0.3684513	49.39557	0.0000000
Treatment	1	0.034982	0.0349822	4.68981	0.0370450
Treatment : Gender	1	0.008897	0.0088970	1.19275	0.2820300
Residuals	36	0.268531	0.0074592		

12.5.2.5 ANOVA table for model on AUC_{last} (excluding the baseline)

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Sequence	1	0.024051	0.0240510	0.32422	0.5725218
Volunteer %in% Sequence	37	2.744678	0.0741805	9.89329	0.0000000
Period	1	0.365943	0.3659435	48.80510	0.0000000
Treatment	1	0.037948	0.0379478	5.06102	0.0305060
Residuals	37	0.277428	0.0074981		

12.5.2.6 ANCOVA table for final model on AUC_{last}

	Df	Sum of Sq	Mean Sq	F Value	Pr(F)
Sequence	1	0.009266	0.00926622	0.276043	0.6024414
Volunteer %in% Sequence	37	1.242019	0.03356807	5.218168	0.0000013
Period	1	0.048225	0.04822544	7.496660	0.0095470
Treatment	1	0.048113	0.04811336	7.479237	0.0096235
Baseline	1	0.045843	0.04584288	7.126291	0.0113238
Residuals	36	0.231585	0.00643292		

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Figure 14. Mean Change from Baseline in Supine Systolic Blood Pressure (mmHg)

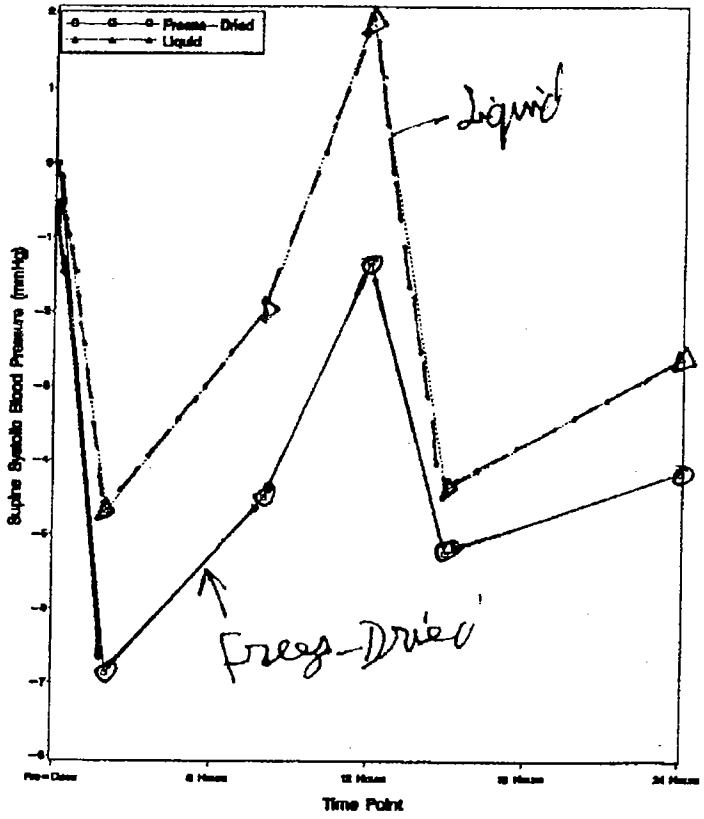

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Figure 15. Mean Change from Baseline in Supine Diastolic Blood Pressure (mmHg)

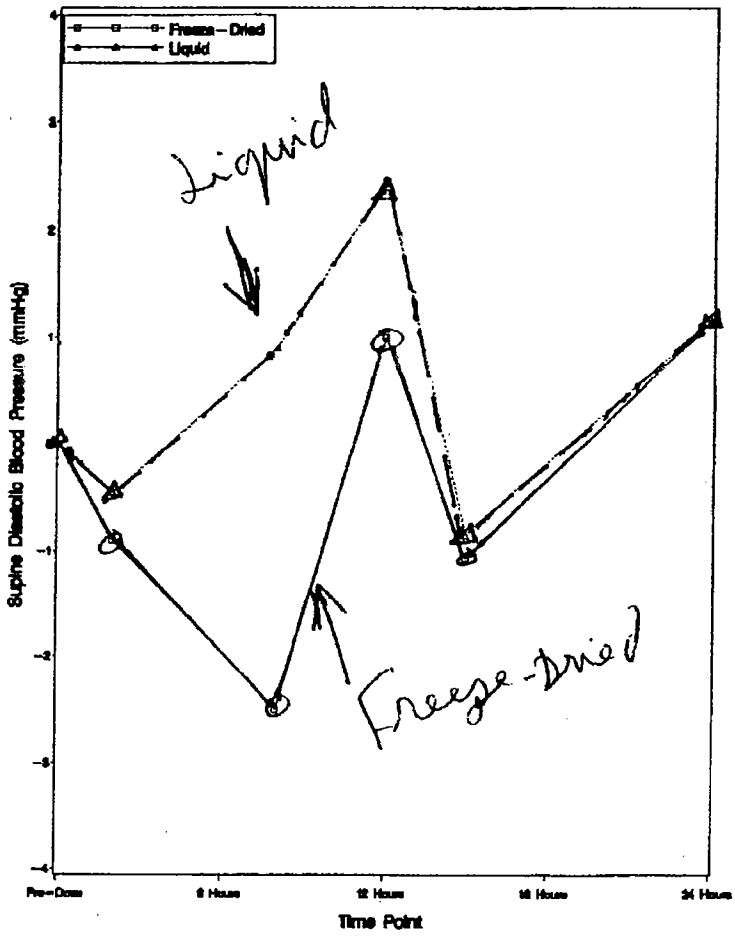

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Figure 16. Mean Change From the Baseline in Supine Pulse Rate (bpm)

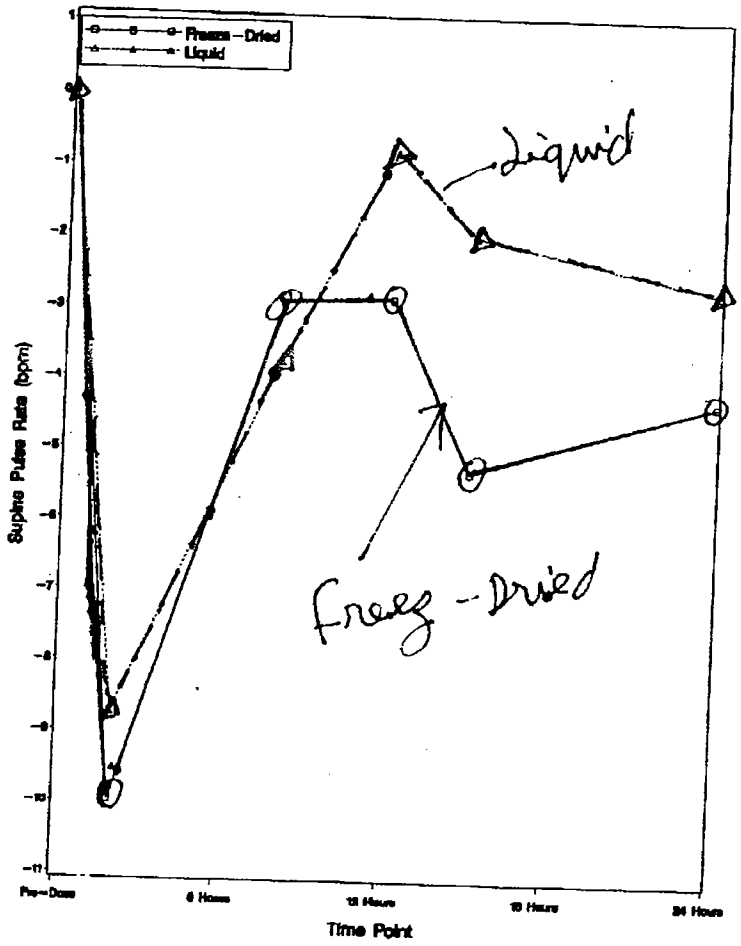

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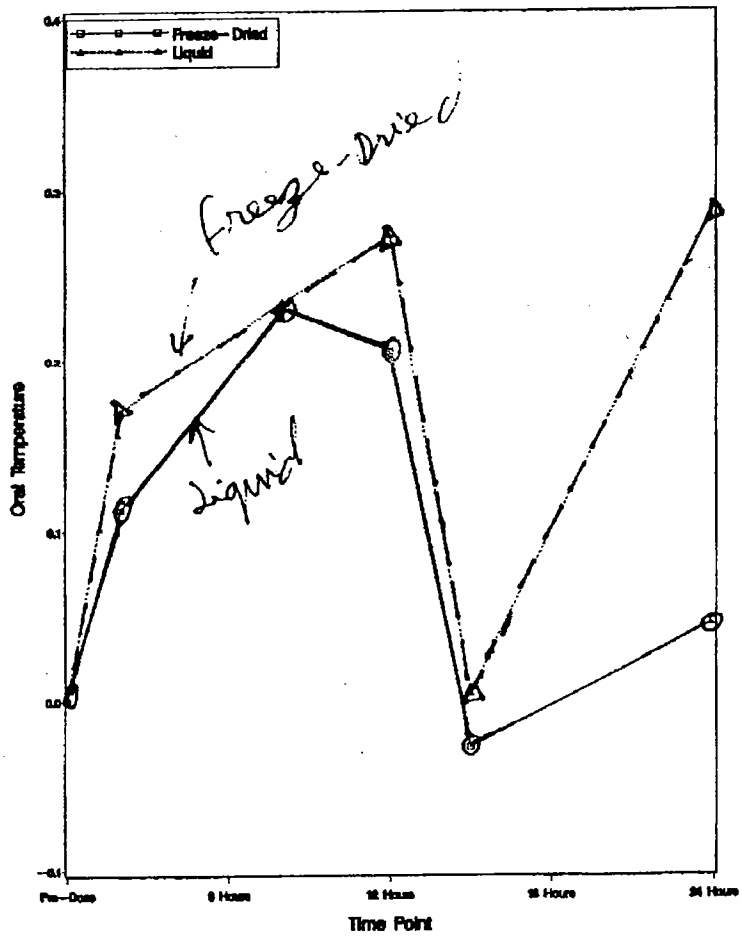
Figure 17. Mean Change From Baseline in Oral Temperature (bpm)



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5 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

Table 14. Individual r-hFSH PK Data For the Test and Reference Formulations

Treatment	Sequence	Volunteer	AUClast (IU·h/L)	Cmax (IU/L)	Tmax (h)
monodose FD (reference)	TR	1101			
	RT	1102			
	RT	1103			
	TR	1104			
	TR	1105			
	RT	1106			
	RT	1107			
	TR	1109			
	TR	1110			
	RT	1111			
	RT	1112			
	RT	1114			
	TR	1115			
	TR	1116			
	RT	1117			
	TR	1119			
	RT	1120			
	TR	1121			
	RT	1122			
	TR	2102			
	RT	2103			
	RT	2104			
	RT	2105			
	RT	2106			
	TR	2107			
	TR	2108			
	TR	2109			
	RT	2110			
	RT	2111			
	TR	2112			
	TR	2113			
	RT	2114			
	TR	2115			
	RT	2116			
	RT	2117			
	TR	2118			
	TR	2119			
	RT	2120			
	RT	2121			
	TR	2122			
		N	40	40	40
		Mean	844	9.51	15.8
		SD	181	2.30	8.24
		Min		—	
		Median	840	9.40	12.0
		Max		—	
		Geometric Mean	824	9.23	14.1
		CV% Geometric Mean	22.8	26.1	51.3

Table 14(continued). Individual r-hFSH PK Data For the Test and Reference Formulations

Treatment	Sequence	Volunteer	AUClast (IU·h/L)	Cmax (IU/L)	Tmax (h)
multidose liquid (test)	TR	1101			
	RT	1102			
	RT	1103			
	TR	1104			
	TR	1105			
	RT	1106			
	TR	1108			
	TR	1109			
	TR	1110			
	RT	1111			
	RT	1112			
	RT	1114			
	TR	1115			
	TR	1116			
	RT	1117			
	TR	1119			
	RT	1120			
	TR	1121			
	RT	1122			
	TR	2101			
	TR	2102			
	RT	2103			
	RT	2104			
	RT	2105			
	RT	2106			
	TR	2107			
	TR	2108			
	TR	2109			
	RT	2110			
	RT	2111			
	TR	2112			
	TR	2113			
	RT	2114			
	TR	2115			
	RT	2116			
	RT	2117			
	TR	2118			
	TR	2119			
	RT	2120			
	RT	2121			
	TR	2122			
	N		41	41	41
	Mean		841	8.99	18.8
	SD		279	2.43	10.6
	Min				
	Median		808	8.90	15.0
	Max				
	Geometric Mean		811	8.69	16.4
	CV% Geometric Mean		26.0	26.5	56.2

Table 14 (continued). Individual r-hFSH PK Data For the Test and Reference Formulations

Parameter	Volunteer	monodose FD Ref.	multidose liquid Test	Ratio
AUClast (IU-h/L)	1101			
	1102			
	1103			
	1104			
	1105			
	1106			
	1109			
	1110			
	1111			
	1112			
	1114			
	1115			
	1116			
	1117			
	1119			
	1120			
	1121			
	1122			
	2102			
	2103			
	2104			
	2105			
	2106			
	2107			
	2108			
	2109			
	2110			
	2111			
	2112			
	2113			
	2114			
	2115			
	2116			
	2117			
	2118			
	2119			
	2120			
	2121			
	2122			
N		39	39	39
Mean		839	802	0.976
SD		181	161	0.182
Min				
Median		829	796	0.962
Max				
Geometric Mean		819	787	0.96
CV% Geometric Mean		22.8	20	18.6

Table 14 (continued). Individual r-hFSH PK Data For the Test and Reference Formulations

Parameter	Volunteer	monodose FD Ref.	multidose liquid Test	Ratio
Ln(Cmax) (IU/L)	1101			
	1102			
	1103			
	1104			
	1105			
	1106			
	1109			
	1110			
	1111			
	1112			
	1114			
	1115			
	1116			
	1117			
	1119			
	1120			
	1121			
	1122			
	2102			
	2103			
	2104			
	2105			
	2106			
	2107			
	2108			
	2109			
	2110			
	2111			
	2112			
	2113			
	2114			
	2115			
	2116			
	2117			
	2118			
	2119			
	2120			
	2121			
	2122			
N		39	39	39
Mean		9.37	8.68	0.942
SD		2.14	2.03	0.162
Min				
Median		9.4	8.7	0.943
Max				
Geometric Mean		9.11	8.46	0.928
CV% Geometric Mean		25.1	23.8	17.8

Briefing: November 10, 2003 at 12:00 noon to 1:00 PM

Briefing Attendees: Drs. Hank Malinowski, John Hunt, Ameeta Parekh, DJ Chatterjee, Shelley Slaughter, Audery Gassman, Suong Tran, and Sayed Al Habet.

Reviewed by:

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Ameeta Parekh, Ph.D. _____

cc: NDAs # 21-684: HFD-580, HFD-870 (Al Habet, Parekh, and Malinowski), and Drug files (Biopharm File, CDR).

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-684**	**Brand Name**	**Gonal-F Pen**
OCPB Division I	**HFD-870**	**Generic Name**	**Follitropin Alfa**
Medical Division	**HFD-580**	**Drug Class**	**Hormone**
OCPB Reviewer	**Sayed Al Habet, R.Ph., Ph.D.**	**Indication(s)**	**Ovulation/ART**
OCPB Team Leader	**Ameeta Parekh, Ph.D.**	**Dosage Form**	**SC Injection**
		Dosing Regimen	**Daily (maximum 45 days)**
Date of Submission	**July 28, 2003**	**Route of Administration**	**SC**
Estimated Due Date of OCPB Review	**April 28, 2004**	**Sponsor**	**Serono, Rockland, MA**
PDUFA Due Date	**May 28, 2004**	**Priority Classification**	
Division Due Date	**May 15, 2004**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:	X	1		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	1		
Population Analyses -				

Data rich:	Yes	1		
Data sparse:	Yes	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**Yes**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**This is a standard crossover BE study in 44 subjects to determine the bioequivalence between freeze-dried formulation (ref) and multi-dose liquid formulation (Test)**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Sayed (Sam) Al Habet, R.Ph., Ph.D.**	
Secondary reviewer Signature and Date	**Ameeta Parekh, Ph.D.**	

CC: NDA HFD-580, HFD-870 (Al Habet, Parekh, Malinowski), CDR (B. Murphy, biopharm file)

Background:

This is an "administrative supplemental NDA" with 4 months review clock per the discussion with the Division held on December 11, 2002. Gonal-f was approved in September 29, 1997 (formulation A). There is another Supplemental NDA (NDA # 20-378, S-032) submitted on May 23, 2003 and is currently under review for ovulation induction and Assisted Reproductive Technology (ART). In the latter NDA a clinical study was conducted (not BE study) to establish clinical equivalency between a new lyophilized formulation (formulation B), filled-by-mass (S-015 and S-016) to the currently marketed formulation (A). The current NDA is for a new liquid formulation (C) that contains a BE study to establish equivalency between the formulation that is currently under review (NDA 20-378, S-032) and the new liquid formulation (i.e., formulation B versus C).

The formulation used in the clinical study (formulation B) that is currently under review in NDA# 20-378, S-032) are the same formulation that were found not bioequivalent to the marketed formulation-A (see OCPB reviewing February 2003 and in December 2001). In the original review the sponsor conducted two studies (#21859 and 22596). In both studies, a single dose of Gonal-F was administered using either a single dose vial (study 21859) or multidose vial (study #22596) of formulation (A) and new single dose of formulation B (vials filled by mass). Both studies show that the two formulations were not bioequivalent. The second study (#22596) was for a single dose using a multidose vial of formulation (A) and new single dose vial of formulation B.

Therefore, the sponsor submitted this new NDA using formulation B (filled by mass) as a reference, which is also used in the clinical study (S-032), and the new multi-dose liquid formulation-PEN (C). In this case the reference used (i.e., formulation B) is not a correct reference since it was found to be not bioequivalent to the approved formulation (A), unless the clinical data from S-032 prove the contrary, otherwise.

Brief Description of a new BE Study (#23572):

This is a crossover study in 44 male and females subjects (n-22 each). Two SC 300 IU injections were give of r-hFSH as either 1 ml of the reconstituted freeze dried monodose formulation (formulation B) or 0.48 ml of new liquid multidose formulation (formulation C). The volumes of 0.48 and 1ml were injected via plastic syringe with 29 gauge needle. Liquid form was supplied in 3 ml glass cartridge. There was a 7 days washout period between treatments. Blood samples were collected over 168 hour after each injection.

In summary:

- Formulation A (currently approved) and Formulation B (filled by mass) are not bioequivalent)

- Formulation A (currently approved) and formulation B (filled by mass) are currently under review for clinical equivalency (NDA 20-378, S-032)

- A bioequivalence study for formulation B (filled by mass) and the new liquid formulation delivered via the PEN (formulation C) is in the current submission under a new NDA (#20-684). At a glance the two formulations appears to be bioequivalent. However, the final conclusion will be made after the review is completed.

General Comments:

- In the submitted BE study, the PEN was not used to inject the product. However, the sponsor did not use the correct reference product. The reference formulation, filled-by mass (B), was found not to be bioequivalent to the approved formulation (A).
- At the pre-NDA meeting held on December 11, 2002 the sponsor was informed that the reference used in the current study is not acceptable, since it is not bioequivalent to the approved products. However, the decision will be made based on the clinical data submitted in S-032 for formulation B (filled by mass) and the approved products (formulation A).
- In the submitted BE study, a plastic syringe was used to inject the reference and the test product. Specifically, the sponsor used the plastic syringe to withdraw the product from the cartridge used in the PEN (device). The consistency in volume delivery for both the plastic syringe and the PEN (device) will be evaluated by CDRH.
- At the pre-NDA meeting held with the sponsor, the use of the plastic syringe to deliver the test and reference products was accepted by the Division (see December 11, 2003 meeting minutes).
- The data, including volume consistency, will be evaluated at the time of NDA review.
- In addition, the link between formulations will also be evaluated based on the data and recommendation from the study in supplement 032 (NDA 20-378).

Recommendation:

This NDA is filable.

However, the use of the plastic syringe instead of the device (PEN) to deliver the test product will be evaluated at the time of NDA submission. In addition, the approval of the new formulation (PEN) is contingent to the clinical data submitted in S-032 for formulation B (filled by mass) and the currently marketed formulation (A).

Appendix I

Bioequivalence Original Review for Gonal-f (Formulation A vs B)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-378	Submission Date: August 3, 2001 December 4, 2001 (Fax)
Compound:	Gonal-F **(Follitropin alfa for injection-FSH)**
Formulation (s):	Sterile Vials for Subcutaneous injection
Sponsor:	Serono, Inc. Norwell, MA
Type of Submission:	Supplement **(Amendment to OCPB Review)**
Indications:	Ovulation
Reviewer:	Sayed Al Habet, R.Ph., Ph.D.
Pharmacometrics:	He Sun, Ph.D., CBS.
PK Team Leader:	Ameeta Parekh, Ph.D.
Pharmacometrics Team Leader:	Peter Lee, Ph.D.
Original Date Review:	November 30, 2001 **(DFS version December 11, 2001)**
Amendment Review:	January 28, 2003

Background:

This is a review amendment for the previously reviewed chemistry supplement and Phase IV commitments reports. Specifically this amendment is to the Clinical Pharmacology and Biopharmaceutics review posted in the DFS on December 11, 2001.

In the approval letter dated September 29, 1997 the sponsor was requested to conduct a Phase IV study to improve the stability of the product and batch-to-batch variability. Therefore, the sponsor modified the formulation by adding methionine and polysorbate 20 — .see below for formulation details and **Table 1**). Since this was a significant formulation change, the sponsor conducted

bioequivalence (BE) studies. Two studies were conducted. The first study was to assess the relative bioavailability between the new formulation and the approved (reference) formulation. The second study was to compare the relative bioavailability of the new single-dose vial with a reference multi-dose vial of r-hFSH (see original OCPB review in **Appendix I**).

The sponsor's submission provided data analysis of two BE studies using the conventional average BE approach (the products were not BE based on the 90% CI criteria of 80-125%), as well as a population BE and a simulation approach. The original review dated December 11, 2001, addresses the findings only from the average BE analysis. The current review is an amendment to the earlier review and provides the regulatory assessment of the alternate approaches used by the sponsor to evaluate BE of the two formulations. These comments have been provided in consultation with the Pharmacometrics group of the Office of Clinical Pharmacology and Biopharmeceutics.

Reviewers Comments:

1. For Study IMP 21859 (Completion Date Aug. 27, 2000)

(a) FDA does NOT support the removal of a particular subject (outliers) in BE analysis. Therefore, only study results with subject 113 included are considered in this regulatory decision making process. This is based on the FDA Guidance for Industry: Statistical Approaches to Establish Bioequivalence (Section VII, subheading C for outlier consideration).

(b) At the current time, average BE (ABE) analysis serves as the primary method of BE assessment although Population BE (PBE) and Individual BE (IBE) are available options. It is generally understood that when there is a clear indication of unbalanced intersubject variability for test and reference formulations, PBE could be applied. From the data submitted, although the difference in variance between test and reference are large (see table 2 below), this difference was not seen in the second study, IMP 22596 (see table 3 below). The inconstancy in variance between the two trials raises the concern of whether the use of Population BE method is well justified.

(c) Please note that "Analysis of BE data using the population approach (section IV.B) should focus first on estimation of the mean difference between the T and R for the log-transformed BA measure and estimation of the total variance for each of the two formulations." (FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence Version of January 2001) and "When the population BE approach is used, in addition to meeting the BE limit based on confidence bounds, the point estimate of the geometric test/reference mean should fall within 80-125%" (page 6 of the Guidance). Since the point estimates for this study were 1.251 and 1.349 for C_{max} and AUC, respectively, the PBE fails to pass the 80-125% test.

2. For study IMP 22596 (completion date Dec. 04, 2001), the average BE analysis on observed single dose data also failed. The sponsor used simulated Cmax and AUC at Steady State to claim BE for the new test formulation. It is clearly described in FDA General BA/BE guidance that single dose data would be the primary evidence for BE since multiple dose data is not sensitive to detect the different absorption characteristics between two formulations (see FDA General BA/BE Guidance), and it is the regulatory practice that simulated study is not acceptable as evidence of BE.

Conclusion: ***Considering the above-mentioned deficiencies in sponsor's PBE analysis, the Office of Clinical Pharmacology and Biopharmaceutics recommends that the PBE approach used by the sponsor NOT be accepted at this time. Based on the ABE analysis, it can be concluded that the new formulation has not been shown to be BE to the currently approved product.***

Product Information/Formulations:
(For details, please see Chemistry Review by Dr. Yvonne Yang dated December 4, 2001)

As stated above the sponsor is proposing a new formulation for the mono-doses by addition of (1) methionine, , and (2) polysorbate 20 (Tween 20), to the current formulation,

Gonal-F is currently filled (by FSH activity) into ampoules for the mono-doses, and into vials for the multi-dose. Each container of Gonal-F is filled to deliver 37.5 IU, 75 IU, and 150 IU (mono-doses), or 1050 IU (multi-dose) of r-hFSH, 30 mg of sucrose, 1.11 mg of dibasic sodium phosphate, and 0.45 mg of monobasic sodium phosphate monohydrate.
This chemistry supplement is also for change in manufacturing of drug product from "filling-by-activity" to "filling-by-mass" (see chemistry review for details".
There were no other changes to the new products except those indicated above and as shown in **Table 1.**

Table 1. Formulation Composition

Ingredient	Per Vial of Drug Product				Function
	Monodose			Multidose	
	37.5 IU	75 IU	150 IU	1,200 IU	
Follitropin alfa (r-hFSH)					Active ingredient
Sucrose	30 mg	30 mg	30 mg	30 mg	
Disodium phosphate dihydrate	1.11 mg	1.11 mg	1.11 mg	1.11 mg	
Sodium dihydrogen phosphate monohydrate	0.45 mg	0.45 mg	0.45 mg	0.45 mg	
Methionine	0.1 mg	0.1 mg	0.1 mg	N/A	
Polysorbate 20	0.05 mg	0.05 mg	0.05 mg	N/A	
o-Phosphoric acid	qs	qs	qs	qs	pH adjustment
Sodium hydroxide	qs	qs	qs	qs	pH adjustment

C:

Table 2. Study IMP 21859 (Completion Date Aug. 27, 2000)

Between subject variability (estimated from the raw data) and within subject variability estimated from the ANOVA model are displayed below.

Parameter	CV within subject %	300 IU GONAL-F			20 µg New r-hFSH		
		N	Mean	CV %	N	Mean	CV %
C_{max} (IU/L)	21	23	6.6	38	23	8.0	27
AUC_{last} (IU·h/L)	31	23	432	44	23	541	22

Table 3. Study IMP 22596 (completion date Dec. 04, 2001).

Pharmacokinetic Results: Some differences in pharmacokinetics were apparent betweer the r-hFSH monodose formulation and the reference r-FSH multidose formulation reflected in estimates of t_{max} and C_{max}.

Pharmacokinetic Parameters by Treatment: PK Dataset

		Pharmacokinetic Parameters				
		C_{max} (IU/L)	$AUC_{0-\infty}$ (IU·h/L)	AUC_{last} (IU·h/L)	t_{max} (h)	$t_{½}$ (h)
Monodose n=22	Mean	7.8	511	474	14	34
	SD	*1.7*	*162*	*109*	*6*	*15*
Multidose n=21	Mean	6.2	506	453	19	43
	SD	*1.3*	*126*	*91*	*6*	*15*
Monodose/ Multidose*	Point Estimate (90% CI)	1.25 (1.19, 1.31)	1.00 (0.87, 1.15)	-	-	-

Note: Data summarised above are located in Tables 12.2.2.1, 12.2.2.2 and 12.2.2.4 to 12.2.2.6.
* These data are derived from adjusted geometric means presented in Tables 12.2.3.1 and 12.2.3.2.

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Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the bioequivalence studies and the analysis conducted by the sponsor and concludes that the two products fail to show bioequivalence. Please convey the following to the sponsor:

The two formulations are not bioequivalent based on the average bioequivalence analysis. The alternate approaches used by the sponsor are also not acceptable due to the following reasons:

- For Study IMP 21859 (Completion Date Aug. 27, 2000)

FDA does NOT support the removal of a particular subject (outliers) in BE analysis. Therefore, only study results with subject 113 included are considered in this regulatory decision making process. In reference to the outlier, the sponsor is advised to refer to the FDA Guidance for Industry: Statistical Approaches to Establish Bioequivalence (Section VII, subheading C for outlier consideration).

At the current time, average BE (ABE) analysis serves as the primary method of BE assessment although Population BE (PBE) and Individual BE (IBE) are available options. It is generally understood that when there is a clear indication of unbalanced intersubject variability for test and reference formulations, PBE could be applied. From the data submitted, although the difference in variance between test and reference are, this difference was not seen in the second study, IMP 22596. The inconstancy in variance between the two trials raises the concern of whether the use of Population BE method is well justified.

Please note that "Analysis of BE data using the population approach (section IV.B) should focus first on estimation of the mean difference between the T and R for the log-transformed BA measure and estimation of the total variance for each of the two formulations." (FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence Version of January 2001) and "When the population BE approach is used, in addition to meeting the BE limit based on confidence bounds, the point estimate of the geometric test/reference mean should fall within 80-125%" (page 6 of the Guidance). Since the point estimates for this study were 1.251 and 1.349 for C_{max} and AUC, respectively, the PBE fails to pass the 80-125% test.

- For study IMP 22596 (completion date Dec. 04, 2001), the average BE analysis on observed single dose data also failed. The sponsor used simulated Cmax and AUC at Steady State to claim BE for the new test formulation. It is clearly described in FDA General BA/BE guidance that single dose data would be the primary evidence for BE since multiple dose data is not sensitive to detect the different absorption

characteristics between two formulations (see FDA General BA/BE Guidance), and it is the regulatory practice that simulated study is not acceptable as evidence of BE.

Reviewers

Sayed Al Habet, R.Ph., Ph.D.
Clinical Pharmacologist/Reviewer
Office of Clinical Pharmacology and Biopharmaceutics

He Sun, Ph.D., CBS.

Pharmacometrics

Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Ameeta Parekh, Ph.D. ----------
Co-signed by Peter Lee, Ph.D.----------
Pharmacometrics Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
cc: HFD-580, HFD-870 (Al-Habet, Parekh, Sun, Lee, and Malinowski), Drug file (Biopharm File, Central Document Room).

Appendix I
(BE Study Original Review)
(Formulation A vs B)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-378	Submission Date: August 3, 2001 December 4, 2001 (Fax)
Compound:	Gonal-F **(Follitropin alfa for injection-FSH)**
Formulation (s):	Sterile Vials for Subcutaneous injection
Sponsor:	Sereno, Inc. Norwell, MA
Type of Submission:	Supplement
Indications:	Ovulation
Reviewer:	Sayed Al Habet, Ph.D.
Date Review:	November 30, 2001

Background:

This is a chemistry supplement to fulfill Phase IV commitments stated in the approval letter dated September 29, 1997. Briefly, the sponsor was requested to improve the stability of the product and batch-to-batch variability. Therefore, the sponsor modified the formulation by adding methionine and polysorbate 20 . Since this was a significant formulation change, the sponsor conducted two bioequivalence studies which are described briefly below:

Study # 21859:

This was a double blind, crossover study to assess the comparative bioavailability of the new formulation with the reference formulation (Gonal-F). The drug was administered subcutaneously (SC) as a single dose of 300 IU (equivalent to 20 μg) of Gonal-F (reference) or 20 μg New r-hFSH (new formulation) to 24 healthy subjects. Blood was collected over 168 days for FSH levels.

Results:

The mean data are shown in Tables 1-3 and Figures 1-3.

Table 1: Mean (± SD) of PK Parameters for Reference (Gonadal-F) and Test r-hFSH Formulations (study # 21859)

Parameter	300 IU GONAL-F		20 μg New r-hFSH	
	N	Value	N	Value
C_{max} (IU/L)	23	6.6 ± 2.5	23	8.0 ± 2.1
t_{max} (h)	23	12 (6 - 24)*	23	15 (8 - 48)*
AUC_{last} (IU·h/L)	23	432 ± 190	23	541 ± 117
AUC_{inf} (IU·h/L)	13	492 ± 167	17	586 ± 122
$t_{½z}$ (h)	13	52 ± 35	17	54 ± 26

* = Median (range)

Table 2: The ratio of mean (test/reference) and calculated 90% CI for Cmax and AUC (study # 21859)

Parameter	Treatment Ratio			p value
	Lower	Point Estimate	Upper	
C_{max}	1.122	1.125	1.396	0.0030
AUC_{last}	1.153	1.349	1.577	0.0055

Table 3: Statistical Reanalysis of The ratio of mean (test/reference) and calculated 90% CI for Cmax and AUC After Removing One Outlier Subject (study # 21859)

Parameter	Treatment Ratio			p value
	Lower	Point Estimate	Upper	
C_{max}	1.110	1.191	1.278	0.0004
AUC_{last}	1.132	1.253	1.387	0.0011

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Figure 1. Mean (± SD) of Serum FSH Concentration-Time Profiles for the New r-hFSH and Gonal-F Formulations (study # 21859)

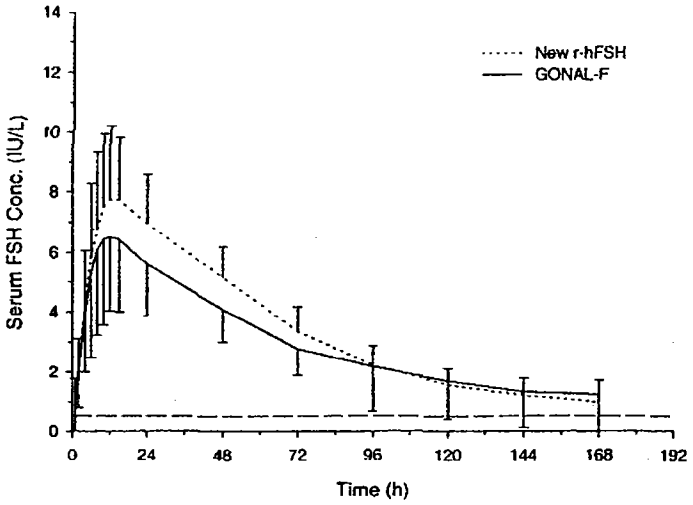


Figure 2. Individual Log $AUC_{0\text{-last}}$ for all subjects Per treatment (study # 21859)

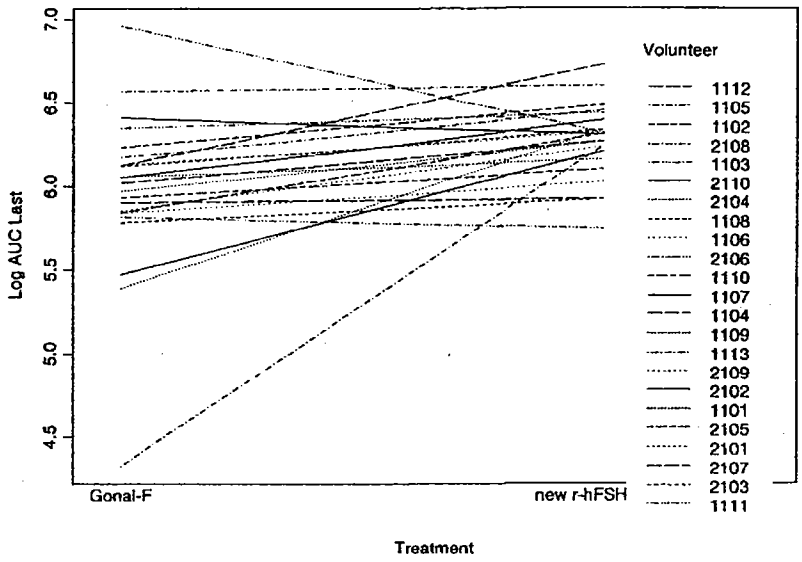
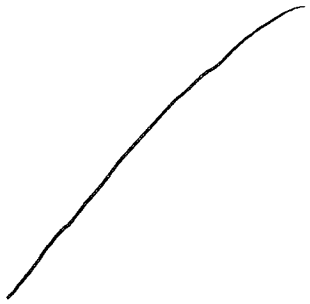


Figure 3. Individual Log Cmax for all subjects Per treatment (study # 21859)



Treatment

Study # 22596

This was also a double blind, single dose, crossover study to assess the comparative bioavailability of the new single-dose vial with a reference multi-dose vial of r-hFSH. The drug was administered subcutaneously (SC) as a single dose of 20 μg of a multi-dose formulation (reference) or 20 μg of single-dose formulation (new formulation) to 23 healthy subjects. Blood was collected over 168 days for FSH levels.

Results:

The mean data are shown in Tables 3 and Figure 4.

Table 4: Mean PK parameters from study # 21859

Pharmacokinetic Parameters by Treatment: PK Dataset						
		Pharmacokinetic Parameters				
		C_{max} (IU/L)	$AUC_{0-\infty}$ (IU·h/L)	AUC_{last} (IU·h/L)	t_{max} (h)	$t_{½}$ (h)
Monodose n=22	Mean	7.8	511	474	14	34
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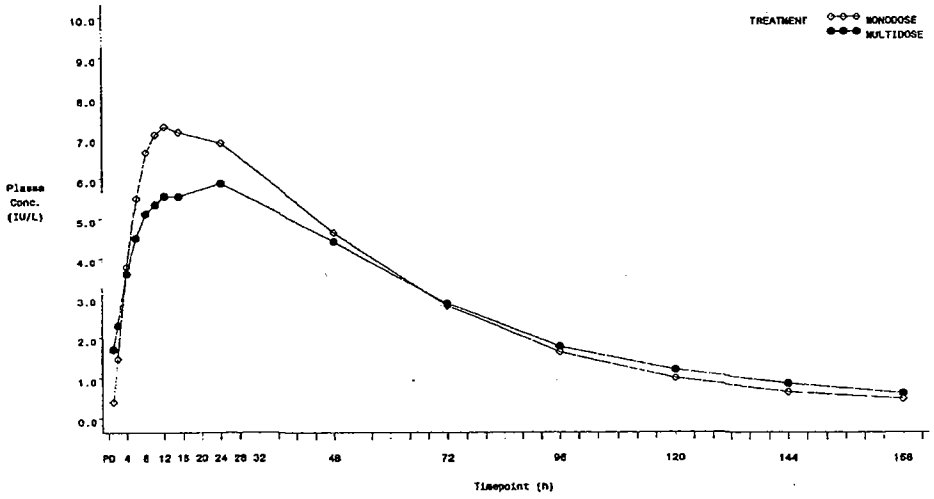
Multidose n=21	Mean	6.2	506	453	19	43
	SD	*1.3*	*126*	*91*	*6*	*15*
Monodose/ Multidose*	Point Estimate (90% CI)	1.25 (1.19, 1.31)	1.00 (0.87, 1.15)	-	-	-

Figure 4. Mean (± SD) of Serum FSH Concentration-Time Profiles for the New Single Dose (mono-dose) and reference multi-dose Formulations (study # 22596)



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Reviewer's Comments:

1. For study # 21859, the Cmax and AUC of the new formulation are higher than that of Gonal-F by approximately 20-30% (Table 1and Figures 1-3). The 90% CI for Cmax was 1.22, 1.39 and for $AUC_{0\text{-last}}$ was 1.15,1.57 (Table 2). It should be noted that one subject was considered an outlier by the sponsor and was removed from the statistical analysis as shown in Table 3. After re-analysis, the 90% CI for Cmax was 1.10,1.27 and for $AUC_{0\text{-last}}$ was 1.13,1.38 (Table 3). Therefore, both parameters are not within the regulatory limits of 0.8-1.25 with and without the outlier.
2. The variability in both Cmax and AUC appears to be greater for Gonal-F than for the new formulation of r-hFSH (Figures 2 and 3).
3. Similarly, for study # 22596, the serum FSH levels for the new single dose vial appears to be higher than that for multidose vial (Table 4 and Figure 4). The 90% CI for Cmax was 1.19,1.31 and for $AUC_{0\text{-last}}$ was 0.87,1.15. Therefore, only Cmax was outside the regulatory limits of 0.8-1.25.
4. Its should be noted that the sponsor did not calculate the 90% CI for the $AUC_{0\text{-}\infty}$. This was due to some technical/analytical problems and variability in the determination of the terminal portion of the FSH serum levels. The sponsor provided additional explanation faxed on December 4, 2001.

Conclusions:

The two formulations did not meet the current regulatory standard for bioequivalence. The new formulation of 20 μg FSH failed at the upper limits for Cmax and AUC when compared to the reference formulation (Gonal-F). However, the new single dose vial failed only at the upper limit of Cmax, but not for $AUC_{0\text{-last}}$, when compared to the reference multidose vial.

Recommendation:

Both studies show that the two formulations are not bioequivalent.

Reviewer

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Ameeta Parekh, Ph.D. ----------

cc: Pre-IND, HFD-580, HFD-870 (Al-Habet, Parekh, and Malinowski), Drug file (Biopharm File, Central Document Room).

Appendix II

CDRH Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

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

Consultation Review

Date: September 16, 2003

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

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

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

I. Purpose

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

II. Device Intended Use and Description:

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

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

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

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

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

III. Recommendation

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

Von Nakayama

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/s/

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

Appendix III

Sponsor's Proposed Label

83 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

/s/

Sayed Al-Habet
11/25/03 02:22:41 PM
BIOPHARMACEUTICS

Dhruba Chatterjee
11/25/03 02:39:36 PM
BIOPHARMACEUTICS
I concur.