

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-211**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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**Clinical Pharmacology and Biopharmaceutics Review**  
**Division of Pharmaceutical Evaluation II**

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<b>NDA:</b>	21-211
<b>Drug:</b>	Follistim -AQ (follitropin beta injection) Cartridge
<b>Sponsor:</b>	Organon Inc
<b>Date of Submission:</b>	01-31-00, 03-30-00, 10-31-00, and 11-06-00
<b>Type of Submission:</b>	Original NDA
<b>Reviewer:</b>	Venkateswar R. Jarugula, Ph.D.

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**SYNOPSIS**

Follistim-AQ (follitropin beta injection) cartridge is a new pharmaceutical presentation of the approved Follistim (follitropin beta for injection), NDA 20-582. The approved product is formulated as a freeze-dried cake; to be administered after reconstitution with water and is available in 75 IU and 150 IU vials. Follistim-AQ cartridge, the product of current NDA, is an injectable aqueous solution of 300 IU and 600 IU follitropin beta (FSH) in a glass/ ~~rubber~~ rubber multidose cartridge, to be administered with a pen-injector device.

According to the sponsor, a multi-dose ready to use product is considered to be more convenient than the approved product since its use requires less handling and it provides a more accurate and precise method of dosing as compared to the conventional syringe.

The concentration of follitropin beta in Follistim-AQ cartridge (833 IU/ml) is higher than that in the reconstituted approved Follistim (75-300 IU/ml). Since absorption from the injection site may be influenced by the concentration of the drug and injection volume, sponsor conducted a bioequivalence study with Follistim-AQ cartridge Vs Follistim reconstituted product. This was an open-label, single-center, single-dose, crossover study in 22 female subjects comparing the bioavailability of a single dose of Follistim-AQ (150 IU) with reconstituted Follistim (150 IU). In this study, Follistim-AQ resulted in 20% higher AUC than the approved Follistim and the two formulations were found to be not bioequivalent. However, in the same study, it was found that the conventional syringe, due to filling, removing excess air and the dead volume of the syringe, actually delivered on average ~~lower~~ lower than the nominal dose of 150 IU FSH, whereas pen-injector was assumed to accurately deliver the dose (150 IU) to which it was set. Consequently, pen-injector dosing was higher than the conventional syringe.

Since the conventional syringe delivered ~~lower~~ lower than the nominal dose, sponsor analyzed the pharmacokinetic data by dose correction. The formulations were shown to be bioequivalent following dose correction of the PK parameters, AUC and Cmax.

The fact that the two products were shown bioequivalent following dose correction to account for losses from conventional syringe indicates that the difference in concentration does not influence the bioavailability in the concentration range tested. However, if used without this dose adjustment, the pen-injector would result in about 20% higher bioavailability than the Follistim reconstituted product that has been tested in clinical trials and has been in use for its indication since approval.

Sponsor stated that the higher bioavailability of pen-injector does not affect the safety and efficacy of Follistim. However, no data was provided to support this statement. Before filing the NDA, sponsor was informed by the clinical division that there was no data to conclude that higher bioavailability of pen-injector does affect the safety and efficacy of this product. In response, sponsor proposed some changes in the dosing and administration section by including a conversion table showing doses of the conventional injection with the corresponding settings for the pen-injector to deliver equivalent doses. In the conversion table, the setting of pen injector was reduced (by approximately 18%) to match the actual dose delivered by conventional syringe. However, the conversion table appears to be confusing to be used appropriately by the patients who are going to self-administer the drug product. This issue is currently under review the clinical review division.

Sponsor has submitted in vitro measurements that estimate the drug loss during reconstitution of lyophilized cake and injection to NDA 21-273. Although this data were submitted to different NDA, it is relevant for this NDA as well. The estimated dose loss determined for Follistim lyophilized cake varied from \_\_\_\_\_ among in vitro measurements in different studies. This variability could be due to different technical persons performing the reconstitution, and also due to differences in methods of measurements. The estimate reported in the BE study of the current NDA is the highest and conservative. Since the therapy of Follistim is dose titrated based on efficacy (follicle growth is monitored by ultrasound), sponsor's proposal to adjust the pen-injector by the highest (conservative) estimate of all the in vitro measurements appears to be appropriate.

The accuracy and precision of the pen-injector device should be evaluated by the devices expert reviewer.

In conclusion, the results of the bioequivalence study showed that pen-injector device provided approximately 20% higher bioavailability than the Follistim reconstituted product. The two products as administered were not shown to be bioequivalent. However, the two products were shown to be bioequivalent when corrected for the dose loss during injection of lyophilized cake. Sponsor proposed to adjust the pen-injector setting in order to deliver a dose that matches the dose delivered by syringe.

## **RECOMMENDATION**

The NDA is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

V. Jarugula 11/15/00

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader \_\_\_\_\_

FT signed by Ameeta Parekh, Ph.D., Team Leader Ameeta Parekh 11/15/00

cc: NDA 21-211, HFD-580 (Bennett, Deguiae), HFD-870 (Malinowski, Parekh, Jarugula), CDR (B.Murphy for Drug).

CPB Briefing Attendies: Drs. H. Malinowski, J. Hunt, A. Parekh, S. Slaughter, R. Bennett, D. Lin, and F. Deguiae.

## SUMMARY

What are the differences between the approved formulation and the proposed formulation in pen-injector device?

Table 1. Composition of the formulations:

Ingredients	Pen-injector		Cake
	300 IU unit	600 IU unit	
FSH	437.5	737.5	75, 150
Sucrose			
Sodium citrate dihydrate			
Polysorbate 20			
Benzyl alcohol			
L-methionine			
Hydrochloric acid — and/or			
Sodium hydroxide —			
Water for Injection			

The approved lyophilized product, Follistim contains 75 or 150 IU per vial and can be reconstituted up to 300 IU/ml. The proposed pen-injector device comes with a multidose cartridge (300 IU or 600 IU) with a concentration of 833 IU/ml. Thus the concentration of FSH in pen-injector device is much higher than the cake. In addition the solution in pen-injector has benzyl alcohol and L-methionine (stabilizer).

**Is the pen-injector bioequivalent to approved product, Follistim?**

Since differences in concentration of the active ingredient may affect the bioavailability following subcutaneous injection, sponsor conducted the following bioequivalence study.

### Bioequivalence Study:

**Objective :** To study whether FSH pharmacokinetics following subcutaneous administration of Org 32489 by a pen-injector of a ready-for-use solution are bioequivalent to that after subcutaneous injection of a reconstituted lyophilized powder.

**Study Design:** open-label, single-center, single-dose, randomized crossover study in 24 healthy female subjects. After one-week pill-free period, the subjects who met screening and inclusion criteria were to start with daily intake of Lyndiol for a total period of six weeks to suppress endogenous gonadotropin secretion. After three weeks of Lyndiol, subjects received one of the following single-dose Org 32489 subcutaneous injections in a randomized fashion:

- A) 150 IU: by subcutaneous pen-injector (cartridge)  
 B) 150 IU: by syringe (dissolved cake)

After a washout period of 14 days, all subjects received a second subcutaneous injection of a single dose of Org 32489 in the alternative presentation.

According to the sponsor, in order to be able to correct for a possible influence of injection losses with the conventional syringe on the pharmacokinetics, the syringe with dissolved cakes was weighed before and after injection.

Blood samples prior to and following drug administration were collected for measurement of serum FSH concentrations.

Table 2. Mean ( $\pm$ SD) Pharmacokinetic parameters and Bioequivalence of Pen-injector Vs Syringe (uncorrected for dose losses)

Parameter	Pen-injector	Syringe	Point estimate	90% Confidence interval
AUC <sub>0-t</sub> (IU.h/L)	156.4 $\pm$ 31.8	134.4 $\pm$ 43.4	1.21	1.10 – 1.33
AUC <sub>0-<math>\infty</math></sub> (IU.h/L)	215.1 $\pm$ 45.8	185.7 $\pm$ 58.8	1.20	1.10 – 1.31
Cmax (IU/L)	3.36 $\pm$ 0.70	2.91 $\pm$ 0.92	1.19	1.06 – 1.33
Tmax (h)	12.9 $\pm$ 6.2	16.2 $\pm$ 8.0	87.9*	62.1 – 101.4

- \* Given as % Vs Mean reference.

As can be seen from the above table, pen-injector resulted in about 20% higher AUC, 19% higher Cmax than the conventional syringe injection. Based on 90% confidence interval analysis, the two products as administered, were shown not bioequivalent.

According to the sponsor, the actual dose administered by conventional syringe was influenced by the following factors:

- Two cakes of 75 IU Follistim were dissolved in 1 ml of diluent
- Due to the formation of foam and liquid remaining in the vial, losses may have occurred while filling the syringe with the dissolved drug.
- Loss may have occurred because of the void volume of the syringe
- Loss may have occurred while removing excess air from the syringe.

To account for possible loss of drug, the syringes were weighed before and after the injection to each patient in the study. The predosing and postdosing weights of syringes are listed in Table 3.

Table 3. Weight of injected reconstituted Follistim.

N=20	Mean	Standard Deviation	Minimum	Maximum
Predosing weight (g)	7.14	1.74	4.98	8.61
Postdosing weight (g)	6.24	1.77	4.03	7.76
Weight difference (g)	0.899	0.078	0.620	0.990

The total weight of two cakes (2x75 IU) was reported as 64.3 mg. Two cakes were dissolved in \_\_\_\_\_ Therefore, the maximum (theoretical) weight of the syringe content would (if 100% recovered from the vials) be 1064.3 mg (assuming the weight of \_\_\_\_\_). Sponsor calculated a correction factor for dose administered for each patient by dividing the maximum weight (1064.3 mg) by the actual weight administered. The mean correction factor was 1.18 (= 1064.3/899). Thus the actual C<sub>max</sub> and AUC values were increased on average by 18% to account for the losses during handling and injection of the reconstituted product.

Based on the weight of amount injected, the calculated fraction of the dose delivered by syringe for individual patient ranged from 0.58 to 0.93 with a mean of 0.84 and median of 0.85. There was one outlier for whom this was 0.58 and all others seem to be around the mean.

The 90% confidence intervals and point estimates were determined again following the dose correction of Follistim syringe arm and the parameters are listed in Table 4.

Table 4. Mean (±SD) Pharmacokinetic parameter and Bioequivalence of Pen-injector Vs Syringe (corrected for dose losses)

Parameter	Pen-injector	Syringe	Point estimate	90% Confidence interval
AUC <sub>0-t</sub> (IU.h/L)	156.4 ± 31.8	159.0	1.02	0.93 – 1.11
AUC <sub>0-∞</sub> (IU.h/L)	215.1 ± 45.8	220.3	1.01	0.93 – 1.10
C <sub>max</sub> (IU/L)	3.36 ± 0.70	3.43	1.00	0.91 – 1.11
T <sub>max</sub> (h)	12.9 ± 6.2	16.2	87.9 <sup>a</sup>	62.1 – 101.4

<sup>a</sup>Given as % Vs Mean reference.

Following dose correction to account for the losses during the syringe injection, the pen-injector was shown to be bioequivalent to Follistim indicating that concentration difference (in the range of 150 IU/ml to 833 IU/ml) does not affect the bioavailability following subcutaneous administration. However based on this study, without dose adjustment, the pen-injector would result in approximately 20% higher bioavailability.

The mean plasma concentration- time profiles of FSH with and without dose-correction for the administration of lyophilized cake by syringe injection are illustrated in Figure 1.

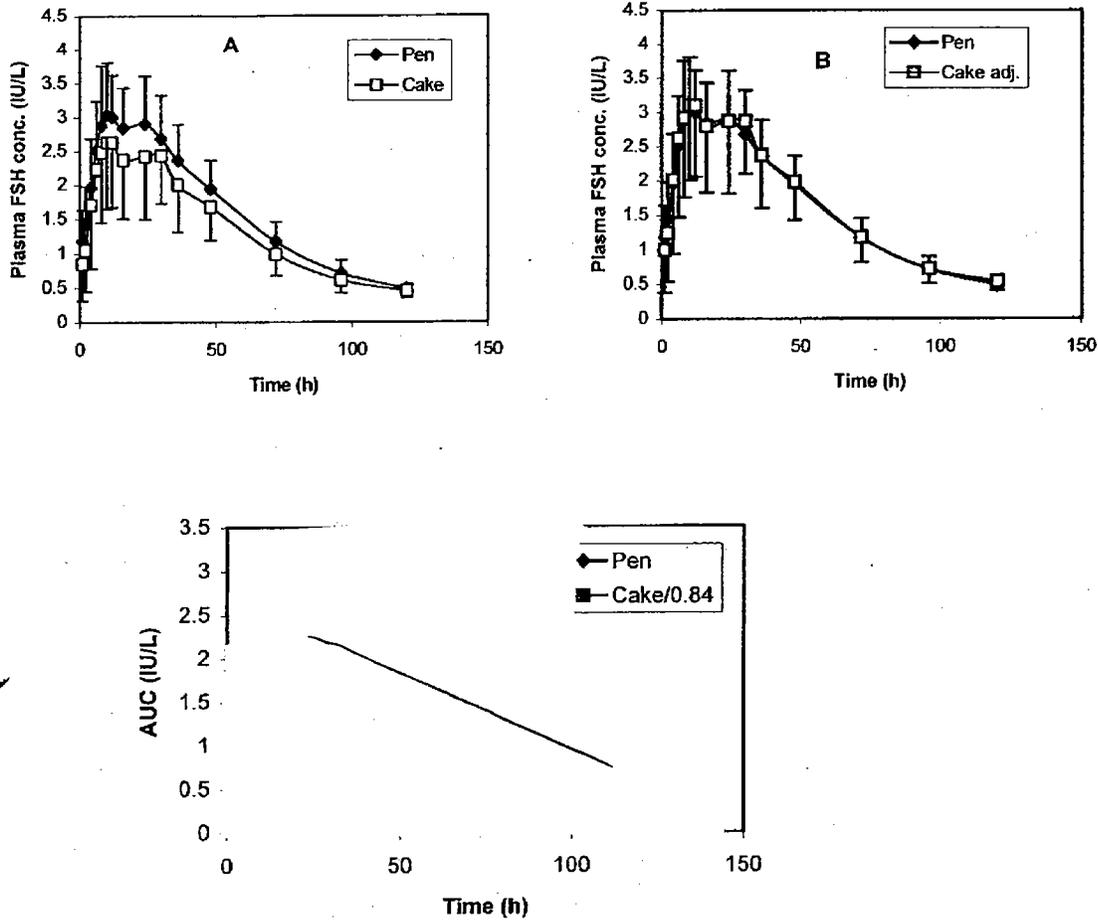
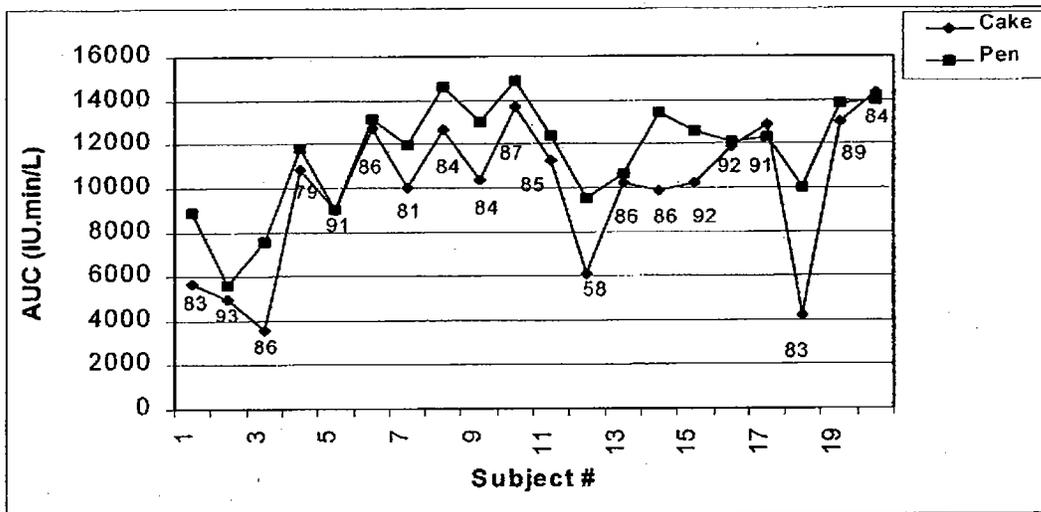


Fig 1. Mean (SD) plasma FSH concentration vs time curves  
 A: without dose-correction for cake administration  
 B: with individual dose-correction for cake formulation  
 C: with average dose-correction for cake formulation.

It is evident from the above figure, the mean profiles after two treatments are overlapping following both individual and average (as proposed in the label) dose-correction. If we look at the individual PK parameters such as AUC (Fig 2), it is also clear that pen injector

resulted in higher AUC values for about 2/3 of the subjects while 1/3 had similar AUC for both cake and pen dosing.



**Fig 2.** Individual  $AUC_{(0-t_{last})}$  values (along with % nominal dose of reconstituted cake injected) following administration of Follistim cake and pen.

In Figure 2, the individual AUC values along with the %dose injected for reconstituted cake are shown. While there is no direct correlation between the % dose injected and AUC values for cake, there is a general trend towards lower AUC when compared to pen when there was more drug loss during injection. However, in some patients even though there was more loss during injection, the difference in AUC between cake and pen was smaller. This could be due to the variability of FSH pharmacokinetics masking the differences due to dose losses for cake.

It should be noted that sponsor used a different pen-injector device in the BE Study and submitted information regarding the differences between the pen used in the BE study (Pen \) and the pen proposed for marketing (Pen \).

According to the information submitted by the sponsor, the accuracy and precision of both pen \ and pen \ are identical. The following differences were noted by the sponsor:

- Pen \ is equipped with a spring-loaded plunger rod. In pen \ the user has to manually advance the plunger rod to the plunger whereas in pen \ the plunger rod comes in contact with the plunger automatically.
- The colors and shape of the Pen \ were slightly modified.
- The maximum administerable dose was increased from 250 IU (Pen1) to 475 IU (Pen 2).

- As the highest administrable dose in Pen \ is higher, the mechanism to reset the dial has been modified. Sponsor stated that reset mechanism of Pen \ functionally remains the same as Pen \

Since the accuracy and precision of Pen \ and Pen \ are identical as reported by the sponsor, and the cartridge formulation is same as final formulation proposed for marketing, the use of Pen \ in BE study is acceptable. Sponsor stated that the accuracy and precision data for Pen \ and Pen \ were submitted in 510(k) and device Master File respectively. This information should be reviewed by the Devices reviewer.

**How did the sponsor address the higher bioavailability of pen-injector compared to approved Follistim?**

In the original NDA submission, sponsor stated that higher bioavailability does not affect the safety and efficacy of the product. However, no data was submitted to support this statement. Since the BE study showed bioequivalence following dose correction for the losses during the injection with conventional syringe, sponsor proposed to reduce the dose of pen-injector by 18% to match the dose delivered by the conventional syringe.

The following conversion table indicating the equivalent pen-injector dose and syringe doses was included in the label.

Table 5. Proposed conversion table in the label

Vial/Syringe (IU)	Cartridge/pen-injector Equivalent (IU)	Dose-setting of the Pen
75	62	50 + 2 marks (= 66.6 IU)
150	123	125
225	185	175 + 1 mark (= 183.3 IU)
300	246	250
450	369	375

\*The pen has a dosage scale with increments of 25 IU and each dose increment of 25 IU is divided in 2 smaller increments of 8.3 IU, each indicated by a mark on the dosage scale.

There is some inconsistency regarding the estimate of dose loss during injection of lyophilized cake between different studies. The *in vitro* data regarding the dose loss during injection of Follistim (cake) submitted in a subsequent NDA 21-273 for Follistim aqueous solution show only about loss with 4 cakes dissolved in compared with loss noted in this study with two cakes dissolved in Sponsor stated that loss was based on the assay of drug substance and not based on weight and since there was no starting weight for this study, it was not possible to calculate the dose loss by weight.

Sponsor conducted another *in vitro* study to document the dose losses during reconstitution and injection of lyophilized cake in support of NDA 21-273. However this data is relevant to the current NDA as well. In this study, the dose loss was estimated to

be around 10%, which is similar to 15% loss. Comparison of dose loss in different studies is presented in Table 6.

Table 6. Dose loss comparison in different studies

Study	# of cakes/ diluent	Mean weight of product injected	% Dose loss (%RSD)
BE study 37626, NDA 21-211	2 cakes	0.90 g	10.0
In Vitro study, NDA 21-273	4 cakes/1ml WFI	1.12 g	
Pilot study, NDA 21-273	4 cakes/1ml WFI	1.08 g	
In vitro study 2, NDA 21-273	2 cakes/1ml WFI	1.002 g	
	4 cakes/1ml WFI	1.057 g	
	2 cakes/1ml	1.010 g	
	4 cakes/1 ml	1.046 g	

WFI = water for injection; weight of 1 cake (75 IU) = 32.8 mg

\* Based on enzyme immunoassay method

The estimate of the dose loss during injection appears to vary from study to study may be because of different technical persons doing the study, and different methods of measurement. It was noted in the above table that the dose loss varied from 10% (based on assay by EIA) to 15% (based on weight method). The estimate of dose loss reported in the BE study of the current NDA is the highest and therefore most conservative for dose adjustments. As was noted from the individual AUC values (Fig 2), dose adjustment of pen-injector may result in slightly lower levels in some patients (about 1/3 of subjects based on the BE study) compared to approved Follistim. Since the therapy of Follistim is dose titrated based on efficacy (follicle growth is monitored by ultrasound at regular intervals), sponsor's proposal to reduce the pen-injector by the highest (conservative) estimate of all the in vitro measurements is considered appropriate from Clinical Pharmacology and Biopharmaceutics perspective.

Because of the limitations of the pen-injector device, the exact equivalents of syringe doses cannot be delivered by the pen-injector. Only the nearest approximate dose is possible by adding extra clicks as noted in the conversion table. Thus the conversion table may lead to confusion when clinicians and patients try to adjust the dose as necessary for their therapy.

The current label for Follistim indicates that anovulatory patients start the therapy at 75 IU and adjust the dose based on response by 37.5 IU. However, with the proposed pen-injector it is not possible to adjust the dose by 37.5 IU increments because each click on the scale gives 8.3 IU. The issues regarding the feasibility of patients self-administering the appropriate dose with the proposed device should be evaluated by clinical division. Sponsor stated that data concerning the accuracy and precision of the pen-injector was submitted in 510K application. The accuracy and precision of the pen injector in delivering the set volume should be evaluated by the devices expert reviewer.

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Ameeta Parekh  
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BIOPHARMACEUTICS  
I concur.