

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-273

APPROVABLE LETTER 3



NDA 21-273

APPROVABLE LETTER

Organon, Inc
Attention: Albert Mayo
Executive Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West orange, NJ 07052

Dear Mr. Mayo:

Please refer to your new drug application (NDA) dated July 21, 2000, received July 24, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim®AQ (follitropin beta injection).

We acknowledge receipt of your submissions dated September 6, 19, 20, 25 and 29, October 9, 10 and 31, November 14, 2000; January 4, March 13, April 20, May 3 and 11, 2001.

We also refer to your submissions dated May 8 and 16, 2001. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry

1. Please revise the Total Oxidation specification to be expressed as the oxidation of the alpha subunit alone.
2. Revise the L-Methionine Content stability specification to _____
3. Based on the stability data provided to the NDA, please revise the Subunit Content stability specification to NMT _____
4. Item #1 in the stability protocol should be revised to the following:

“The first three commercial batches will be tested at the following intervals, which are shown on the table presented below. These testing intervals are based on and intend to support the proposed expiration dating of Follistim® AQ (follitropin injection) of _____

5. The proposed expiration date [redacted] during which time the product can be stored for [redacted] months at a temperature of [redacted] prior to or after storage for [redacted] temperature" is not acceptable. Based on the data provided, we recommend a [redacted] during which time the product can be stored for [redacted] at a temperature of [redacted] after storage for [redacted] temperature. However, if additional stability data are available, they could be used to support a longer expiration date.

6. [redacted]

7. Please perform direct inoculation of rubber components or provide a scientific study that demonstrates the D-value of spores is sufficiently unchanged on the stoppers [redacted]

8. Please provide appropriate data and calculations for the acceptance criteria. To maintain general compliance, we recommend these changes be enacted for other products using these calculations. You reference the pre-submission information submitted on November 13, 1998 to NDA 20-582. [redacted]

[redacted]

9. You indicate the [redacted] has been used in other facilities and is to be used as an alternate. Since the intended use of this [redacted] was not identified in the manufacturing process description in the original submission, it has not been reviewed and is not approved. A supplement may be provided for this change after approval, or this [redacted] may be added to the manufacturing process description in an amendment. Please provide appropriate references or resubmit the validation data to speed the review [redacted]

Facility

Satisfactory inspections at your manufacturing facility located at 375 Mt. Pleasant Avenue, West orange, New Jersey, will be required before this application may be approved.

1 Page(s) Withheld

 Trade Secret / Confidential

 ✓ Draft Labeling

 Deliberative Process

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - a) Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b) Present tabulations of the new safety data combined with the original NDA data.
 - c) Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d) For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
 - e) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
3. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
4. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
5. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
6. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Susan Allen, M.D.

Director

Division of Reproductive and Urologic Drug Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
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/s/

Daniel A. Shames
5/24/01 04:11:12 PM
For Susan Allen MD