DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resear
1401 Rockville Pike
Rockville MD 20852-1448

May 23, 2006

FEDEX

Dr. Nicholas Jacobson
COO and General Manager
Octapharma Pharmazeutika
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Dear Dr. Jacobson:

The Food and Drug Administration (FDA) conducted an inspection of Octapharma Pharmazeutika, Oberlaaer Strasse 235, Vienna, Austria, between January 16 and January 20, 2006. During this inspection, the FDA investigators documented deviations from the applicable standards and requirements of Subchapter C, Parts 210 and 211, and Subchapter F, Parts 600-680, Title 21, Code of Federal Regulations (CFR). Notably, deviations on the Form FDA 483, Inspectional Observations included, but were not limited to, the following:

1. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192] For example, no manufacturing investigations have been performed for Octagam® batches [redacted] and [redacted] that did not meet specifications for [redacted] content.

2. Failure to establish laboratory controls that shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures [21 CFR 211.160 (b)]. Your procedure inappropriately allows for out of specification (OOS) results to be re-tested multiple times, (which may yield individual OOS value) and to report the averaged re-testing results. For example, Octagam® batches [redacted] and [redacted] with initially out of specification results were re-tested multiple times. Individual out of specification values were then averaged with other test results,

3. Failure to supplement the supplier's certificate of testing with at least a visual identification of containers and closures [21 CFR 211.84(d)(3)]. Your procedure does not require incoming glass vials to be visually inspected for defects. Between January and July 2004, numerous investigations were initiated for final container vials of Octagam® due to glass defects.

4. Failure to examine visually, at least once a year, reserve samples from representative sample lots or batches of drug products that were statistically selected for visual inspection for evidence of deterioration [21 CFR 211.170(b)]. Your visual inspection program allows for the selection of a [redacted] representative sample lots or batches and [redacted] reserve samples to be examined once a year. There is no justification for the number of representative sample lots or batches selected to be examined visually on an annual basis.

5. Failure to provide the results of applicable tests in lot release protocols for Octagam® 5%, Intravenous Immunoglobulin Human 5%SD, batches 5240498431 and 5260538431, as required by CBER [21 CFR 610.2]. Rather than provide CBER with the applicable test results under the lot release protocols, you omitted individual out of specification test results and submitted only averaged re-test results.

We have reviewed your February 6, 2006 response to the January 20, 2006 Form FDA 483 and have the following comments. Each comment is numbered in reference to the Form FDA 483 observation cited.

FDA 483 Observation #2: We have reviewed your response and have concerns with your out-of-specification (OOS) procedures. Please be advised that when unexpected test results are obtained an immediate assessment of the accuracy of the laboratory data should be performed. When the initial assessment cannot document laboratory error and results appear accurate, then a complete failure investigation should follow using a pre-determined and defined procedure. As part of the investigation a portion of the original sample may be re-tested and this decision should be based on the objectives of the testing and sound scientific judgment. The number of re-tests to be performed by an analyst other than the one who performed the original test should be specified in advance in a written procedure. This procedure should contain a point at which the testing ends and product is evaluated. If no laboratory or statistical error can be identified, then there is no scientific basis for invalidating the initial OOS results in favor of passing re-test results. Where an OOS investigation is inconclusive, the OOS result should be retained in the record and be given full consideration in the lot disposition decision. Please provide an English translation version of your [redacted] test method for review.

FDA 483 Observation #9A: Your response states that, during the September 2004 deviation management meeting, your firm decided to perform [redacted] inspection of glass vials for defects prior to [redacted] You also implemented a signed quality agreement with the glass supplier including an AQL test program. We acknowledge these improvements, however, please be advised that containers need to be examined and tested for conformance with all appropriate written procedures. In lieu of such testing, a certificate of testing from the supplier may be accepted provided that you conduct at least visual identification on such containers and that you establish the reliability of the supplier's test results through validation at appropriate intervals.

FDA 483 Observation #13: Your response indicated that you have revised your procedure for visual examination of retention samples to include [redacted] retention samples" to be inspected once a year. Please be advised that the regulations require reserve samples (that represent each lot or batch of drug product and consists of at least twice the quantity necessary to perform all required tests, except those for sterility and pyrogens) from a statistically selected number of lots or batches be visually examined at least once a year.

During the March 22 through 31, 2006 [redacted] Center for Biologics Evaluation and Research [redacted]

Neither the above deviations, nor the observations listed on the Form FDA 483 presented to your firm at the conclusion of the inspection, are intended to be an all-inclusive list of deviations at your establishment. It is your responsibility to ensure adherence to all requirements of applicable federal regulations.

Your response to this letter should be sent to me at the following address: Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville, MD 20852-1448. If you have any questions regarding this letter, please contact Diane Alexander, Chief, Biological Drug and Device Compliance Branch, at (301) 827-6201.

Sincerely,

Anita Richardson

for Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research