

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103471

CHEMISTRY REVIEW(S)

MEMORANDUM

FDA/CBER/OTRR/Division of Cell and Gene Therapy

Date: 4/20/93

From: Kurt Gunter 

Subject: Review of Stability studies for PLA 92-0495

To: The File
Andrew Larner, PLA Chair
Lloyd Johnson

I have reviewed the stability studies in the original submission and the sponsor's March 9, 1993 response to our letter on chemistry, manufacturing and controls of January 12, 1993 (henceforth referred to as their "CMC submission").

1. Stability of the 
Original Submission: Page 003 043-046
CMC submission: Response number 13

Although the sponsor had originally requested a  expiration dating based on these data, in the CMC submission, the sponsor has agreed to a 24 month expiration.

The sponsor states that no correlation has been found between failure of final product lots and  although no data are presented.

Assessment: The data support a 24 month expiration dating period.

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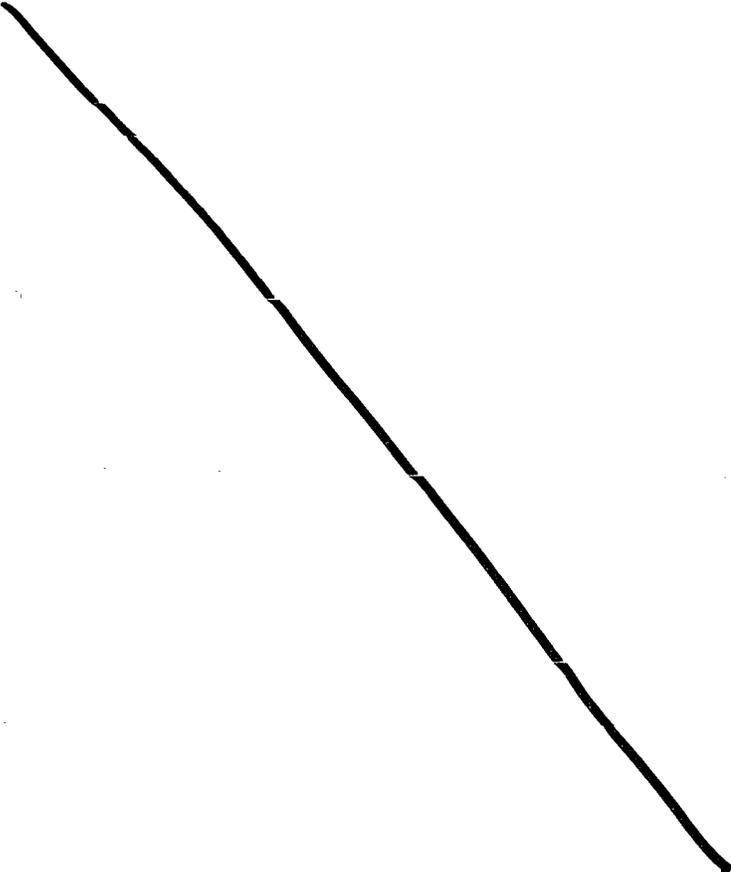
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OVERALL SUMMARY:

The tests used to evaluate stability were appropriate, and the data support the proposed expiration dating periods in most cases. There are two major issues which, in my opinion, should be resolved prior to licensure: 1) Validation of an appropriate assay for quantitation of aggregates should be provided along with an assessment of the changes in the quality and quantity of over time at the proposed storage condition in both the final and reconstituted product; and 2) The sponsor should provide the validated procedures for stopper drying with data on moisture contents in the final product using the new procedures.

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Memorandum

Date November 23, 1992
From Blair A. Fraser, Ph.D. *Blair Fraser*
Subject Manufacturing Questions, Betaseron, Chiron Corp., PLA #92-0495
To Andrew Larner, M.D., Ph.D., Chairperson

The following questions can be included in a letter to the sponsor.

1. Several Quality Assurance Procedures (QAP) presented in Volumes 19 and 20 and several validation studies presented in Volume 21 do not specifically identify the in-house reference for Betaseron. Please identify the in-house reference standard and provide data qualifying this standard.

2. The final container product, upon reconstitution, contains aggregates (Volume 3, pages 135-136). Presence of these aggregates can be determined and estimated by analytical size exclusion chromatography (Volume 3, pages 132-136). Please provide such analytical data, accompanied by procedures and validation studies, for those final container lots used in the clinical trial. Also, should a specification for aggregates be established for reconstituted final container product?

5. The _____ (Volume 19, pages 56-61) appears to be used at several stages of production to identify and quantify the product. Please provide copies of the validation study for this procedure.

6. Please provide examples of how _____ accepted or rejected for use in manufacture. What analytical data is used in support of this decision? Have any lots been rejected?

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September 17, 1992

Blair A. Fraser, Ph.D.

Review of PLA #92-0495, Betaseron, Chiron Corporation

Andrew Lerner, M.D., Ph.D., Chairperson

Product license application #92-0495 for recombinant DNA-derived human interferon beta _{ser17} (IFN- β_{ser17}) has been submitted by Chiron Corporation. This product, known as Betaseron, is classified as a type I interferon. Type I interferons are acid stable and contain approximately 165 amino acid residues.

Betaseron is a single chain protein containing one disulfide bond (cys₃₁-cys₁₄₁), has an apparent molecular weight of approximately 18,500 daltons , calculated), and is produced in Escherichia coli. It differs from native human interferon beta in three ways:

1. The protein is not glycosylated.
2. The protein lacks the N-terminal methionine.
3. The cysteine amino acid residue found at position 17 of native human interferon beta has been replaced with a serine residue.

The purpose of this memorandum will be to review key features of manufacturing and stability.

A summary of the method of manufacture, final product formulation, characterization, stability, and specifications for Betaseron is presented in Volume 1: pp. 108-127 (viz, 1:108-127). Briefly, a plasmid containing the Ser₁₇ form of the interferon-beta gene was introduced into an E. coli host. Large scale fermentation afforded expression of the protein and sequestration in inclusion bodies. Cells were harvested (flow diagram, 1:114) and then lysed.

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