

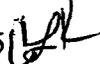
Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: July 19, 2002

To: Melanie Hartsough, BLA Committee Chair, HFM-536

From: Deborah Trout, BLA Committee Member, HFM-675 

Through: Cynthia L. Kelley, Branch 1 Chief, HFM-675 

Subject: Review of Prior Approval Supplement from Biogen Inc., for the HSA-free liquid formulation in a pre-filled syringe as an alternate dosage form for Interferon beta-1a; STN Number 103628/5021

My review includes an evaluation of the following sections submitted in Biogen's BLA supplement (reference is made to CMC Table of Contents in the electronic submission): Item 1: Drug Substance (sections 1.1 - 1.3), Item 1: Biological Product (sections 1.1 - 1.4.3.12, 1.4.5-1.4.8.1, 1.4.9, 1.5.2.12, 1.5.2.13, 1.5.5, and 1.7)

This review memorandum is comprised of three sections. The first section are issues that can be addressed in an information request or complete review letter, the second section are issues that can be addressed in the pre-license inspection and the third section is my review narrative.

Section I: Outstanding Issues that can be addressed in an Information Request or Complete Response letter.

1. Outstanding inspectional issues identified on the FDA Form 483 dated _____, issued at the conclusion of the pre-approval inspection of your contract manufacturer, _____ location have yet to be resolved.
2. The submission states accelerated studies using extreme surface area to product volume ratios were performed on the BG9418- _____ container closure system to assess compatibility. Please describe the analytical method used to assess compatibility of the tip caps and rubber stoppers. In addition, please provide the detection limit of the analytical method, sample preparation for individual tests, and results for compatibility testing.
3. Please provide in-process _____ limits associated with the concentration and _____ of the acetate drug substance during routine manufacturing.

4. Please amend your BLA to include a description of agreements to ensure that the drug product manufacturer will inform you of all important proposed changes to production and facilities.

Section II: Pre-license Inspection Issues

5. Tip caps and plunger stoppers are _____ to enhance machine ability in the filling line. Please review verification and validation of the _____ process.

6. Please review the following regarding equipment cleaning of the _____ compounding vessel (dedicated), _____ tanks (dedicated), and _____ filling needles (dedicated): the frequency of routine or periodic testing following the cleaning procedure, sampling procedure, residual _____ detection, and frequency of revalidation. If the cleaning procedure is manual, the firm should have validation demonstrating reproducibility and routine testing to ensure validated process is maintained. In addition, residual limits and acceptance criteria should be achievable and verifiable. The manufacturer should be able to document by means of data that the level of residuals and acceptance criteria are scientifically sound.

7. The BG9418- _____ drug product and the ancillary components will be manufactured in a multi-product facility. The compounding rooms and aseptic filling suites located in the _____ facility are used to manufacture and fill a variety of drug products in addition to the BG9418- _____ drug product. After processing steps are completed, the supplement indicates that equipment and facility cleaning and changeover are performed according to established written procedures, prior to the introduction of a subsequent product into the area. Please review cleaning and changeover procedures for all critical manufacturing areas.

8. Please review the most current six months of Water for Injection (WFI) water monitoring data for points of use servicing the _____ facility.

9. During the pre-license inspection, the following items should be evaluated: (re)validation of the HVAC system; HEPA filter certification frequency and tests performed; environmental monitoring for both viable and non-viable particulates; monitoring of differential pressures, air temperatures, and humidity.

10. Page 61, section 1.4.9.12 states all media filled units are incubated at _____ for a minimum of _____. Please verify that this incubation temperature and schedule is suitable for recovery and visual detection of environmental isolates, particularly molds.

11. Please review all media fill data for the last two years for Clean Room _____ used in the filling of BG9418- _____ drug product. In addition, please review related SOPs, Protocols and Reports

associated with media fill activates.

12. Page 22, section 1.4.3.7, states tip caps are either washed in the _____ component washing machine and then _____, or are _____ and _____ by the component _____. The stoppers are _____ component washing machine _____, or are delivered to the component preparation area _____ by the component _____; and ready for sterilization. Please verify that the _____ tip caps and stoppers have been assessed as to the uniformity of the _____ and the capability of the washing process to remove _____. _____ could rely on a supplier's Certificate of Analysis provided that the supplier's test results are periodically shown to be valid by doing their own testing, which, when compared to the supplier's data, shows agreement. Once that reliability is established, then the level of testing may be reduced.

13. Syringes are delivered to the component preparation area _____. Syringes are _____. After _____ the syringes are _____ then transferred to sterilization boxes and _____ sterilized _____. Please review the syringe _____ process validation, and confirm that validation demonstrated a minimum _____.

14. Please confirm stopper and tip cap _____ validation demonstrates a minimum _____. In addition to _____ the firm should have data supporting particulate removal for stoppers.

15. The acetate drug substance is _____ in a " _____ for approximately _____. Please review equipment qualification for the _____ used in _____ process.

16. Prior to filling of the BG9418- _____ drug product an _____ is aseptically removed following compounding. Confirm on the pre-license inspection that sampling occurs prior to filtration procedures.

17. Please review all hold periods for in-process bulk product and process buffers with associated _____ during the pre-license inspection.

18. Please confirm that fluid pathways such as tubing are compatible with the BG9418- _____ drug product (i.e., do not absorb in-process materials, and do not leach unintended substances into in-process materials or the drug product).

19. Please confirm that any tubing used for an extended duration of time is suitable for the

longest anticipated time period, together with the maximum number of lots manufactured between replacement. In addition, the length of time that a tubing system is to remain in place must be validated to ensure that _____ is under control for the entire time period between replacement under worst case operating conditions.

20. The acetate drug substance is shipped from Biogen's Cambridge, MA, facility with a _____ release specification of _____. Subsequently during compounding and transfer to the dispensing vessel just prior to filling at the _____ facility the acetate drug substance receives a _____ specification of _____. Please verify that validation data is available to support the increase of the _____ specification at the _____ facility.

Section III: Review Narrative

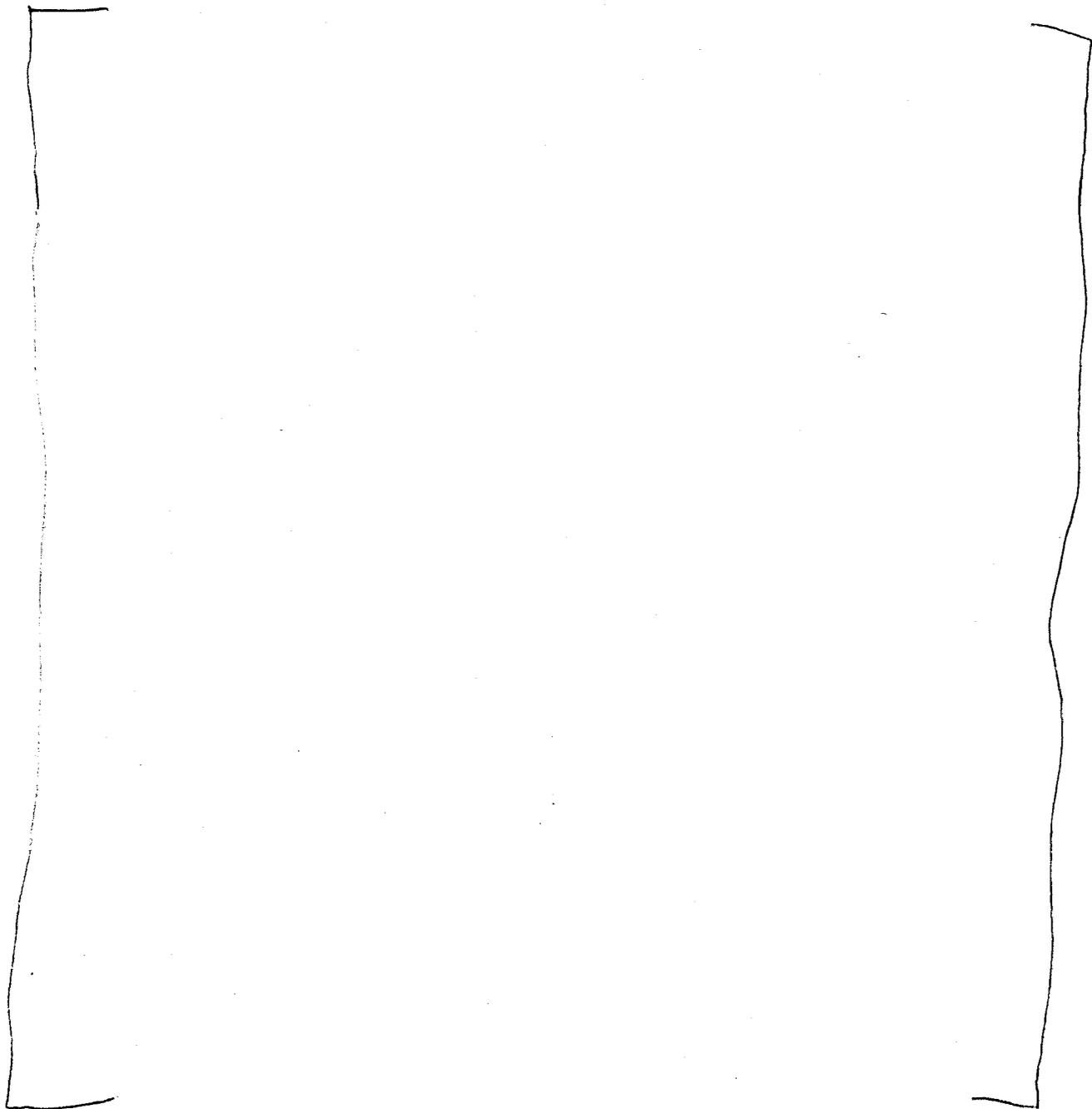
Drug Substance

Biogen Inc., has submitted a supplement to their Biologics License Application to provide for an alternative dosage form for Avonex[®] (Interferon beta-1a). The currently approved formulation of Avonex[®] contains Human Serum Albumin (HAS) and is supplied as a vial for reconstitution. The new formulation is a HAS-free liquid formulation in a pre-filled syringe.

The acetate drug substance used in the manufacture of the liquid-formulated Interferon beta-1a drug product is produced via an _____ step from the currently approved phosphate drug substance PLA (Reference No. 95-0979). The acetate drug substance is manufactured at the Biogen Cambridge facility and shipped _____ Liquid-formulated Interferon beta-1a drug product (BG9418-A- _____ is manufactured at _____

[]

[]



The supplement indicates that process validation was performed on — consecutive batches of acetate drug substance manufactured at Biogen, Cambridge, MA, to demonstrate that the process is consistent and robust. Batches processed were _____ system. In addition, the supplement states all — batches of acetate drug substance in the process validation study passed all release tests and were subsequently used to produce liquid-formulated Interferon beta-1a drug product (BG9418- _____). In-process parameters were monitored during the production of the acetate drug substance and all parameters were within the acceptance criteria range for all — batches.

The acetate drug substance is transported to the _____ facility in _____
_____ A validation study was performed to determine if the method of transport meets the
required acetate drug substance temperature specification of _____ for the duration of
any supply chain transportation segment. Validation was performed in an environmental
chamber set at a constant _____, water was used to simulate _____ acetate drug
substance. _____

_____ was used for the test. The _____ was validated to hold between one and
four _____ of acetate drug substance _____ Temperature probes
were placed inside the _____ water to record the internal temperature of the
simulated product. The testing was conducted _____ times to demonstrate reproducibility. The
average transit time is _____, allowing for a significant safety margin for any in-transit
delays.

Biological Product

The _____ manufacturing complex consist of three main facilities:

1. Production facility in _____, location _____
2. Warehouse and packaging area in _____ location _____
2. Production facility in _____

Release and stability testing are performed at Biogen, who also stores the drug product after
manufacture at _____ for US distribution.

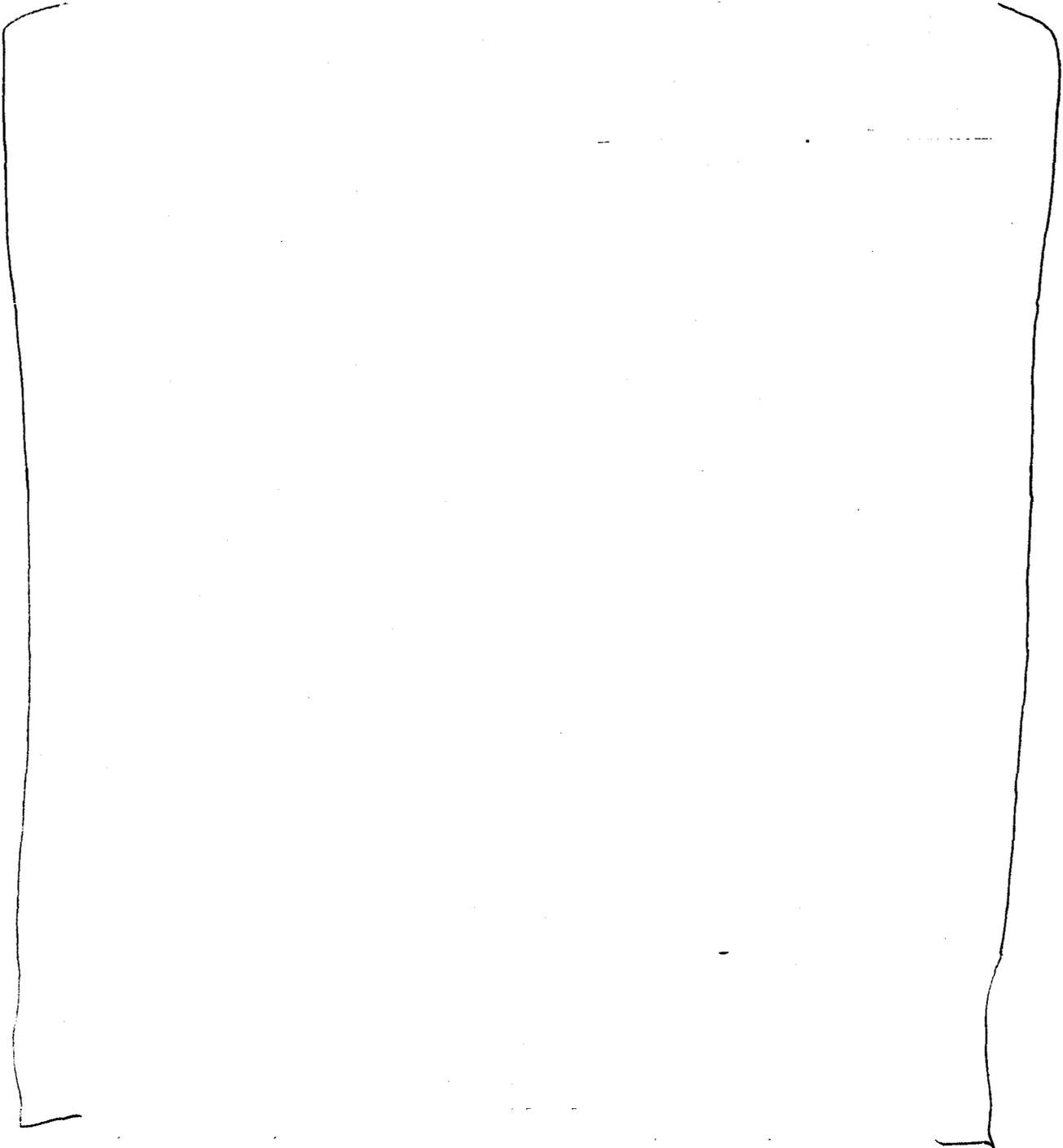
Interferon beta-1a drug product (BG9418-A-_____) is formulated to a target in process
concentration of _____ of Interferon beta-1a in order to deliver 30 mcg per 0.5 mL dose.
Approximately _____ of formulated solution are required to fill a batch size of _____

The manufacturing process for BG9418-_____ performed at _____ in _____
consisting of compounding rooms and aseptic filling suites, located in the _____
complex. Compounding is performed under Class _____ conditions. Compounding consists of
_____ acetate drug substance, _____

_____ After compounding, the
formulated product is _____
_____ The formulated product is filled into sterilized syringes in a Class _____
area. The aseptic filling operation consists of delivering formulated drug product through a _____
_____ sterilized syringe barrels with tip caps. A plunger
stopper is then placed into the syringe barrels.

Product contact equipment for compounding and filling is dedicated to the drug product. All
other product contact items are one time use and are disposed of after use.

_____ of the Acetate drug substance occurs in a _____ Average
time is approximately _____ are inspected during _____ to check status of _____
Once all _____ are completely _____ they are moved into _____ storage until further
processing.





Temperature during visual control and packaging is maintained between _____ Syringes are 100% visually inspected for _____

_____ The inspected syringes are packed in trays, each tray is individually labeled with part number, Biogen lot number, quantity, and date.

After inspection and packaging, the syringes are transported for final packaging or shipment to the _____ facility. Whether awaiting final packaging or shipment, the syringes are stored at _____

Equipment Used During Manufacture of BG9418- _____ Drug Product

Washing and _____ machines (_____)

_____ component washing machines ' _____

_____ sterilizers ' _____

Filling and stoppering machine (_____

_____ vessels | _____

_____ vessel

Vessel _____ unit

_____ tanks

_____ filling pumps

_____ filling needles

Filter integrity testers (_____

Material washing machines (_____

Environmental Assessment

Claim of Categorical Exclusion

As allowed under 21 CFR 25.31(c), Biogen request categorical exclusion from the requirement for preparation of an environmental assessment report in that no potential adverse environmental impacts are identified for action on this product, and no extraordinary circumstances exist. The product contains the following excipients: sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, Polysorbate 20, and water for injection. Since no biodegradation products are released into the environment with the use of Avonex[®] (Interferon beta-1a) 30 mcg Pre-filled Syringe for Intramuscular Injection, the impact on the environment is negligible and no environmental assessment is needed.