Memo

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 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 by the component, 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 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 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 no 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 (RG9418—). 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 , location

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 ___)
- Vcissc ___ 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.