CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125290

CHEMISTRY REVIEW(S)

MEMORANDUM
Date: 28 Mar 09 (updated 27 Aug 09).
Through: Susan Kirshner and Barry Cherney.

From: Ralph Bernstein (**RMB**).

Re: CMC Review of BLA STN 125290, Extavia ™ (aka NVF233), currently identical to Betaseron ™ (IFN β -1b).

Filed: 06 May 08
Action date: 06 Jun 09

Indication: Relapsing forms of multiple sclerosis.

Formulation: lyophilized vials of 0.3 mg IFN β 1b, 15mg HSA, and 15 mg Mannitol. Provided in a 15 blister pack unit carton, with 1.2 mLs of 0.54% NaCl diluent, 27 gauge needle and 1 mL syringe, (b) (4) vial adaptor and 2 alcohol pads per blister pack.

Recommendation: I recommend that this BLA be approved (pending the resolution of labeling and PI issues) with the PMC, below. Novartis has sufficiently demonstrated adequate QA oversight over Bayer's manufacturing of Novartis's IFN b (Extavia/ NVF233), (currently) an exact clone of Betaseron. Bayer has committed not only to answer the questions and issues raised on inspection, but also to improve the Novartis QA oversight process and personnel training. Additionally, it is my opinion that future CMC review and inspectional activities pay close attention to segregation of the two products and Novartis's QA oversight.

Post marketing commitments: Novartis commits to develop an analytical test method for use in release and stability testing of the drug product to monitor the size and bioactivity of IFN /HSA complexes by Q1 2010. The commitment must be modified by describing the month and year the information will be submitted to the FDA.

Background: Betaseron is a recombinant IFN β produced in *E.coli.* Betaseron was originally approved and licensed to Chiron (Emeryville CA) in 1993 under BLA 103471. Chiron and Germany based Berlex/Schering AG, co-developed Betaseron, but the two processes have diverged since that time (Schering's IFN β is termed Betaferon, manufactured in Germany, and is not licensed for distribution in the US). Schering was subsequently acquired by Bayer, and Chiron was acquired by Novartis in 20 Apr 06. Novartis was briefly the license holder for Betaseron, until 13 Sept 07, wherein Bayer became the license holder. As part of the negotiations encompassing this arrangement, Bayer agreed to manufacture Betaseron for Novartis, under a separate BLA. Bayer has given Novartis the right (in a letter to the Agency dated 13 Sept 07) to "irrevocably" cross reference the entirety of Bayer's license (103471) until Dec 2006 (*This letter can be found in CBSFS03/OTRR/DTP/Licensed products folders/Extavia (IFN B-1b)*). In this BLA (125290), Novartis has submitted all changes subsequent to Dec 2006, which,

coincidentally, this reviewer (RMB) reviewed and approved (these will be summarized below).

There are currently no major CMC differences between the 2 drugs; Bayer has filed a supplement (103471/5125, which was approved) to reduce the number of blister packs to 14 per carton, to change to a thinner 30 gauge needle (in part to differentiate Betaseron from Extavia's 15 per carton and 27 gauge needle) and to change the colour of the (b) (4) vial adaptor. This new needle, and the associated advertising and website ("NEW Thinner needle") has generated a response from DDMAC (*This letter/consult from DDMAC can be found in CBSFS03/OTRR/DTP/Licensed products folders/Extavia (IFN B-1b)*)), but this new configuration is currently still on the market.

During Agency/Novartis pre-approval meetings the Agency stated that Novartis, as the new BLA holder, must demonstrate full QA oversight of the manufacture of Extavia. In addition, supplements for changes must be filed by both Firms (ostensibly, concurrently). To this end, the Agency, Bayer and Novartis scheduled a PAI at the Emeryville manufacturing site for Jan 09. The PAI was conducted, with a result of a non approvable recommendation from the inspection team/district (see PAI Inspection, below). Novartis implemented changes, and was re inspected 11-13 May 09, with an approvable recommendation by the district.

Manufacturing: For clarity's sake, n.b., the manufacturer of both Extiva and Betaseron are Bayer, while the license holder of Extavia is Novartis. Although the Extavia manufacturing process is currently identical to that of Betaseron (except for the final packaging and supplied needle differences noted above), and cross referenced in its entirety from Bayer, a brief description of drug substance and drug product is provided below. This is done primarily to help secondary and tertiary reviewers (and future primary reviewers) understand the process and recall the importance of the post marketing commitments that Novartis will implement regarding complexes of HSA and IFN β molecules (see PAI results, below).

(b) (4)

4 pp withheld immediately after this page as (b)(4) CCI/TS.

Figure 1-2 **Flow diagram for the sterile filtration and lyophilization of the drug product**

Changes since cross reference to manufacturing: Novartis has included all the supplements that have been submitted (by Bayer) and approved (by the Agency) to the Agency in the BLA package. Notably, there are 2 differences; as noted above, Bayer has a supplement in place to differentiate the Novartis product from their own (package size and gauge needle). (b) (4)

Changes implemented after 31 Dec 06: (changes 1-3 apply to Novartis, and have been reviewed and approved).

1) (b) (4)

Novartis withdrew this supplement in Sept 07).

2) A change in the drug product storage temperature from (b) (4) to 25 °C. This change was submitted on March 16, 2007. (This was the drug product storage on stability).
3) Replacement of the (b) (4) for the (b) (4) step. This change was submitted on May 2, 2007. (This was an upgrade of the (b) (4) on the (b) column).
4) (b) (4)

Inspectional history/ PAI results: As stated briefly above, the initial PAI of Novartis at Bayer's Emeryville facility, plus the subsequent Novartis PAI at Novartis Vacaville yielded a non approvable judgment by the ORA field investigation team, for QA oversight issues (see 483 items below). A subsequent PAI at Novartis Vacaville yielded an approvable rating from the ORA field inspection team, and the actions put in place by Novartis are summarized below.

Novartis 483 items: (these items are from the first Novartis PAI. The issues are significant and included in this review as they clearly demonstrate that Novartis lacked appropriate QA oversight of the manufacture of Extavia).

OBSERVATION 1
Written procedures are not established for evaluations done at least annually and including provisions for a review of complaints and investigations conducted for each drug product.

Specifically, no Standard Operating Procedures are in effect for evaluations by the Quality Assurance Unit for Annual Product Reviews manufactured by the contract manufacturer for all products. For example, the Annual Product Review for Proleukin (IL-2; aldesleukin) for the time period 7/01/07-6/30/08, was composed and signed off by the contract manufacturer on 8/28/08. No additional documentation could be provided to demonstrate Quality Assurance Unit oversight, evaluation, fitness for use or review of this document.

OBSERVATION 2
The responsibilities and procedures applicable to the quality control unit are not in writing.

Specifically, no Standard Operating Procedures are in effect to govern the Quality Assurance Units activities in regards to evaulation of manufacturing deviations and appropriateness of corrective actions implemented by the contract manufacturer for all products manufactured.

OBSERVATION 3
Failure to assure that personnel have a thorough understanding of the operations which they perform.

Specifically, Quality Assurance Unit personnel training records do not evaluate the thorough understanding of the operations which they perform in evaluating manufacturing deviations and laboratory methodology to assess product quality. Training files state, "read and understood", for procedures pertaining to the Quality Assurance Unit activities with no evaluation that the employees understood. For example, (b) (4) , have been identified as direct personnel for performing QA activities to evaluate production, manufacturing deviations and laboratory methodology to assess product quality of products manufactured for their firm by a contract manufacturer. Training records for these employees only document the title of the course and dates of attendance. No evaluation for the following courses attended since 10/07 through 11/08 could be provided:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

OBSERVATION 4

Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures.

Specifically, no data could be presented to document Quality Assurance Unit activities to evaluate manufacturing procedures, batch records and laboratory analytical methodology performed by the contract manufacturer for all products.

For example:

A. Manufacturing Procedures: The critica (b) (4) There is no developmental data demonstrating complete (b) (4), which may affect the number and size distribution of HSA-IFN complexes.

B. In-process Impurities: In-process impurities are not controlled in the final drug product, e.g., (b) (4) and (b) Developmental data clearly demonstrate that (b) levels affects turbidity and aggregation.

C. Batch Records: Inadequate in that certain critical process steps are not adequately documented, such as:

(b) (4)

[redacted]

Reviewer comment: Observations 4 and 5 are particularly important from the CMC view point as they reveal that Novartis had not reviewed or questioned any of Bayer's manufacturing processes (which would be indicative of complete QA oversight). Novartis's corrective actions (and PMCs) are summarized below. Novartis has committed (along w/ Bayer) to have the responses to items 4 and 5 completed by 1Q10. This includes:

The preparation of an investigational master plan: March 09;

Establishment and evaluation of analytical methods: Q3 09;

The characterization of the IFN b /HSA complex: Q1 10.

These time frames, due to the complexity of the task, appear appropriate to this reviewer (RMB). It is my recommendation that Bayer and Novartis be allowed to proceed at this rate, and consequently approve this BLA prior to completion of the resolution of items 4 and 5, as the currently manufactured Betaseron was approved without said tests, and has a reasonable safety profile.

OBSERVATION 5
The suitability of all testing methods is not verified under actual conditions of use.

Specifically, release and stability tests for the final lyophilized drug product do not adequately monitor final drug product composition or stability. For example, there are no techniques in place to adequately monitor the size, number or distribution of IFN-HSA complexes; these complexes have been demonstrated to vary in size and are responsible for IFN bioactivity.

Summary of Quality oversight (Novartis): Novartis and the Novartis QA staff demonstrated adequate QA oversight of the Extavia manufacturing process thusly:

Novartis stated: "Initial changes to the manufacturing procedure include a quality assurance agreement:
Quality Assurance Agreement Key Points

The Quality Assurance Agreement requires the following measures to establish Novartis control over the production of NVF233:

(b) (4)

Reviewer comment: while these QA agreement items seemed appropriate prior to the PAI in Jan 09, during the inspection it immediately became apparent that Novartis did not have good QA oversight (see PAI 483 items, above, and "Novartis PAI EIR" at CBSFS03/OTRR/DTP/DTP_BLAs/Licensed products folders/).
A second PAI was performed, as indicated above, and the re inspection was found acceptable to the PAI ORA field team. The changes to be and being implemented are listed in a letter to the ORA field investigator (and can be found in CBSFS03/OTRR/DTP/DTP_BLAs/Licensed products folders/).

The issues can be summarized as:

1) Procedural: Novartis hired a 3rd party consultancy firm, (b) (4) to review all existing SOPs and control systems. Novartis implemented the suggested changes and they were acceptable to the ORA Field investigator upon re-inspection.
2) Organizational: Novartis created a new (b) (4) third party management (TPM) organization to oversee Bayer manufacture of Extevia. This includes two QA associates for all three Novartis products produced by Bayer (Extavia, Proleukin (b) (4) and a third associate who will provide technical input to evaluate changes, deviation investigations and to support other cGMP processes, as needed.
3) Infrastructure: Novartis created a work flow management system that will track all change controls, audits of Bayer at that facility, and eventually all quality system events.

Novartis also committed to review all master batch records for Proleukin and Extavia to ensure that all process steps are clearly defined and adequately detailed (13 May 09

letter, page 3 of 4, also in CBSF03 DTP folder). Additionally, Novartis will revise the APRs for (b) (4) and Proleukin (as part of the 2nd PAI inspection of Novartis).

Conclusion:
Based on the results of the second inspection and the changes to Novaritis' QA program summarized above we find that Novartis can maintain control over the manufacturing process for NVF233.

Labeling issues: Novartis submitted multiple PI changes, some of which the Agency does not agree with. The CMC additions to the PI are as follows:

1) Initial date of Betaseron approval: 7-23-93

2) Additionally, the statement regarding IFN and IFN families has been modified from:

(b) (4)

To:
"Four major groups of interferons have been distinguished: alpha, beta, gamma and lambda. Interferons-alpha and -beta comprise the Type I interferons, interferon-gamma is the sole Type II interferon, and interferon-lambda is designated as Type-III interferon. Type I interferons have considerably overlapping but also distinct biologic activities. The bioactivities of IFNs are mediated by their interactions with specific receptors found on the surfaces of human cells. Differences in bioactivites induced by IFNs likely reflect divergences in the signal transduction process induced by IFN-receptor binding."