Running list of CMC Questions for Amgen BLA 125518

10/31/2014

1) **3.2.S.2 Manufacturing Process:** Please provide a detailed description of the product manufacturing process, including the type of (b) (4) used, types of purification (b) (4) used with capacity, flow rates and any relevant additional details such as number of (b) (4) used and time taken to complete each specific purification step, types of (b) (4) used for in-process storage.

    a. In the manufacturing process description, include details such as type and number of (b) (4) used for cell expansion during passages (b) (4), for virus manufacture.

    b. Details of (b) (4), such as: is (b) (4) an automated process? Is it a (b) (4)? Is there a (b) (4) (b) (4) How is (b) (4) checked? How many (b) (4) were checked for (b) (4)?

    c. Provide justification for the large range ((b) (4)) for initiating virus infection in (b) (4).

    d. Is (b) (4) adjusted or media (b) (4) (b) (4)

    e. How is the temperature change accomplished? Is this a programmable feature?

    f. What is the capacity of the (b) (4)

    g. Provide details of the harvesting and (b) (4) process – are these manual or automated processes?

    h. Provide leachable and extractable information for (b) (4)

    i. How is the sampling done for in-process (b) (4) tests after transfer to the (b) (4)

    j. Provide key operating parameters for (b) (4)

    k. Provide acceptable range for the (b) (4).

2) Please provide leachables and extractables study information for all materials that come in contact with the (b) (4) (including in process storage (b) (4)).

3) **3.2.P.6 Reference standards:**

   a. Please explain exactly how the results of qualification runs of the (b) (4) and (b) (4) are used to determine the performance ranges for the talimogene laherparepvec reference standard (section 1.4.2.2).

   b. Please explain how assay performance criteria may be adjusted based on ongoing reevaluations (1.4.2.2).

   c. In the acceptance criteria in table 12, please explain what you mean by "comparable to previous reference standard."

   d. In section 1.5 you state that an expiration date for the reference standard will be determined when sufficient data are available. For the commercial drug product you have set an expiration date of 48 months based on extensive stability studies. Please explain why the data are not sufficient to also set an expiration date for the reference standard.

4) **3.2.P.8.3 Stability data:**

   a. When conducting stability tests on reference standard (b) (4) (table 2), which standard do you use as a reference in the (b) (4) ?

5) **Sections 3.2.S.4.2, 3.2.S.4.3 and 3.2R:** Please provide the assay description and assay validation information for the (b) (4)

6) **In vivo In vitro assays:**

   a. The in vivo test is done on (b) (4) Is the test article volume and dose equivalents used for both the same? Was the same amount of (b) (4) used to qualify the (b) (4) in the in vitro test as that used to test the (b) (4) during production?

   b. It is stated in the application that in vivo and in vitro tests are done in compliance with the 2010 CBER Guidance for Industry: "Characterization and qualification of cell substrates and other biological materials used in the production of viral vaccines for infectious disease indications". However, the Firms response indicates a much smaller number of dose equivalents tested than recommended in the guidance. In vitro testing historically requires 500 doses or a 50ml volume (whichever represents more virus) for each indicator cell line. The in vivo test requires at least 100 doses or a 10 ml volume (whichever represents more virus). Please provide justification for the dose equivalents of product used in the in vivo and in vitro testing.

7) Environmental Analysis:

a. In the environmental analyses section of the BLA, you state that an estimated (b) (4) of product will be used in any 12 month period following BLA approval (section 4.4.2 on page 9). You have not presented quantitative metabolic data to indicate the amount of product released into the environment. Without additional information regarding the environmental release of shed material, it is assumed that (b) (4) /year of product is introduced into the environment. Do you have additional data to support a different level of environmental exposure that could be included in the EA? If so, please revise the EA to include this information.

b. You have not provided sufficient survival data to understand the half-life of the product in different environmental conditions. You cite references in which HSV1 routinely survives for a (b) (4) , but may be detectable for up to (b) (4) . Without additional information regarding environmental decay, it may be reasonable to assume that the product may persist under different environmental conditions. Do you have additional data on whether the virus will persist in the environment (for example cleaning validation data) that could be included in the EA? If so, please revise the EA to include this information.

c. You have not addressed the possibility of latency and reactivation of the product in the environmental analysis. A document in your submission (#4648-00015 Version 1 titled "A comparative assessment of 17syn+ and OncoVEX reactivation from latency in the peripheral nervous system of BALB/c mice") indicates that the product may undergo latency and reactivation in mice. Without additional information regarding latency and reactivation, it may be reasonable to assume longer environmental release times. Do you have any additional data addressing latency and reactivation? If so, please revise the EA to include this information.

d. You have not addressed the possibility of recombination with other viral species. Assuming a large amount of product is released into an environment in which it may persist, it is reasonable to assume exposure to plant and animal species. The potential for recombination and pathogenicity of any recombinants should be assessed as needed. Do you have any data regarding the possibility of recombination with other closely related animal species? If so, please revise the EA to include this information.