Information Request for Amgen BLA STN125518/0

As follow up to Teleconference on 10/3/2014 and 10/17/2014

The requests for additional information are based on facility changes that were reported during the BLA review and information not included in submission as outlined in "Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for Vaccine or Related Product" and "Guidance for Industry: for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

1. In reference to the facility changes that were provided in Table 12 Facility Modifications provided in submission amendment STN125518/0.3 (eCTD 0003) and discussed in the Oct 17, 2014 teleconference, please indicate dates for when each change was implemented and when the re-qualification studies to support these changes were completed.

2. Please provide the change control documentation for the specific changes to the filling suite. In addition, please provide a detailed schematic of the reconfigured fill suite that shows the location of the (b) (4) filters and the location of the (b) (4) within the filling suite.

3. Please provide the re-qualification media fill validation studies that were performed to support the changes to the filling suite. The validation summary should include all information outlined in section IV **Information for Aseptic Fill Manufacturing Processes Which Should Be Included in Drug Applications** parts D and E of the "*Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*". In particular, this information should include but not limited to the following:
    - a detailed description of the simulation performed including details of the interventions performed that would simulate issues during a filling run
    - a detailed narrative of the environmental monitoring performed during the fill and a summary of the results
    - a description of the EM sampling plan and justification for sampling locations, and personnel monitoring during the media run and filling process
    - a listing of the acceptance criteria of the media fill and a description of actions taken when there is a failure to meet the acceptance criteria

4. Please clarify if the product lots manufactured before the changes to the filling suite are going to be commercially distributed. If so, please provide the validation summary and results of the media fills pre-changes to the filling suite that support the filling of these lots. The validation summary should include the information outlined in parts D and E of the "*Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*".

5. Please provide validation summaries for the HVAC system including the re-qualification documentation of the changes to the facility (as per "*Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for Vaccine or Related Product"*. At a minimum, the information in these summaries should include but is not limited to the following:
    - A narrative description of the validation process (or protocol), including the acceptance criteria and dates performed
    - Certification that IQ, OQ and certification of filters has been completed
    - Length of the validation period
    - A validation data summary (validation data should include Performance Qualification data accumulated during actual processing)
    - Explanation of all excursions or failures, including deviation reports and results of investigations.
    - A narrative description of the routine monitoring program including tests performed and frequency of testing for viable and nonviable particulate monitoring parameters, viable and nonviable particulate action and alert limits for production operations for each manufacturing area, and a summary of actions to be taken when limits are exceeded
6. Please provide qualification/validation (description of IQ/OQ and a summary or report for the PQ) of major equipment used in the manufacturing process.

7. Please provide a detailed description of how the product contact components of the filling machine are cleaned and sterilized and provide the appropriate validation studies that support these activities.

8. Please provide a detailed narrative of all aseptic activities occurring in room (b) (4) This narrative should include the flow of activities beginning with the (b) (4)

9. Please provide a table listing all product contact equipment, container/closures etc. utilized in your process and indicate if these items are disposable and come ready to use or are sterilized in house. Please also indicate the method of sterilization for all items. If product contact equipment or items are sterilized in-house, please reference the corresponding validation study.

10. In reference to "*Guidance for Industry: For the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"*, please provide the following in regards to sterilization of product contact equipment (filling equipment) and container/closures (stoppers) using autoclaves:

- A description of autoclave process such as cycle type, cycle parameters and performance specifications such as temperature, pressure, time and minimum and maximum F_o
- A description of representative autoclave loading patterns and validation studies that demonstrate the efficacy (lethality) of the production cycle
- Methods and controls used to monitor routine production cycles
- A description of routine and unscheduled requalification of autoclaves and frequency
- Heat distribution and penetration study protocol and data
- The number of thermal monitors used and their locations in the chamber
- Data generated from minimum and maximum loads

11. Please provide the following in reference to your water systems:
    - Validation summary which should include description of the validation process, acceptance criteria, parameters monitored and tests performed, frequency of monitoring each point of use during validation, summary of data and explanations of all excursions or failures, including deviations reports and results of investigations.

    - A description of the routine monitoring program which includes tests that are performed, frequency of testing at points of use, alert and action limits and actions taken when limits are exceeded.

    - Any other additional information noted in CMC Section IIIA Water Systems described in "*Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for Vaccine or Related Product"*

12. Please provide the acceptance criteria, testing performed, and indicate the testing frequency all gas systems that contact the product.

13. In reference to "*Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls and Establishment Description Information for Vaccine or Related Product"*, please provide the following information in regards to all computer related systems that are associated with critical manufacturing processes:
    - Developer name and whether in-house or a contractor
    - A brief description of procedures for changes to the computer system
    - A list of the manufacturing steps which are computer controlled
    - A narrative description of the validation process (or protocol), including acceptance criteria
    - Certification that IQ and OQ have been completed
    - Explanation of the parameters monitored and tests performed
    - Validation data summary
    - Explanation of all excursions or failures
    - Deviation reports and results of investigations for all excursions or failures

14. Please provide a detailed description of facility cleaning and sanitization procedures including the disinfectants used, frequency of routine cleaning/sanitizing, and studies on disinfectant effectiveness of inactivating viral product contamination after manufacturing. In addition, please include the cleaning/decontamination validation of the new (b) (4) used for filling activities.