From: Rabia Ballica
Date: 01/05/2015

DMPQ Information Request due January 16, 2015

1. Regarding drug product container closure system:

   a) We note from the information provided in Sections 3.2.P.2.5, 3.2.P.7 and 3.2.P.8.1 of your BLA submission that a (b) (4) detection method is validated to evaluate the integrity of the container closure system (CCIT) stored at sub-zero temperatures (80°C ± 10°C). Please provide actual validation report (including validation protocol and associated data) for this (b) (4) detection test method. Please also provide information as to how the (b) (4) acceptance criteria (indicated in the submission (b) (4) for pass/fail outcome) was established if not included in the requested validation report.

   b) Please also provide actual study report for (b) (4) in that the integrity of the drug product container closure system was evaluated. Please ensure that, if not included in the requested report, the following information is included in your response:

      - Please include a detailed clear description of sample preparation for each sample group (defective group with known defect sizes/positive control group and non-defective group) and range of hole/defect sizes tested
      - We note that elastomeric stoppers were pierced with a (b) (4) gauge needle (approximately a (b) (4) inner diameter) to prepare positive controls for (b) (4), but it is unclear how you maintained this defect size because stopper has elasticity to close defects that are made (e.g., have you maintained this hole size by (b) (4). Please comment.
      - (b) (4) hole size appears to be large compared to published ranges (e.g., (b) (4)). Therefore, please describe how you determined this particular test hole/defect size (e.g., have you determined (b) (4) defect size by testing various known size of holes pierced in stoppers?). Please also provide associated study data if not contained in the requested report and/or publications (if any) you utilized in establishing this defect size.

   c) It is unclear from the information provided in the BLA submission (04/30/2014) whether any correlation has been established between (b) (4) measurements and (b) (4). Please comment. If you utilized any literature data to establish this correlation, please provide related publication(s). If not established, please provide a rationale/justification for not establishing the correlation.

2. Regarding transportation validation:

a) Please provide a detailed description of the shipping container (such as indicate, but not limited to, number of test samples and its dimension, materials of construction and contents)

b) It is unclear from the information provided in Table 1 of the transportation validation document included in Section 3.2.P.3.5 (transportation-validation.pdf) whether all three separate PQ shipments had both air and ground transportation (combined transportation including both modes). Please clarify

c) It is also unclear from Table 3 why pressure change is not indicated for airplane while it is indicated for both ground and ocean transportation. Please comment and indicate the pressure change for airplane transportation

d) Please also indicate validated shipment duration for each of three shipment modes (ground, airplane and ocean transportation modes)

3. Regarding drug product freezing validation:

   a) Please indicate duration for each of the drug product freezing steps indicated in Section 3.2.P.3.5 (Process Validation and/or Evaluation) of the BLA submission (04/30/2014).

   b) (b) (4) different system numbers and (b) (4) OQ reports for the same control rate freezer are listed in Table 32 of your November 26th amendment. Please indicate what this system number stands for. If more than one controlled rate freezer is qualified, please indicate whether those freezers are identical, and submit actual qualification reports for the controlled rate freezers used in the process validation (PV) runs (OQ summary reports listed in Table 32).

   c) Please provide empty temperature mapping study performed for temperature distribution qualification if not contained in the reports requested in b) above

   d) Please submit a summary of (b) (4) qualification for minimum and maximum (b) (4) if not contained in the reports requested in b) above. Please also describe minimum and maximum loads with respect to, but not limited to, number of the trays used per freezer and number of the vials per tray)

   e) It is also unclear from the information submitted in both April 30th and November 26th, 2014 submissions whether drug product freezing (or freezing of (b) (4) representative mock solution) in the actual (b) (4) container closure system was monitored at pre-determined locations during process performance qualification runs. Please comment and submit associated study report including protocol and product freezing/temperature profiles/data along with a description of sampling locations.

4. Regarding (b) (4) of drug product:

   Please provide the actual (b) (4) validation report including validation protocol and associated results for both (b) (4) (described in 3.2.P.3.5 – Process Validation and/or Evaluation)

5. Regarding autoclave validation:

   a) Please indicate (b) (4) used in autoclave validation

   b) We note from the information provided in November 26th amendment that sterilization conditions are indicated for (b) (4), but not for overkill approach. Please indicate sterilization conditions (e.g., exposure duration and temperature) for overkill approach. If indicated in the submission, please identify its location (e.g., section and page)

6. Regarding media fill runs executed in post-change filling room:

   a) According to the FDA guidance on aseptic processing ("Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, 2004"), each media run should evaluate a single line speed, but Table 6 of your November 26th amendment submission does not indicate a single fill line speed for each of the media fill runs. Please indicate the single fill line speed used for each of the media fill runs executed post - facility modification, in particular for the media fill runs (b) (4) (listed in Table 6). If a single speed for each of the runs was not evaluated, please provide a rationale/justification.

   b) Please compare the media fill runs executed (b) (4) modification in a table with respect to fill line speed, filling duration, filling temperature, number of units filled and interventions implemented (routine and non-routine)

7. Regarding cleaning/sanitization of equipment and facility:

      a) Please submit summary reports 4690-00526 (for (b) (4) 4690-00526 (for (b) (4)), 46-00516 (for (b) (4)) and 4647-00100 (for (b) (4)), which are listed in November 26th amendment

   b) Please submit actual reports for disinfectant efficacy studies conducted to assess cleaning and sanitization of surface types

8. Regarding post - change filling room (b) (4):

Please provide information on flow rate and air changes measured in room (b) (4) and (b) (4) after the filling room modification. Please also indicate their acceptance criteria.

9. Regarding deviations:

   a) Please provide the actual deviation/incident/excursion report 4513-00161 resulted in non-conformance during stability evaluation of a lot

   b) Please also provide actual excursion reports 4526-00020, 4526-00012, 4526-00010, 4526-00015/NC4512-00602, 4525-00009, 4526-00007, 4526-00006 and 4526-00005

   Please ensure that the reports requested above include incident description, summary of investigation, root-cause analysis and implemented CAPA (if any)