

RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA Submission ID: 125668/o
Office: OTAT and OCBQ
Product name: Immune Globulin Subcutaneous (Human)
Applicant: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Telecon Date/Time: June 20, 2018 at 10:00 am Initiated by FDA? Yes
Telephone Number: 1 866 380 4181
Communication Category: Clarification Request by FDA

Drafted: Randa Melhem/ June 20, 2018

Telecon Summary: Clarification on information submitted about container closure, cleaning validation, sterilization, mixing studies, feeding tanks, and visual inspections. Also a request for additional information which will be submitted in a follow-up IR.

FDA Participants:
Randa Melhem, CBER/OCBQ/DMPQ/BII

Non-FDA Participants:

Barbara Rangetiner	General Manager OPG, Director International Drug Regulatory Affairs (OPG)
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Jana Zimmermann	Head of Quality Unit (ODE)
Daniel Sternsdorf	Operation Support (ODE)
Stanley Ammons	Local Agent / Sr. Director Government Policy & Corporate Compliance (Octapharma USA Inc.)

Telecon Body:
FDA stated that the submission included contradictory information – could be due to translation and/or oversight. FDA requested clarification about the following points:

- Usage of vessels (b) (4) for the production of cutaquig.

FDA stated that Annex 1 (list of equipment used in the production of (b) (4) /cutaquig) and other documents provided in the submission, stated that vessels (b) (4) are used as feeding vessels for the production of cutaquig. However, in Cleaning Validation Report

087RPQ16097.000, it was stated that only vessels (b) (4) are used as feeding vessels for Cutaquig. Please clarify.

Octapharma explained that, at this point, only the (b) (4) vessels are used for the production of cutaquiug. They clarified that all vessels were subjected to cleaning validation using placebo ((b) (4)). They added that in case there is a need to use the (b) (4) vessels, then the cleaning validation of the (b) (4) (following cutaquiug soiling) will be performed prior to use.

- Sanitization/Sterilization of Equipment in areas “Basic Fractionation” and pre v.i. area of “Purification (b) (4)”

FDA stated that Octapharma reported that for the OPG Vienna Facility (section 3.2.A.1 - Sanitization/Sterilization Validation Strategy) “*Generally, equipment used in the post-v.i. area of “Purification (b) (4)” and “Aseptic Production” is sanitized/sterilized. In the areas “Basic Fractionation” and pre v.i. area of “Purification (b) (4)” sanitation/sterilization is not performed*”. However, during the May 22 telecon and in amendment 125668/0.9 Octapharma stated that “*Sanitation/sterilization of equipment used in the pre-v.i. and post-v.i. area is performed by (b) (4) autoclaves ((b) (4)) with the difference that equipment used in the pre-v.i. area is (b) (4) (in clean room class (b) (4)) whereas equipment used in the aseptic area is (b) (4)*

. Please clarify.

Octapharma clarified that autoclaves ((b) (4)) are used for sanitization of (b) (4)

(b) (4) used in the Basic Fractionation and pre-vi. areas. However, the vessels used for manufacturing in these departments are generally not sanitized.

- Aseptic Filling of Cutaquig.

FDA stated that in Section 3.2.A.1 - Air Handling Units for the Production Areas, it was reported that “*filling and stoppering of (b) (4) on filling line (b) (4) is performed within a (b) (4) equipped with (b) (4) grade filters and unidirectional airflow (Unit (b) (4)) placed in a class (b) (4) environment (room (b) (4) Filling (b) (4)). The unidirectional airflow within the (b) (4) maintains class (b) (4) conditions during operations. A pressure difference of (b) (4) between (b) (4) during operation and the clean room class (b) (4) background is also maintained.*

Crimping is performed within an (b) (4), reducing dissemination of particles to the clean room (room (b) (4) Filling (b) (4)) during operation”.

FDA added that Octapharma reported throughout the submission, and provided data to validate the filling of cutaquiug on Line (b) (4). Please explain.

Octapharma clarified that this is a typo, and that filling of (b) (4) /cutquig is performed on Line (b) (4).

- Report 087RPQ16202.000: Sampling of final containers during cleaning validation in (b) (4).

FDA stated that report 087RPQ16202.000 stated that “*In course of validation the samples were drawn from the injection vials after routine filling procedure of Mediafill (batch (b) (4)) and (b) (4) 16,5 % (batches (b) (4))*”. It is also stated in the same report that “*Sampling of the vials took place (b) (4) the equipment left the bottle washing machine (b) (4) they entered the depyrogenation tunnel (b) (4)*”. Please clarify.

Octapharma clarified that for the cleaning validation, the cleaned vials are collected (b) (4). The first sentence “samples were drawn from the injection vials after routine filling procedure of Mediafill” was a translation issue.

- Mixing Studies

FDA stated that two reports 089PQR15521.103/US and 089PQR15522.103 were submitted to demonstrate the homogeneity of (b) (4) /cutaqui final formulation in vessels (b) (4). Both reports seem to describe the same studies; however, there are differences in the reported information.

Octapharma clarified that the two reports described (b) (4) separate steps for addition of maltose. The first report 089PQR15521.103/US described the mixing after addition of maltose (b) (4), and Sample (b) (4) was collected. In case, more maltose was needed, (b) (4) maltose (b) (4) solution was added (report 089PQR15522.103), followed by mixing and collection of Sample (b) (4).

FDA stated that each report has a flow diagram which did not show the (b) (4) steps for addition of maltose, and that each report described the mixing after (b) (4) of the steps. **FDA** asked if there was a general introduction for the mixing which explained the (b) (4) steps

Octapharma said that the information was not spelled out in the submission.

- Visual Inspection

FDA asked for clarification regarding the naming of the manufacturing steps for cutaqui. In the description of cutaqui manufacturing process, Octapharma listed “Visual Inspection” as Step (b) (4) at the OPG Vienna facility and Step (b) (4) at the ODE Dessau facility. Please clarify.

Octapharma clarified that the “Visual Inspection” is Step (b) (4)

In addition to the clarification questions, FDA briefly discussed other pending issues that will be covered in an information request to be sent to the sponsor by Friday June 22, 2018 with a response date by July 6, 2018.

– Container closure/ Container Closure Integrity Testing

FDA asked if all the FC vials and stoppers for cutaquig are used for other US licensed products.

Octapharma said they will check on that. Additional information would be requested in the IR.

FDA asked about the CCIT using the (b) (4) method ((b) (4)) during stability studies as presented in the following intermediate reports: 000SSR991.16P005.01/INT (media filled vials) and 000SSR81x.16P011.01/INT (product filled vials).

In report 000SSR991.16P005.01/INT (media filled vials), Octapharma stated that the results met the acceptance criteria (up to 12 months' time point), indicating the containers are integral up to that point.

FDA stated that it was not clear why the media filled vials were placed on stability, as the microbiological media may not be stable or support growth after long storage periods.

Octapharma clarified that the media filled vials were not used to demonstrate stability of media or microbial ingress. They were used as an additional study to demonstrate that filled and stoppered/capped vials can maintain integrity (vacuum decay method).

– Cleaning Validation

Octapharma provided a list of major equipment and their uses for (b) (4) /cutaquig production. Some of the equipment is used in several manufacturing steps. Per Octapharma protocol, the cleaning validation should verify cleaning following placebo and product/intermediate runs.

FDA asked for a clarification about the product(s)/intermediate(s) used for vessels that are used for more than one manufacturing step.

Octapharma explained that a cleaning validation run is performed (b) (4) . Thus, if a vessel is used for Sep ^{(b) (4)} and Step ^{(b) (4)}, the cleaning validation will include (b) (4) with Step ^{(b) (4)} product/intermediate, and (b) (4) with Step ^{(b) (4)} product/intermediate.

– Transport Validation

FDA asked if Octapharma performed transport validation for the shipping of the final product overseas (truck/plane).

Octapharma stated that they performed the ground transport validation which covers a longer shipping time. They said that they are preparing a protocol for the

“shipping to overseas distributors”, and that would be executed with the first shipping of cutaquig after approval. They added that their shipping process was validated for other products.

– Environmental Monitoring (EM)

FDA stated that Octapharma provided a description of the environmental monitoring program, but they did not submit EM data collected during the manufacture of cutaquig PPQ lots or the media simulation studies. This information would be requested in the IR.

Octapharma stated that they will submit the EM data in their written response.

END