

Meeting Response

Our Reference: CRMTS #10516; BLA 125587/0.39

TODAY'S DATE: January 17, 2017 **PAGES:** 7

TO: Mr. Stanley Ammons
Octapharma Pharmazeutika Prod.ges.m.b.H.
Email address: stanley.ammons@octapharma.com

FROM: Mark Levi
Regulatory Project Manager
Office of Blood Research and Review
Phone number: (240) 402-9662
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SUBJECT: Summary of FDA Internal Meeting

PRODUCT: Panzyga; Immunoglobulin G (IgG)

INDICATION: Primary humoral immunodeficiency (PI)
Chronic immune thrombocytopenia (ITP) in adults

Although we continue to reserve January 19, 2017, from 10:00 AM to 11:30 AM, EDT, for a teleconference with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us in writing as soon as possible so that we may clear the meeting time. These responses would then become the official FDA responses to your questions.

Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review committee can provide clarification during the reserved meeting time. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our pre-meeting (preliminary) responses, we may not be prepared to discuss and/or to reach agreement on such changes at the meeting.

Please include a reference to CRMTS #10516 in your future submissions related to the subject product.

Questions from Octapharma:

Inspectional Issues

Octapharma Question 1.1:

Does FDA consider that our implemented corrective actions associated with PQ non-conformities are comprehensive and satisfactorily address underlying issues including quality oversight?

FDA Response to Question 1.1:

The revisions to local SOP No. 713SOP002, Deviation Handling, to include systematic escalation of non-conformances during qualifications and re-qualifications (including cleaning validations) as deviations in (b) (4), weekly presentation of any associated CAPAs to the Quality Review Board (QRB), and enhancements to CAPA timelines and the effectiveness check rules generally appear to be acceptable. However, please note that a complete evaluation of the effectiveness of these changes in addressing the underlying issues (including Quality oversight) cannot be performed prior to the re-inspection of the Lingolsheim facility.

Octapharma Question 1.2:

Does FDA consider that our implemented corrective actions in regards to the HVAC are comprehensive and satisfactorily address underlying issues including quality oversight?

FDA Response to Question 1.2:

The modifications to the Grade (b) (4) HVAC system and the walls within Room (b) (4) (and the (b) (4) corridor) generally appear to be acceptable. However, in order for us to fully evaluate the comprehensive nature and effectiveness of these changes, please submit the following documentation:

- Change Control No. 49722
- IQ/OQ Report No. 777QIO045/00
- PQ 1 Smoke Studies: Report Nos. 777RQP041/00 and 777RQP042/00
- PQ2 Room Classification (In operation) & Media Fill Tests: Report Nos. 777RQP040/00 and 757RQP005/26

Octapharma Question 1.3:

Does FDA consider that our implemented corrective actions in relation to equipment cleaning and maintenance are comprehensive and satisfactorily address underlying issues including quality oversights?

FDA Response to Question 1.3:

In general your response to the validation and maintenance of the cleaning of equipment provides a step in the right direction. We have the following comments which should be addressed in your response to the CR letter.

- a. You defined visibly clean per SOP 780SOP024 – Visual inspection of production equipment after cleaning “(b) (4)”

(b) (4)”, however, you did not include discoloration and roughness. Please explain.

b. You stated that for the equipment whose surfaces were restored by (b) (4), three placebo validation runs and (b) (4) was performed for each piece of equipment that will be used in the production of the three new conformance lots. However, you stated that future restoration of the equipment's surfaces by (b) (4) will be validated with (b) (4), and the (b) (4) of equipment surfaces will not be validated based on risk assessment. You need to provide, in the re-submission, additional information about the specific (b) (4), and data (beside detailed risk assessment) to support the lack of validation following (b) (4), and the reduced validation for (b) (4) actions.

Container Closure Integrity (CCIT)

Octapharma Question 2.1:

Does FDA agree that the already submitted data with the (b) (4) method is adequate to show CCIT?

FDA Response to Question 2.1:

No, we do not agree that the submitted data is sufficient to demonstrate CCIT of the Panzyga final container. You need to describe the (b) (4) method, the protocol and the acceptance criteria, as well as the number of runs performed using the different vial/stopper presentations, and the results of testing including positive and negative controls to demonstrate the sensitivity and validity of the method.

Octapharma Question 2.2:

CCIT by (b) (4) test will be utilized on the (b) (4) additional consecutive lots (CR letter question 16) and the related stability study. Is this acceptable?

FDA Response to Question 2.2:

That is acceptable, provided you submit the validation data, acceptance criteria, and results demonstrating container closure integrity for Panzyga different presentations. Please also clarify in the re-submission if the CCIT (b) (4) testing is performed only at the OPG Vienna facility or if it is also implemented at OSA Lingolsheim facility, and justify your response.

Process Performance Qualification (PPQ) of additional consecutive lots

Octapharma Question 3.1:

Process performance qualification of the (b) (4) additional consecutive lots covers (b) (4)

(b) (4)

(b) (4)

In addition, the changes described in Question 6 of this meeting request letter will be qualified. Is this process performance qualification approach acceptable?

FDA Response to Question 3.1:

FDA does not object to the process performance qualification approach. FDA reserves the right to make additional request(s) depending on the data submitted.

Octapharma Question 3.2:

Does FDA agree that the process performance qualification of the (b) (4) additional consecutive lots covers all filling sizes (10 mL, 25 mL, 50 mL, 100 mL, 200 mL and 300 mL at OPG and 50 mL, 100 mL, 200 mL and 300 mL at OSA) for licensure?

FDA Response to Question 3.2:

Filling Line (b) (4) is a new filling line at the OPG Vienna facility for small volume parenterals (SVP), and the 300mL bottle is a new presentation for filling on Line (b) (4) at OPG. In addition, the OSA site including the filling line is not a US licensed facility. Your proposal may be acceptable if the filling operations are representative of routine filling operations.

Stability data

Octapharma Question 4.1:

According to review issue 16 of FDA's CR letter, (b) (4) additional consecutive lots should be placed on real-time and accelerated stability studies. Does FDA accept the submission of the complete response with 3 months stability data based on the fact that at the time of re-submission (b) (4) and 24 months data of the batches manufactured in 2013 and 2014 are available?

FDA Response to Question 4.1:

It is acceptable to have 3 months stability data for your (b) (4) additional consecutive lots at the time of re-submission.

Octapharma Question 4.2:

Does the FDA accept our approach regarding accelerated stability studies, which includes stability studies at +25°C for up to (b) (4) months, but no further studies at (b) (4)?

FDA Response to Question 4.2:

The Agency disagrees with your approach. Please include the accelerated stability studies at (b) (4) for comparison purposes.

Equipment changes

Octapharma Question 5:

During summer shut down 2016 the following new equipment was implemented in the Panzyga manufacturing area:

- New autoclave in (b) (4) production
- New washing machine in (b) (4) production
- Additional product tank for (b) (4) step

The new/additional equipment will already be used for the manufacture of the (b) (4) additional lots. The corresponding documentation will be submitted with our re-submission. Does FDA agree with this approach?

FDA Response to Question 5:

It is acceptable to use the new equipment for the manufacture of the (b) (4) conformance lots. However, you need to validate the equipment before use in the manufacture of the three conformance lots, and to provide the validation data in the submission.

Please note that the autoclave validation should include empty chamber temperature mapping, and use of biological indicators (BIs) and thermocouples (TCs) in the validation of the different loads used for Panzyga manufacturing. For the new washing machine, the validation should include coverage study of the loads. Also the validation should include the dirty and clean hold times. As this washing machine is used for the (b) (4), you need to include Total Organic Carbon (TOC), Total Viable Count (TVC), endotoxin and conductivity sampling, and to provide the respective acceptance criteria, and supportive data. For the new tank you need to qualify the tank and validate the cleaning (including coverage study) and sterilization, including dirty, clean and sterile hold times.

Proposed changes to the manufacturing process to be validated in response to Q16 of the CR letter

Octapharma Question 6.1:

At STEF (b) (4) of the Panzyga process, (b) (4)

Is it acceptable for FDA that these changes are included in our re-submission?

FDA Response to Question 6.1:

It is acceptable to submit the information in the submission as long as you provide sufficient information to support the changes.

In report, 450RPT721 (b) (4) /00,

(b) (4)



FDA Response to Question 6.2:

We intend to include editorial changes in the method of preparation. In addition we propose to tighten the limit for (b) (4) in in-process sample (b) (4) in order to harmonize with the limit in the final product specification. Is it acceptable for FDA that these changes are included in our re-submission?

FDA Response to Question 6.2:

It is acceptable to submit the information in the submission as long as you provide sufficient information to support the changes.

Octapharma Question 7.1:

We intend to submit updated documentation (e.g. facilities and equipment, master batch records, analytical Master SOPs) in our re-submission that covers changes classified as annual reportable. Is this acceptable for FDA?

FDA Response to Question 7.1:

It is acceptable to submit the information in the submission as long as you provide sufficient information to support the changes.

Octapharma Question 7.2:

In addition, does FDA agree that these changes do not need to be reported again in the first annual report submission after a potential licensure?

FDA Response to Question 7.2:

Your proposal is acceptable.

Additional comments:

1. Please explain how the acceptance criteria for the (b) (4) concentration in-process control at Step (b) (4) were established (in Process Performance Qualification Master Plan, 150PPQMP1606/01). The (b) (4) concentration acceptance criteria in your current Master Plan are lower than what you submitted previously.
2. Please provide the validation data for all the mixing time and speed ranges (minimum and maximum) in the response to the CR Letter.

3. Please note that there should be no changes to the acceptance criteria from the approved Process Validation Protocol following the manufacture of the Conformance Lots.
4. Please submit 2 vials each of your conformance lots, and 50 mL of your formulation buffer per conformance lot, for research purposes, to the following address:

FDA/CBER/OBRR

Attn: M. Norton /Nancy Eller/Dr. Dorothy Scott

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Please notify Dr. Dorothy Scott (dorothy.scott@fda.hhs.gov), Ms. Nancy Eller (nancy.eller@fda.hhs.gov), and Ms. Malgorzata Norton (malgorzata.norton@fda.hhs.gov) when the samples are being shipped, and please include the tracking number in the email.

END