



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

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**To:** NDA BN125552/0, Cord Blood Sterile Collection Bags with Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD)

**From:** Ellen Huang, CSO, OCBQ/DMPQ/MRB II, HFM-676

**Through:** Marion Michaelis, Branch Chief, OCBQ/DMPQ/MRB II, HFM-676

**Cc:** Ramani Sista, CSO, OCTGT/RMS  
Mercy Quagraine, Biologist, OCTGT/DCGT/CTB

**Subject:** Review of the NDA submitted by MacoProductions S.A.S., Cord Blood Sterile Collection Bags with Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD)

**Due Date:** April 30, 2015

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### REVIEW RECOMMENDATIONS

I recommend approval. However, I do not approve the use of parametric release.

### REVIEW SUMMARY

MacoProductions S.A.S. submitted a New Drug Application (NDA) BN125552/0 for Cord Blood Sterile Collection Bags with Anticoagulant Citrate Phosphate Dextrose Solution USP (CPD). The drug product is manufactured, processed, packaged, labeled, and tested by MacoProductions Polaonia SP Z.o.o. in Wroclaw, Poland. The final container-closure system is terminally sterilized by <sup>(b) (4)</sup>-steam **(b) (4)** process. The firm stated that the sterilization process is an overkill approach.

Information Requests (IR) from DMPQ were communicated to the firm. The firm provided a response on September 22, October 10, and October 27, 2014 in Amendment BN125552/0/1, BN125552/0/2, and BN125552/0/3, respectively. Additionally, the firm provided responses in emails on March 6 and March 16, 2015.

### NARRATIVE REVIEW

#### Items Reviewed

- NDA BN125552/0 and Amendments (items related to sterilization and container closure integrity of the final container)
- Amendments BN125552/0/1, BN125552/0/2, and BN125552/0/3

- Emails from March 6, 2015 and March 16, 2015
- Telecon on September 22, 2014

**Background**

The proposed indication and use of this product is for collection of 40 to 250 ml of umbilical cord blood from either vaginal birth or within the sterile field of a cesarean section. The firm stated the product is sterile with a non-pyrogenic fluid pathway. The firm has two different configurations:

- MSC1207DD: 300 mL collection back containing 27 ml of CPD, a 40 mL rinsing bag containing 8 mL of CPD and two 12 gauge needles with a protective shield (Secuvam) for the used needle. Refer to Figure 1.
- MSC1208DD: 300 mL collection back containing 21 ml of CPD, a 40 mL rinsing bag containing 8 mL of CPD and two 12 gauge needles with a protective shield (Secuvam) for the used needle. This unit also has a graduation label. Refer to Figure 2.

(b) (4)



MacoProductions Polonia SP Z.o.o is the manufacturer of the drug substance and drug product. The firm also states that some steps of manufacture can be sub-contracted to (b) (4) in (b) (4) and MacoProductions (b) (4).




***Reviewer's Comments***



- **It is not clear is sterilization will be occurring at these sub-contractors. If so, the firm needs to perform sterilization validation at these locations. Please refer to IR Question 9 below.**

**Sterilization**

(b) (4)



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**Parametric Release**

The firm stated that the final release by quality control will include a parametric verification of sterilization. Parametric release was approved under BN040083 with the approval of the MTL1 product configuration on November 21, 2005, performed on the manufacturing site of MacoProduction S.A.S in France. The firm stated that the cord blood sterile collection bags will be also released parametrically.

***Reviewer's Comments***

- **I do not recommend the firm be approved for parametric release. The Poland facility does not have a compliance history with the Agency. Per FDA's Compliance Policy Guides Section 490.200 (Parametric Release – Parenteral Drug Products Terminally Sterilized by Moist Heat), "A firm may rely on a parametric release strategy and need not perform end-product sterility testing when the firm meets and documents assurances for both of the following conditions: First, the firm's sterility assurance program must be in a state of control. Second, for application products, the firm must have submitted all appropriate regulatory filings to FDA and be operating in conformance with its approved application." FDA approval of the parametric release program will be based on how well the firm has addressed the risks to product sterility. Additionally, per FDA's Guidance for Industry Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes (February 2010), the firm should have "prior manufacturing experience and knowledge were incorporated into the risk assessment." Since there is no established compliance history or prior experience with this firm, the firm is not able to demonstrate they have a sterility assurance program in a state of control. Therefore, I do not recommend the firm be approved for parametric release. This was communicated to the firm during the September 22, 2014 telecon. Please refer to IR Question 21 below.**

**Validation**

The firm performed validation of the sterilization cycle. The firm stated that the aim of the validation was to demonstrate that the sterilization program allows sterilizing a load of (b) (4) assuring a Sterility Assurance Level (SAL) of a minimum of (b) (4) according to the standard (b) (4).

The firm used (b) (4) during their validation runs.

(b) (4)

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(b) (4)

The firm stated that the validation of sterilization of a minimum load will be performed for further productions.

Additionally, there is a (b) (4)

#### *Reviewer's Comments*

- It appears that the subject units of this NDA and the PCD are similar. The bags and needles have the same component number. However, is not clear if the tubing and overwrap are identical. Please refer to IR Question 2 below.
- It appears that the PQ was performed on the maximum load; however, it is not clearly defined. The firm was asked for clarification. Please refer to IR Question 3 below.
- It is not clear if the firm will only sterilize the maximum load for routine production since they have indicated that they will perform validation on the minimum load in the future. If the firm plans on using any other load other than validated, they need to perform additional studies to bracket their validated load size. Please refer to IR Question 4.
- The firm placed the PCD on the (b) (4). The firm was asked for the rationale for this placement. Please refer to IR Question 5.
- The firm is placing (b) (4). It is unclear if this is also done for during routine production on the subjected unit. Please refer to IR Question 6.
- During the heat penetration study, (b) (4) sensors did not register the correct data ( $F_0$ -value of (b) (4)). The firm stated they were retesting those failed sensors. The firm did not provide the results of those repeated run(s). Please refer to IR Question 7.
- It is not clear if the product or a surrogate was in the bags. Please refer to IR Question 8 below.

#### Container Closure Integrity Testing

The firm has performed container closure integrity testing (CCIT) according to the draft standard (b) (4). The firm stated that this tests for impermeability to microorganisms.

For this test, the (b) (4) containers were (b) (4)

***Reviewer's Comments:***

- (b) (4) is the preferred organism to be used for CCIT. However, other organisms can be used. (b) (4) is not listed as a challenge organism for (b) (4) testing in the PDA Technical Report 27 (Pharmaceutical Packaging Integrity). The firm was asked for their rationale for selecting (b) (4). Please refer to IR Question 10.
- It is not clear if the units tested for CCIT were tested after sterilization. Please refer to IR Question 11.
- It is not clear if these units were filled on their filling machines. It appears that the firm has (b) (4) filling machines. To demonstrate that all filling machines can create an integral unit, units filled on each filling machine should be tested for CCIT. Please refer to IR Question 12.
- The firm did not use a defective unit for their positive control; they spiked the unit with (b) (4). It is not clear what the sensitivity of the firm's test method is. Please refer to IR Question 13.

**REVIEW QUESTIONS**

Review questions were communicated to the sponsor on August 19, 2014, September 22, 2014, October 10, 2014, February 9, 2015, and February 17, 2015. CBER received responses from the sponsor on September 22, 2014, October 10, 2014, February 20, 2015, and March 6, 2015. A summary of my review questions (in *Italics*), MacoProductions' responses (in regular text) and my comments (in **bold**) are below:

- 1. Please provide the results of your OQ (empty chamber temperature distribution study and heat distribution study) for your (b) (4) autoclaves.*

Per BN125552/0/1, the OQ (empty chamber temperature and heat distribution studies) protocols, reports and results for (b) (4) are were provided. For the study, (b) (4)

All acceptance criteria were met. The firm also provided the probe number for the maximum temperature during holding time and the maximum and minimum time to meet the sterilization temperature.

**While the firm provided the probes for the maximum and minimum time, it is unclear if the probe numbers change for each run. Therefore, I cannot assess if there were any cold spots. Please refer to IR Question 14 below for clarification from the firm.**

2. *Please compare the subject units of the NDA to the PCD. Specifically, please provide a side-by-side comparison of each unit, including but not limited to, the dimensions, material of construction, and volume.*

The firm provided Table 1 to compare the subject unit and PCD in BN125552/0/1.

**Table 1: Comparison between NDA and PCD Units**

(b) (4)



**For most of the parameters, it appears that the worst case conditions were used. However, it is not clear why (b) (4) is the worst case. Please refer to IR Question 15 below.**

3. *Please clarify if the PQ for sterilization was performed on the maximum load.*

Per BN125552/0/1, the PQ was performed on the maximum load. Specifically, as follows:

(b) (4)

**The response is acceptable.**

4. *Please clarify if all of your sterilization loads for production purposes will be at the maximum load. If not, provide a justification on why the minimum load was not validated.*

Per BN125552/0/1, all loads for production purposes will be at the maximum load.

Validation of a minimum load will be conducted as a need is determined.

**During the September 22, 2014 telecon, the firm stated that they are performing the minimum load validation and will have it completed by the end of October. The firm requested to submit this information to the NDA. Refer to IR Question 16 for the review of the minimum load.**

5. *Please provide your rationale for the placement of the PCD with biological indicators and sensors.*

Per BN125552/0/1, the PCD were placed according to our procedures and as described in Protocol (b) (4) and Report (b) (4) (see Section 2.5.2 Scheme of Autoclave Loading) because we were unable to identify the fixed location of any cold spot. Protocol (b) (4) and Report (b) (4) were included in the 22 April 2014 NDA filing (Volume 4-Module 3 Quality Drug Product – Vol. 2 of 2).

**The response is acceptable. The BI and TC locations are acceptable. There are in the (b) (4) These appear to capture the geometric extremes.**

6. *In the sterilization PQ, you placed (b) (4). Please clarify if this practice is also performed during routine production on the subjected unit.*

Per BN125552/0/1, in the PQ, (b) (4) was placed (b) (4) since the validation evaluated the worst case scenario. During routine production, (b) (4) is used.

**It is not clear why the firm uses (b) (4). The firm was asked to provide their rationale in IR Question 15 below.**

7. *During the heat penetration study, (b) (4) sensors did not register the correct data ( $F_0$ -value of (b) (4)). You stated that retesting on those failed sensors would be performed. Please provide the results to those repeated run(s).*

Per BN125552/0/1, after investigation into the failure of (b) (4) sensors during the penetration study, the root cause was attributed to battery failure and corrected. Retesting of these probes has not yet been performed but is planned for September/October 2014. The results will be provided after retesting is completed.

**During the September 22, 2014 telecon, the firm stated that they will submit the new runs by the end of October. Refer to IR Question 17 below.**

8. *Please clarify if product was in the PCD with biological indicators and sensors.*

Per BN125552/0/1, yes, product was in the PCD with biological indicators (BI) and sensors. This information is detailed in report (b) (4) that was included in the original NDA filing (22 April 2014) as part of Module 3, Volume 4 of 8, pages 44-79.

The microbiological process qualification was carried out at the same time as the heat penetration study inside the product. The details of the BI are included in the Table 2 below:

**Table 2: D-value and Location of Biological Indicators**

(b) (4)

**The response is acceptable. Actual product is used for the validation.**

9. *You stated that some of the manufacturing steps can be sub-contracted to (b) (4) in (b) (4) or MacoProductions (b) (4). Please clarify if sterilization will and can be sub-contracted to (b) (4) and/or MacoProductions (b) (4). If so, please submit the sterilization validation for these sub-contractors.*

Per BN125552/0/1, sterilization will not be sub-contracted to (b) (4) or MacoProductions (b) (4). All sterilization will be performed at MacoProductions Polonia.

**The response is acceptable.**

10. *Please provide your rationale for selecting (b) (4) as your challenge organism for your container closure integrity testing (CCIT).*

Per BN125552/0/1, the bacterial challenge proposed for the impermeability assays and given as example in the standard (b) (4)

The bacterial challenge used for the assays is an equivalent challenge organism distributed in other collection: (b) (4)

**The response is acceptable. I confirmed that (b) (4) is equivalent to (b) (4).**

11. *Please clarify if the units tested for CCIT were sterilized.*

Per BN125552/0/1, yes, the units tested for CCIT were steam sterilized.

**The response is acceptable.**

12. Please clarify which filling lines the units tested for CCIT were filled on. It appears that you have (b) (4) filling machines. To demonstrate that all filling machines can create an integral unit, units should be filled on each filling machine and tested for CCIT.

(b) (4)

[illegible]

integrity.

Since the units are (b) (4) the bags, the firm does not need to perform CCIT for each filling machine. However, since the units are (b) (4) the bags, the firm was asked how they account for the variability between the operators. Refer to **IR Question 18**.

13. Please provide the sensitivity of your CCIT method.

Per BN125552/0/1, the test consists of an analysis of (b) (4) challenge organism as follows:

(b) (4)

**I confirmed that the positive control method utilized by the firm is consistent with (b) (4) (b) (4). This test method is supportive of CCIT. I asked the firm if they performed any**

**other CCIT test, such as pressure tests to supportive of the integrity of the unit. Please refer to IR Question 19. I also asked if the bags are 510(k) cleared bags (refer to IR Question 20).**

14. *Regarding IR Question 1, it was not clear from your empty chamber study if there were any cold spots. Please provide a summary of your data or the probe locations to clarify this information.*

In BN125552/0/2, the firm provided a summary of their cold spots. The cold spots were found on (b) (4).

**It's not clear if TCs and BIs were placed in those cold spots since the exact location on the shelf was not provided. Please refer to IR Question 22 below.**

15. *Regarding IR Questions 2 and 6, please explain why (b) (4) is placed (b) (4). Please clarify if the (b) (4). Please clarify if there are any standard reference methods or published papers using this method of placing (b) (4) for sterilization. Please provide a picture of where the (b) (4) is in comparison to the unit. Please explain why (b) (4) is the worst-case (versus the (b) (4) that is used for production).*

(b) (4)

**There is concern about having (b) (4), as this could encourage microbial growth. The firm did not provide any standard reference methods or published literature to support this method. It is not clear how the firm knows if the (b) (4) actually becomes sterilized. The firm was asked if they tested this with inoculation. Also, is not clear how they confirm that the (b) (4) will stay sterile. Furthermore, it is not clear if the bags of the actual unit are porous and could let in contamination if (b) (4). Please refer to IR Question 23 below.**







16. *You have indicated during the teleconference that you are performing minimum load validation studies. Please submit the summary reports for the minimum load. Please provide a timeframe of when that will be completed.*

Per BN125552/0/2, the report for the minimum load validation will be completed in during the week of 03 November 2014 (week 45). The firm committed to submitting a copy of the report at the time of completion.

On March 6, 2015, the firm submitted their PQ protocols ((b) (4) -1: Protocol of validation: Process qualification of new product MSC1207DD – Process of steam sterilization in the (b) (4) in autoclaves (b) (4)

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(b) (4)




**The response is acceptable.**

17. *Regarding IR Question 7, please provide a timeframe of when you will have the data for the repeated runs for the (b) (4) sensors and please provide the responses.*

Per BN125552/0/2, the report with the results for the retesting of the sensors will be completed during the week of 27 October 2014 (week 44). The firm committed to submitting a copy of the report at the time of completion.

(b) (4)



**The response is acceptable. The retested loggers passed the acceptance criterion.**

18. *Regarding IR Question 12, since the units are (b) (4) the bags, how do you account for variability between operators?*

Per BN125552/0/2, MacoProductions Polonia facility manufactures approximately (b) (4) (b) (4) Blood Collection kits each year involving more than (b) (4) operations of similar, if not identical, components. All manufacturing operators receive practical skill and on the job training. New operators are accompanied by experienced

operators until the quality of their work has been confirmed. All operators are evaluated on a (b) (4) basis.

The firm also has in-process controls where (b) (4) final assembly process units are visually inspected every (b) (4) for (b) (4) quality (b) (4)

Final product control includes a visual control test where the integrity of the complete system is (b) (4). The firm also performs a (b) (4) test for (b) (4) minimum. The sampling size depends on the batch size and Acceptable Quality Limit (AQL).

In-process QC data for 2013 and YTD 2014 revealed (b) (4) defects on (b) (4) products produced or (b) (4) Defects Per Million Opportunities (DPMO).

Post market data from 2010-2014 revealed (b) (4) DPMO related to (b) (4).

**The response is acceptable. It appears that the firm has controls in place to ensure the consistency of the (b) (4) process.**

19. *Regarding IR Question 13, please clarify if any other CCIT tests are performed (stability testing, in-process testing, and/or final product testing), such as pressure tests to supportive of the integrity of the unit. If so, please provide a description of the test method and the number of units tested.*

Per BN125552/0/2, the firm stated they perform the following CCIT methods.

In Process Control:

- (b) (4)

Final Product Control:

A visual control test is performed where the integrity of the complete system is (b) (4) (b) (4). The firm also performs a (b) (4) test for (b) (4) minimum. The sampling size depends on the batch size and AQL.

Stability Study Testing for Integrity:

As provided with the NDA and described in the stability study protocols, the product integrity is tested periodically throughout the duration of the study (i.e. the variability between operators on (b) (4) and CCIT tested during stability studies on (b) (4) different batches by (b) (4)

are performed on (b) (4) kits per batch at each control date during (b) (4) (Appendix stability study MSC1207DD intermediate report at 12 months).

**The firm did not provide the details for the in-process control testing (b) (4) for the containers and transfusion ports). Refer to IR Question 24.**

20. *Please clarify if the bags are 510(k) cleared. If they are cleared, please provide the 510(k) number.*

Per BN125552/0/2, each Cord Blood Sterile Collection Bag is a wholly integrated set of blood bags, with anticoagulant solution CPD. Most of the individual components of these products have been approved under Macropharma's NDA BN040083 for Leuoflex MTL1 and 510(k) cleared under BK030008, BK050041, and BK120071 for CGP Leukocyte Reduction Filter System. The (b) (4). The injection site is the only blood contacting component. Further details on the choice of these materials are included in sections 3.2.P.2.4 of the original NDA filing.

**The response is acceptable.**

21. *Regarding parametric release for sterilization, your Poland facility does not have a compliance history with the Agency. Per FDA's Compliance Policy Guides Section 490.200 (Parametric Release – Parenteral Drug Products Terminally Sterilized by Moist Heat), "A firm may rely on a parametric release strategy and need not perform end-product sterility testing when the firm meets and documents assurances for both of the following conditions: First, the firm's sterility assurance program must be in a state of control. Second, for application products, the firm must have submitted all appropriate regulatory filings to FDA and be operating in conformance with its approved application." Additionally, per FDA's Guidance for Industry Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes (February 2010), the firm should have "prior manufacturing experience and knowledge were incorporated into the risk assessment." Since the Agency does not have an established history with this facility, we cannot approve you for parametric release for this NDA. Please ensure you perform sterility testing of your final units. Please clarify if you have submitted your sterility test method in the submission, and if so, please indicate what section it is in your submission. If not, please submit it.*

Per BN125552/0/2, MacoProductions Polonia will perform sterility testing of the final units for references MSC1207DD and MSC1208DD following FDA guidance "Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes" and submit for FDA approval under separate application. The sterility test method performed according to (b) (4) was not submitted in the original NDA filing. IS8A0105F, *The Sterility Test Method*, was provided in the amendment.

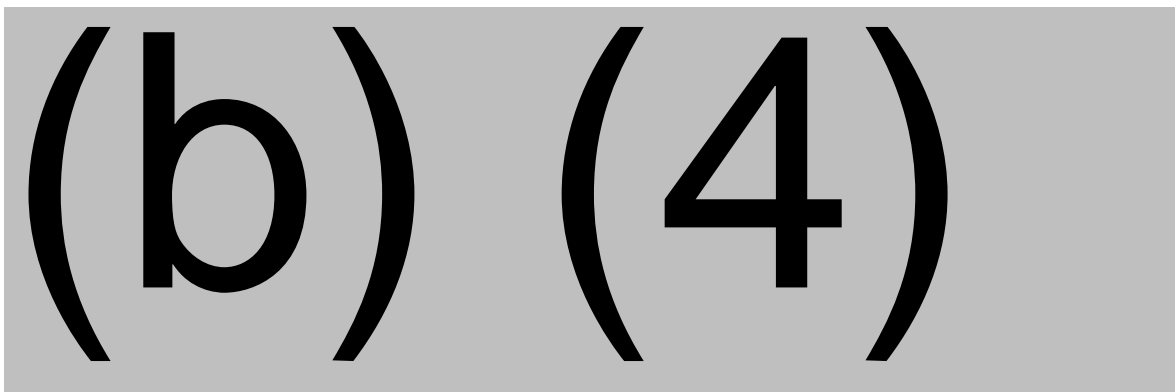
**The response is acceptable; the firm will not be approved for parametric release for this NDA and will perform sterility testing. I defer to the DBSQC to review the test method.**

22. *Please provide the exact location of the cold spots identified during the empty chamber study. Please clarify if these locations are the same locations that thermocouples and biological indicators were placed during the PQ.*



Per Amendment BN125552/0/3, during the PQ the biological indicators and thermocouples were placed on the (b) (4) were identified.

Figure: Location of Cold Spots and Position of TCs and BIs



The response is acceptable. TCs and BIs were located close to the (b) (4) locations.

23. Regarding the (b) (4)

- a. Having (b) (4) and storing the units (b) (4) could encourage microbial growth. Please address this concern.

In order to prevent microbial contamination due to (b) (4) between the drug product and the (b) (4) the maximum holding time between start filling of units, (b) (4) and sterilization has been defined and limited to (b) (4)

**It is not clear if the (b) (4) is sterile. Please refer to IR Question 25.**

- b. Please clarify how you know if the (b) (4) actually becomes sterilized. Do you test the (b) (4) with inoculation?

Sterility testing is performed on the (b) (4) ) in order to demonstrate its sterility and that the (b) (4) becomes sterilized.

**I requested the firm's test method validation for sterility testing of the (b) (4) and requested DBSQC to review it. Please refer to their consult review memo.**

- c. Please explain how you confirm the (b) (4) stays sterile, even during storage and shipping.

In order to confirm that the (b) (4) and the product remains sterile all along the shelf life of the product, sterility testing is performed at each period of the stability study.

**I requested the firm to provide their sterility testing results for the (b) (4) and product. Please refer to IR Question 26.**

- d. Typically the purpose of the (b) (4) . Please clarify the purpose of your (b) (4)

(b) (4)

Since the firm is claiming that the exterior surface of the unit is sterile and that the (b) (4) is a sterile barrier, additional information is required. It is not clear how the firm ensures the (b) (4) materials allows for steam penetration and how they ensure the sterile barrier maintains over the duration of shelf-life. Please refer to IR Question 27.

- e. Please clarify if the bags of the actual unit are porous or semi-permeable and could let in contamination if stored (b) (4)

The bags of the individual units are flexible (b) (4) and semi-permeable. This semi-permeable material has been successfully tested for (b) (4). The testing is performed during stability studies in order to demonstrate that the semi-permeable (b) (4) bags offer a barrier to contamination even if stored (b) (4).

The response is acceptable.

24. Please provide additional details for the in-process (b) (4) test for the (b) (4). The test method details should include information such as the (b) (4).

Per Amendment BN125552/0/3,  
(b) (4)



(b) (4)

The firm performs (b) (4) in-process (b) (4) test for CCIT. In totality, the firm's tests for CCIT are supportive of the integrity of the unit.

25. Regarding the (b) (4), please clarify if the (b) (4) is sterile.

(b) (4)

I defer to DBSQC to evaluate the sterility test method for the (b) (4) to assess if the (b) (4) is sterile after sterilization of the units.

26. Please provide your sterility testing results for the (b) (4) product.

Per the firm's email on March 6, 2015, the sterility testing results are located in the Stability Testing Intermediate 12 Month Reports that were included in the 22 April 2014 NDA Original filing. [Volume 4-Module 3, Quality Drug Product (Volume 2 of 2, pages 260 - 429)] The firm also provided a copy of the report in the email.

The report showed that the sterility test of the (b) (4) under normal aging and accelerated aging show no growth after (b) (4). Additionally, there was no culture when testing for impermeability test to microorganism according to (b) (4)

**The response is acceptable.**

27. Since you are claiming that the exterior surface of the unit is sterile, please address the following concerns regarding your (b) (4) bag ((b) (4)) that you produce in house:

- a. Please clarify how you ensure the (b) (4) materials allows for steam penetration. To address this concern, we recommend that you provide the labeling from the (b) (4) manufacturer which indicates that material is intended to be used as a sterile barrier for steam sterilization. If the (b) (4) material is not indicated as a sterile barrier by the manufacturer, then additional testing information should be provided to support this intended use. This information can include:
  - i. Physical properties testing such as tensile strength, thickness variation, tear resistance, air permanence, burst strength, etc. before and after sterilization. This information should be compared to known sterile barrier (b) (4) materials to ensure adequacy.
  - ii. Alternatively, biological indicator testing (b) (4).
- b. Provides a sterile integral barrier over the duration of shelf. This additional testing should include:
  - i. Description of sealing process and validated sealing parameters.
  - ii. Whole package integrity testing such as dye penetration or bubble testing following shipping stress.
  - iii. Accelerated aging to support shelf life claim.

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

During the stability studies performed on the drug products:

- The sterile barrier properties of the package were shown to maintain the sterility of the (b) (4) of the unit contained within it until expiry.
- Sterility (b) (4) was tested at both accelerated and normal conditions.
- (b) (4) testing as well as (b) (4) was also performed in addition to the requirements of the stability study.
- (b) (4) testing as described above will be performed at (b) (4) months.

The final stability report will be available mid-April 2015.

**The response is acceptable. I have reviewed the (b) (4) and both the (b) (4) meet the requirements of ISO 11607-1 (Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems). I have confirmed that ISO 11607-1 is a recognized consensus standard (recognition number 14-454) by CDRH and the extent of recognition is the complete standard and any annexes. The stability is under the product office's purview and the sterility test method for the (b) (4) is deferred to DBSQC.**

(b) (4)