

CBER CMC BLA Review Memorandum

BLA STN 125685

Allogeneic processed thymus tissue-agdc

Ekaterina Allen, PhD, RAC/Consumer Safety Officer/ CBER/OCBQ/DMPQ

1. BLA#: STN 125685

2. APPLICANT NAME AND LICENSE NUMBER

Enzyvant Therapeutics GmbH, Lic.# 2100

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: Allogeneic processed thymus tissue-agdc

Proprietary Name: RETHYMIC

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Partially T cell Depleted, Cultured Allogeneic Post-natal Thymus Tissue Slices [RETHYMIC; RVT-802] is a processed thymus tissue-derived product surgically implanted into a thigh muscle for immune reconstitution in athymic patients. The overall appearance of the product is yellow to brown tissue slices of varying thickness and shape, up to (b) (4) slices per lot.

5. MAJOR MILESTONES

7/6/2018 Module 1 and 4 submitted

12/20/2018 Module 5 submitted

4/5/2019 Module 3 submitted, start of PDFUA clock

6/4/2019 Filing date

9/8/2019 Midcycle meeting

9/27/2019 Late cycle meeting

12/4/2019 PDUFA action date

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Ekaterina Allen, OCBQ/DMPQ/MRB2	CMC/Facilities

7. INTER-CENTER CONSULTS REQUESTED

None

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
12/20/2018	125685/0.2	CE

4/5/2019	125685/0.3	Module 3 of rolling submission
6/17/2019	125685/0.9	Information on 3rd party testing laboratories; (b) (4) facility information; copy of (b) (4) batch record
6/28/2019	125685/0.12	In-process container closures; (b) (4) final container closure, acceptable endotoxin level in materials and final product; calculation of residual excipient administered to patient; in-house testing of critical materials
7/17/2019	125685/0.14	Source material (b) (4) storage; culture medium; final product shipping and handling; (b) (4) filters
7/17/2019	125685/0.15	Facility environmental monitoring; TOM medium preparation; (b) (4) validation studies; (b) (4) sampling; facility equipment and procedures; final product visual inspection; aseptic process validation; (b) (4) final container closure; drug product packaging and shipping procedures; container; DP endotoxin levels; DP shipping temperature.
7/18/2019	125685/0.16	Facility environmental monitoring; (b) (4) sampling
8/23/2019	125685/0.20	15 day response to 483 observations
9/13/2019	125685/0.28	Source material container closures; 6 month T cell counts on subjects (b) (6) who received products lots formulated and stored in (b) (4) final container
9/26/2019	125685/0.33	Cross-reference to IND 9836
10/1/2019	125685/0.36	Slicer Performance Qualification Protocol
10/15/2019	125685/0.42	Amendment to 483 response (part 1): Material qualification sterility and endotoxin testing; (b) (4) sterility assurance method; ancillary material shelf life; facility environmental monitoring; telecon summary of 483 discussions
10/23/2019	125685/0.43	Results of tissue slicer qualification
10/28/2019	125685/0.45	Request for extension to update BLA eCTD with (b) (4) final container information
11/1/2019	125685/0.47	Updated Module 3 with (b) (4) culture dish final container closure

11/1/2019	125685/0.49	Amendment to 483 response (part 2)
11/7/2019	125685/0.51	(b) (4) final container closure transport study report

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

None

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

B. RECOMMENDATION

I. COMPLETE RESPONSE (CR)

Remaining Deficiencies:

1. You failed to assure sterility of direct product contact materials. Specifically, (b) (4) validation of the (b) (4) container used for source material transport and (b) (4) storage was deficient. The study was performed on a different container and (b) (4) was not performed. Please provide the summary report for sterilization validation of the (b) (4) container.
2. Transport study (b) (4)-2019-050-A failed to demonstrate microbial protection of DP during packaging, transportation to the OR, and hold in the OR in the (b) (4) culture dish and (b) (4) secondary container. If you intend to proceed with commercialization of the (b) (4) final DP container, please investigate the media growth promotion failures and take appropriate corrective actions prior to conducting a new study demonstrating that the final DP container adequately maintains a sterile environment. Please submit the summary reports.
3. Adopting the (b) (4) culture dish as your primary DP container changed your DP packaging and configuration of the shipping container used for DP transport to the OR. Therefore, the validation of this shipping container to maintain the appropriate temperature is no longer valid. Please revalidate and provide the summary report.
4. Regarding your (b) (4) system:
 - a. Qualification of (b) (4) system is deficient in scope and duration. Specifically, it did not include monitoring of (b) (4) quality over a period of time and only a limited number of locations were sampled. (b) (4) sampling did not demonstrate (b) (4) particulate is within ISO (b) (4) acceptance limits.
 - b. Your strategy and schedule for routine (b) (4) sampling is unclear as not all testing is performed (b) (4), and locations (b) (4)

(b) (4). The sampling procedure description is inconsistent (e.g. use of (b) (4)) and vague about (b) (4) use during sampling, which could interfere with bioburden testing.

Please provide the necessary information and/or data to address these issues.

5. The personnel flows at your multi-product facility create an increased risk of product contamination and cross-contamination. Specifically,

- You allow (b) (4) of your facility. This allows simultaneous presence of personnel working on different products in (b) (4).
- Additionally, personnel enter Gown-In Room (b) (4) and exit Gown-Out Room (b) (4) of the facility through the same Receiving/Supply Room (b) (4). This allows simultaneous presence of personnel entering and exiting the manufacturing areas in Room (b) (4).

Please provide a description of procedural and/or engineering controls in place that ensure correct personnel flows, prevent exceedance of maximum number of allowed personnel in Rooms (b) (4) and (b) (4), and mitigate risk of product contamination and cross-contamination due to personnel flows described above.

6. Due to the nature of your primary DP container, the environment inside your secondary (b) (4) container becomes more critical to ensure microbial protection of the product. We recommend cleaning and/or sterilization validation of the secondary container and packing of the (b) (4) container in the ISO (b) (4) environment. Additionally, please implement and provide procedures and lot disposition for spill incidents in transport.

Inspectional Follow-Up:

1. During the PLI the inspection team noted that (b) (4) does not use (b) (4) container for tissue transfer during (b) (4) and for its (b) (4) storage as described in the BLA and follow-up IRs responses. I recommend inspectional follow up for the (b) (4) storage container. Unless (b) (4) specimen cup is used, qualification of the container (including sterilization validation) should be verified.
2. (b) (4) made multiple changes to DP manufacturing process and EM during manufacture, such as implementation of (b) (4) tissue dish as the final DP container and of (b) (4) air monitoring using (b) (4). I recommend inspectional follow up to ensure the (b) (4) studies were expanded to cover the new process as well as the new (b) (4) set up.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Ekaterina Allen, Reviewer, OCBQ/DMPQ/MRB2	Concur	
Qiao Bobo, Branch Chief, OCBQ/DMPQ/MRB2	Concur	
Jay Eltermann, Director, OCBQ/DMPQ	Concur	

Review of CTD

Please note that during Late-Cycle meeting held on 09/27/2019 and in the communication with Enzyvant immediately following the meeting, CBER was informed that the applicant will revert to the previously used DP container (b) (4) culture dish). To reflect this change and to address other substantive review issues raised during the meeting, Enzyvant provided a BLA update in eCTD 0049 (amendment STN125685/0.47) received by CBER on 11/01/2019. The applicant did not submit a redlined version of the update. Instead, a summary of Module 3 updates was included in the amendment.

Submitted updates were tagged UPDATE and appended at the end of respective section summaries. No additional information requests (IRs) were sent or received after the BLA update. All of the IRs reviewed pertain to the original BLA submission and some might no longer be relevant. The impact of the update on the overall reviewer assessment of each section was evaluated and included at the beginning of all section assessments in DMPQ purview (also tagged UPDATE).

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Module 3

3.2.S DRUG SUBSTANCE²

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Partially T cell Depleted, Cultured Allogeneic Post-natal Thymus Tissue Slices [RETHYMIC; RVT-802] is a processed thymus tissue-derived product surgically implanted into a thigh muscle for immune reconstitution in athymic patients. The overall appearance of the product is yellow to brown tissue slices of varying thickness and shape, up to (b) (4) slices per lot.

The thymus tissue is obtained from infants undergoing open heart surgeries, aseptically sliced and cultured to deplete the tissue from donor thymocytes (CD3+ T-cell progenitor cells). Depletion of donor thymocytes is due to cell death and degradation or flushing out during manufacturing and is important for prevention of potential graft vs host disease. Viable thymic epithelial cells forming (b) (4) morphological characteristics of thymus tissue, are retained throughout the manufacture.


The proposed mechanism of action involves donor thymic epithelial cells attracting recipient's lymphoid progenitor cells via cytokine release and developing donor thymocytes into naïve immunocompetent T cells within the transplant. Immunocompetent T cells are tolerant of both donor and recipient, the latter is thought

to be due to migration of donor dendritic cells into the transplant. Evidence of thymic function (naïve T cells in peripheral blood) can be observed 6-12 month after implantation.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

1. (b) (4)



3.2.S.2.2 Description of Manufacturing Process


RETHYMIC drug substance (DS) and drug product (DP) are essentially the same (b) (4) and are reviewed together under respective DS sections.

Thymus tissue is removed by a surgeon from infants under 9 months of age, placed into a sterile specimen container by surgical team, and (b) (4) facility (b) (4) facility) is notified that tissue is available. The tissue container is packed into an insulated shipping container and transported to (b) (4) facility at ambient conditions. Manufacturing steps consist of receipt of (b) (4)

(b) (4) drug product packaging and labeling (Step (b) (4) and shipping to the OR for implantation.

□ Manufacturing process steps

(b) (4)



46 pages determined to be not releasable: (b)(4)

(b) (4)

3.2.P DRUG PRODUCT³

3.2.P.1 Description and Composition of the Drug Product

Each of 100 mL polypropylene DP containers contains a single (b) (4) filter with one slice of adhered thymus tissue in (b) (4) of TOM (b) (4) Thymus slices are an active ingredient, TOM media components are used for cell growth support, and the filter provides mechanical support for thymus tissue.

DP from up to (b) (4) containers (a single batch) can be used for treatment of one patient, with final dose of (b) (4)-22,000 mm² of tissue/m² of recipient body surface area. TOM from the final container is not intended for patient treatment, however, trace amounts of it are transferred from the final container into the patient together with thymus slices. Similarly, support filters are not implanted.

DP manufacturer established specifications for QC of the active ingredient, TOM, and final container (endotoxin).

UPDATE: With the final container change, each DP container contains 1-4 slices of thymus tissue, each adhered to a filter on top of a surgical sponge in 5 mL of TOM (b) (4) with DP on top of each.

Surgical sponge is used for mechanical support of tissue slices and filters. The container is the same 100 mm diameter polystyrene culture dish with lid that is used (b) (4). Up to (b) (4) containers are supplied to the operating room for treating each patient. Only thymus tissue slice is administered to the patient.

Reviewer Comment: Quantities of TOM that are being implanted together with the tissue and the impact on total endotoxin levels are not clear. This information was requested in a joint IR with PO on 6/14/2019 and the response was received on 6/28/2019 in eCTD 0013 (amendment STN 125685/0.12):

Q.3: Your final product includes TOM medium (b) (4) as an excipient, though not directly administered to the patient, residual amounts are likely to be transferred during implantation to the patient. You have not indicated how much excipient could be transferred into the patient as part of the surgical procedure. Please estimate how much excipient could be transferred to the patient in a worst-case scenario, assuming the maximum dose and number of slices.

Enzyvant estimates that about (b) (4) of TOM (b) (4) is transferred with each of (b) (4) slices of tissue, which would amount to (b) (4). However, as a part of pre-implantation procedure, slices are removed from TOM and placed into a dish with saline. This would dramatically reduce the amount of excipient administered to patient and make it difficult to estimate.

Reviewer Comment: This response is acceptable from DMPQ perspective. Further evaluation of patient impact is deferred to PO.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

DS and DP are essentially the same. DP is formulated in TOM media, on support filters, both of which are used in (b) (4) culture and have been used throughout of the product development.

3.2.P.2.1.2 Excipients

Description provided in 3.2.P.1 above.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

DP is formulated in TOM media, on support filters, both of which are used in (b) (4) culture and have been used throughout of the product development. Through 2006 (b) (4) were included in TOM, and thus into the final formulation. Proposed commercial formulation is identical to that used for clinical lots since 2007.

3.2.P.2.2.2 Overages

NA

Reviewer Comment: Overages in a traditional sense are not applicable to the product and no further information was included in this eCTD section. However, each lot of tissue is designated, and the dose is calculated for a specific patient. As such, it is possible that only some slices will be implanted (e.g. total dose in a lot exceeds maximum dose for the patient). It is not clear whether the number of containers delivered to the OR is reduced or how slices are selected for implantation in such cases. This is deferred to the PO.

3.2.P.2.2.3 Physicochemical and Biological Properties

NA. DS and DP are essentially the same.

3.2.P.2.3 Manufacturing Process Development

DP manufacturing process consists of transferring of individual filters with adhered thymus tissue into the final container. This step was implemented together with the improved DP container closure in 2018. Prior to that tissue slices were transported to OR in the DS container (tissue culture dish, reviewed above) they were cultured in.

UPDATE: The section was significantly re-written. The following information was included:

The culture dish historically used for transport of DP to OR was not integral prompting implementation of leakproof screw cap (b) (4) container (b) (4) for DP transport in 2018. With this container, each tissue slice, adhered to a piece of membrane filter, was placed in its own polypropylene container for transport. Up to (b) (4) containers (b) (4) were placed in (b) (4) and then in a labeled, (b) (4) and in insulated shipping boxes for transport were transported to OR with each lot.

(b) (4) patients were administered DP supplied in the (b) (4) containers. Container change in 2018 involved a number of additional process changes, including

- A new drug product presentation: tissue slices adhered to the filters were (b) (4) in TOM medium instead of sitting on top of sponges
- (b) (4) in time required for DP packaging
- Introduction of a (b) (4) hold time in order to coordinate with the surgical team while (b) (4)

Due to the PO's concerns about insufficient stability and clinical outcome data available to support licensure of DP using (b) (4) container, use of this container was discontinued in 2019 and the previous process of transporting thymus tissue slices to the operating room in the same container closure used for culturing the tissue slices was re-implemented.

When (b) (4) culture dish is used for DP transport, DP is not removed from the incubator, labelled and shipped until notification is received from the OR that drug product will be required in approximately (b) (4).

The applicant evaluated DP processing and hold times for (b) (4) and (b) (4) culture dishes as final container for DP manufactured in (b) (4) and (b) (4) (used (b) (4) dishes only).

Prior experience with the product shows that the time from start of shipment to the completion of the surgery (time out of the incubator) has ranged from (b) (4) (lot (b) (4)) (lot (b) (4)); typical range is be (b) (4). The total time out of the incubator prior to receipt of product in the OR for DP in Starplex container ranged from (b) (4). The total time out of the incubator ranged from (b) (4) to (b) (4) for (b) (4) lots transported to OR in (b) (4) culture dish. Data were provided for 25 subjects transplanted with lots manufactured in (b) (4) between 2009 and 2015; the maximum elapsed time from removal from incubator to end of thymus transplant was (b) (4) for a successful clinical outcome, and (b) (4) for Subject (b) (6), who died 24 days after implantation from a pre-existing parainfluenza viral infection. Prior to 2009 time out of incubator was not recorded and data for (b) (4) additional lots manufactured in (b) (4) between 2002 and 2018 was derived from a review of anesthesia records from the recipient's transplant surgery. Duration of surgery associated with successful clinical outcomes is (b) (4). The applicant stated that given positive clinical efficacy data for lot (b) (4) (DP in (b) (4)), which had a total time out of incubator of (b) (4), they intend to set hold time of (b) (4). I defer to the PO to determine if the hold time is acceptable.

3.2.P.2.4 Container Closure System

Polypropylene container with leakproof polyethylene screw cap ((b) (4)) was selected for final DP packaging based on the following requirements:

- Maintains CCI
- Container is sterile and contributes minimally to the endotoxin levels of the product
- Ease of use in both (b) (4) and OR environment
- Acceptable (b) (4) profile (deferred to PO).

The container is used for up to (b) (4) hold and transport of DP to OR. The container is purchased sterile (b) (4) and each lot is tested for endotoxin. The applicant stated that they attempted to achieve (b) (4), but such sterilization process was considered unsuitable due to the change in containers' color.

Size of the container was the main consideration for ease of use, as it should allow for easy removal of slices without inadvertently touching the outside of the container. Packaging slices (b) (4) in a tissue culture dish) also adds additional time to the implantation. The applicant stated that the surgery time is not significantly extended comparing to other container options.

Container integrity was validated during the APV and was reviewed above in 3.2.S.2.5 *Process Validation*.

UPDATE: The section was significantly rewritten to describe (b) (4) culture dish as DP container and provide risk assessment of its use.

The majority of clinical and manufacturing history was obtained using this final container.

During selection of final container during DP development in 2018, (b) (4) container was selected as it met the following requirements:

- Container closure integrity must be maintained
- The container must be sterile and contribute minimally to the endotoxin of the product
- The container and cap must be easy to use in the (b) (4) facility and in the surgical suite
- Acceptable extractables and leacheables profile
- Stability of the product under conditions of use must be maintained

Due to lack of clinical data to support the use of (b) (4) container for commercial manufacture, the applicant reverted to the original (b) (4) culture dish as final DP container.

The (b) (4) culture dishes are supplied as sterile, non-pyrogenic dishes. The dishes are cleaned by (b) (4) treatment and sterilized by (b) (4) to a (b) (4) by the manufacturer. These culture dishes will be tested for endotoxin and sterility on a (b) (4) basis.

The main consideration for ease-of-use was that the containers should be appropriately sized for easy placement and removal of tissue slices to prevent inadvertent touching the outside of the container. The applicant stated that the (b) (4) culture dish is large enough that it can be manipulated easily and is therefore appropriate for the surgical suite.

The applicant determined the following risks associated with use of (b) (4) culture dish: poor aseptic technique, spilling of media/DP during transport, and extended out-of-incubator hold time. A summary of current controls mitigating each of the risks was provided.

As stated earlier, traditional CCI cannot be demonstrated with the (b) (4) culture dish. Per 21 CFR 211.94 (b), the “container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product. To demonstrate the container closure provides protection from foreseeable external factors, a new transport study was conducted using media. Refer to Section 3.2.S.2.5 for a review of the transport study of the (b) (4) culture dish, which was deficient.

3.2.P.2.5 Microbiological Attributes

Microbiological attributes of the final container DP are not tested. Instead, (b) (4) from all (b) (4) culture dishes (up to (b) (4) on the day of release and is tested for endotoxin (b) (4) and (b) (4) (no bacteria observed). These results are used for DP release. Same (b) (4) media is also tested for mycoplasma and sterility.

DP is not labeled sterile and is released at risk due to final sterility and mycoplasma testing results not being available until after the implantation.

The only process step performed after testing of (b) (4) media is transfer of slices into final containers with (b) (4) TOM. Testing of (b) (4) media rather than final container DP reduces the number of aseptic manipulations (no additional sampling) as well as the necessary hold time required to confirm results prior to release. The latter is particularly important for this product, which expiry dating is (b) (4) from the start of final container packaging.

The applicant stated that there is no additional value in testing (b) (4) media in the final container for endotoxin given that each lot of media and DP container closures are tested for endotoxin, and all product contact materials are either certified endotoxin-free or contribute minimally to endotoxin levels as per endotoxin risk assessment reviewed in 3.2.S.2.3 *Control of Materials* above.

All product contact materials are either sterilized or purchased sterile (reviewed in 3.2.S.2.3 *Control of Materials* above). Aseptic process and container closure integrity of the final container were validated (reviewed in 3.2.S.2.5 *Process Validation* above). Effect of any potential sterility breach during transfer of the slices into the final container is further minimized by the short expiry dating.

UPDATE: The section was updated with endotoxin risk assessment for materials with direct product contact (in a table format). The applicant stated that sterility of critical product-contact materials will be verified via periodic sampling of incoming lots for sterility and endotoxin. The table included newly established acceptance criteria for endotoxin. Please refer to 483 response review memo for more detail as this information was also provided in response to 483 Observation 8.

3.2.P.2.6 Compatibility

NA. The product is not reconstituted or deliver via a device.

Overall Reviewer's Assessment of Section 3.2.P.2:

UPDATE: The update was due to a change in DP container to (b) (4) culture dish. Though the applicant does have significant clinical experience with this container, due to the fact that the container is not sealed makes it prone to microbiological contamination. As such, this risk should be extensively mitigated.

The applicant failed to demonstrate they can maintain sterility during transport of DP to OR as the transportation study using media did not pass growth promotion testing (refer to Section 3.2.S.2.5). The risk mitigation of (b) (4) dish focuses mainly on controlling aseptic process (b) (4) from DP packaging and transport, reducing risk of spillage, and (b) (4) out-of-incubator hold time. The following controls are not in place:

- Aseptic technique during packaging (currently packaging of secondary container is performed in unmonitored ISO (b) (4) area)

- Sanitization/cleaning validation of secondary container (currently wiped with (b) (4), but not validated)
- Procedures and lot disposition for spill incidents in transport
- Periodic sampling of incoming lots of (b) (4) container for sterility and endotoxin (refer to EIR and 483 Observation 8).

I recommend a comment be sent to the firm (refer to Item 6 in Remaining Deficiencies section).

The main change during DP development is the implementation of a new DP container closure instead of a culture dish for holding and transporting of the final product. The change itself and CCIT approach were discussed with the applicant extensively during a Type B meeting on 1/19/2018. During the meeting CBER agreed that (b) (4) is acceptable given the limited time DP is held in the final container (b) (4) the time was increased to (b) (4) in the BLA. It was also suggested that the applicant evaluates the clinical impact of the final container change under IND. Risk assessment including considerations of end users and impact on clinical outcome was recommended. CCIT was performed within the APV and is reviewed above in 3.2.S.2.5 *Process Validation and/or Evaluation*.

The information provided in this section is limited and does not fully address concerns raised in the past. Clarification of issues noticed during the review was requested in IR on 06/24/2019. The response was received on 7/17/2019 in eCTD seq 0014 (amendment STN 125685/0.15) and is reviewed below:

Q.12: Regarding your new DP container implemented in 2018:

- c. Please provide a summary of clinical experience with the new (b) (4) container, if any. Please include a table with side-by-side comparison of packaging for transport procedure and duration, surgical procedure and duration, and clinical outcome before and after implementation of the new DP container.**

Enzyvant stated that the new DP container was implemented in February 2019 and used in manufacture of lots implanted in subjects (b) (6). All treated patients were alive two-month post-implantation (July 2019). The following comparison was provided:

	Petri Dish [estimated duration]	(b) (4) [estimated duration; validated max duration]
Primary Packaging	NA. Culture media is replaced with 5ml of (b) (4) TOM in the morning of the surgery. Culturing continues until the recipient is under anesthesia.	Slices are packaged into DP containers individually, one Petri dish at a time. (b) (4)

Secondary Packaging	Dishes are placed in the secondary container and into the insulated cooled (in use since 2016). (b) (4)	Containers are placed in racks (b) (4) which are placed in sterile bags, labeled, and placed in the coolers until the recipient is under anesthesia. (b) (4)
Transport	Coolers/containers are (b) (4) to OR (b) (4)	Coolers are (b) (4) to OR (b) (4)
OR Use	Individual Petri dishes are removed from the cooler and opened in the sterile field. Scrub nurse removes filters with tissue and places them in a Petri dish with saline. Same nurse then removes tissue from filters and places into another Petri dish with saline, until the surgeon implants the slice. (b) (4)	Individual DP containers are removed from each rack and opened in the sterile field. Scrub nurse removes filters with tissue and places them in a Petri dish with saline. Same nurse then removes tissue from filters and places into another Petri dish with saline, until the surgeon implants the slice. (b) (4) NA]

Enzyvant stated that the DP unpacking and prep for implantation is not a rate limiting step in the surgery regardless of which DP container is used.

Reviewer Comment: Implementation of the new DP container results in a significant increase of duration the product spends at room temperature and (b) (4) levels. Though Enzyvant estimates secondary packaging of Petri dishes to take up to (b) (4), it appears to be unlikely given that it does not start until the notification is received from OR that patient is under anesthesia.

Also, the proposed maximum allowable time from initiation of packaging to delivery should take into consideration duration of the surgery; the product cannot expire before the implantation is completed. This was noted during review of 3.2.S.2.3 above.

According to 3.2.S.4.1, endotoxin release specification is (b) (4) body weight/hr assumes (b) (4) implantation time; however, reported surgery duration is (b) (4). The decision regarding the ultimate impact of surgery time on endotoxin specification (if any) was deferred to PO.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

1. (b) (4)

(b) (4)

Manufacturing, packaging, and labeling of the drug product; testing for visual inspection (DP; identity); dose, (b) (4) testing of DS for final release.

2. (b) (4)

testing of DS for final release.

3. (b) (4)

Mycoplasma testing of (b) (4) for final release.

4. (b) (4)

(b) (4) histology testing of source material and (b) (4) for final release.

3.2.P.3.2 Batch Formula

Batch size will vary based on the amount of available donor thymus tissue, but will not exceed (b) (4) containers each containing a slice of processed tissue on a support filter in (b) (4) of TOM. The batch formula for the largest batch size is:

- RETHYMIC, (b) (4) slices
- (b) (4) filters, (b) (4)
- Thymus Organ Media, (b) (4), including:
 - (b) (4)

Testing of the batch components was reviewed in 3.2.S.2.3 *Control of Materials* (TOM, filters) and 3.2.S.2.4. *Control of Critical Steps and Intermediates* (DP) above as most testing used for final release of DP is performed on DS. The final container DP is only tested for identity by visual inspection prior to release.

UPDATE: Batch formula was updated to indicate that final product will be delivered in the (b) (4) culture dish, which contains the tissue slices, filters, sponges and media. Quantities of TOM components were updated to match the largest batch size of (b) (4) culture dishes.

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

UPDATE: Additional information had no impact on the reviewer's overall assessment of these sections (below). The applicant only included the (b) (4) on the list of DP manufacturers. The facilities testing DS for DP

release were added to the DP manufacturers' list above based on the information provided in Form FDA356h and in 3.2.S.2.1 *Manufacturer(s)*. DMPQ and OCBQ management was consulted and a decision was made to consider any testing of DS used for DP release to be equivalent to DP testing. It was the upper management decision to not require registration of (b) (4) [REDACTED], or inspection of the (b) (4) [REDACTED]

Form FDA356h for an original BLA should include complete establishment information on the locations of all manufacturing, packaging, and control sites for both drug substance and drug product. The applicant did not include (b) (4) [REDACTED]

[REDACTED] that perform DS testing for final release. I recommend this to be resolved in the next review cycle given that histology testing lab might change due to implementation of quantitative histology testing recommended by PO.

3.2.P.3.3 Description of Manufacturing Process

DP manufacture consists of packaging and labeling of DP. Packaging is performed in a (b) (4) [REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)



The final DP container and bag placed over a filled rack are both labeled with lot and NDC numbers. A patient label with recipient MRN is placed on the bag as well. NDC and lot numbers are included in the batch record together with ISBT number, and the following information is recorded: start time/date of processing and first slice transfer, end time of packaging, slice tracking and labeling, and sampling. A single dish exit is recorded in the incubator log with lot and ISBT numbers.

Product release and shipment are documented in batch record (lot and ISBT numbers; verification of product and bag label, packing of shipping boxes, their number, and shipping process, custody transfer to OR), preliminary CofA (lot, ISBT, recipient MRN numbers; expiration of date and time and product release verification), and DP Chain of Custody (lot, ISBT, recipient MRN numbers; shipping start and end times, verification of transfer from the facility to transport representative, and then to OR). The full lot release acceptance criteria are included in the final CofA issued >14 days after DP administration along with the lot, ISBT, and recipient MRN numbers.

Dose Administration of the DP documents expiration date/time, total dose released, the number of slices/containers transplanted, and remaining dose (if any) and includes ISBT and recipient MRN numbers.

Remaining thymus material identified with lot and ISBT numbers is discarded, which is documented and justified in Discard Form (lot and ISBT numbers, date tissue received).

UPDATE: Changes to the DP manufacturing process related to the final container change were reviewed together with DS manufacture above (see Section 3.2.S.2.2). Chain of identity information provided in the section remained essentially the same.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

UPDATE: Overall the scope of the change is sufficiently clear. Even though certain details of DP manufacture (e.g. delivery coordination) were provided elsewhere in the submission.

Description of manufacturing process is lacking sufficient detail, for example division of responsibilities for unpacking of DP and packing of the unused DP was not described. This was followed up during the inspection (refer to EIR); additional information was requested through IR (see below). Review of labeling and timing of CofA issuance is deferred to the PO. It appears that important labeling information present on the DP container is omitted from bag label (expiration time). Also, given the lack of data showing that agitation of the final container has no effect on CCI, it might be appropriate to include "do not agitate" on the container and bag labels. This is discussed in the 3.2.S.2.5 *Process Validation and/or Evaluation* above. This issue was communicated to the labeling group. Chain of custody documentation appears to be acceptable. Product and sample tracking/tracing were further evaluated on the inspection and there were no observations associated with this topic.

The following information was requested on 07/03/2019 and the response was provided on 7/17/2019 in eCTD seq 0015 (amendment STN 125685/0.14) and is reviewed below. Additionally, clarification of DP "Hold Time In Insulated Shipping Boxes Prior To Shipment" conditions were requested during review of PV in Section 3.2.S.2.5 above and were found acceptable.

Q.4: You have specified a culture harvest window for DP preparation of Days 12-21. It appears that the majority of product lots listed across your clinical protocols received product that was held in culture for (b) (4) days or less:

a. Please describe your strategy to schedule manufacturing of the product with transplant date.

The implantation procedure is scheduled after the manufacture is initiated, due to thymus availability being a limited factor. The surgery date is decided collaboratively between clinical, surgical, and manufacturing teams after a patient is approved for implantation. The process is typically coordinated by the treating immunologist. For patients requiring RATGAM prior to surgery, target release window is Day 16-21. RATGAM administration cannot be initiated before donor screening results are available and approved (Day 12) and takes 5 days (3 daily doses and 2 days of rest). Overall earlier dates of release are targeted as these patients are clinically unstable and surgery might need to be delayed. Occasionally HLA matching is required. Cultures are released on first-in first-out basis and are generally are not designated for a specific patient until after dose is calculated on the day prior to release. There's slight variation in the procedure based on number of lots in culture and patients waiting for the product.

Reviewer Comment: Review of this response is deferred to PO.

Q.5: For the final product, please clarify:

- a. Please describe your procedures for coordinating DP delivery to OR, and responsibilities of OR staff and (b) (4) personnel as it relates to delivery, unpacking of DP, packing of DP remaining after the implantation, and its delivery to the (b) (4) facility.***

Estimated start time of the surgery is communicated to (b) (4) personnel several days in advance. DP packaging starts in the morning of the surgery day; exact time is dependent on the communicated surgery start time. Shipping of DP is initiated after OR staff communicates to (b) (4) personnel that they are ready to start procedure in (b) (4) technicians (b) (4) deliver the product; this is done carefully, to minimize drops and shaking. Operators gown in as directed by OR staff and document beginning and end of transport in the chain of custody. (b) (4) OR staff member sign chain of custody form. (b) (4) unpacks a shipping box, removes (b) (4) operators perform visual inspection for leaks and damage. (b) (4) transfers individual DP containers with unscrewed lids to the scrub nurse, who transfers product to an OR-supplied sterile dish with preservative-free saline using forceps. (b) (4) places empty container back on the cart. The steps are repeated until “all DP has been implanted” or the surgeon decides that no more tissue should be implanted. (b) (4) performs all documentation.

Any unused DP containers are placed back into the racks and the shipping box by (b) (4) and are transported back to (b) (4) by the operators for disposal. If any tissue remains, the dose is recalculated. Unused tissue is discarded in a biohazard bin in Room (b) (4).

Reviewer Comment: This is highly unusual that (b) (4) personnel is involved in the implantation procedures of DP and should be addressed in labeling (deferred to PO). Actual shipping conditions (minimal shaking) was verified during the inspection and found acceptable. Though only transport of source material was observed during PLI, the route and mode of transportation (hand held in (b) (4) shipping container) are identical to those of DP, and are therefore representative of DP shipping.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The only testing performed during DP manufacture is identity by visual inspection on the final container DP. Review is deferred to PO.

Overall Reviewer’s Assessment of Section 3.2.P.3.4:

Deferred to PO.

3.2.P.3.5 Process Validation and/or Evaluation

Process validation and aseptic process validation were reviewed in 3.2.S.2.5 Process Validation and/or Evaluation above and covered both DS and DP. DP shipping validation was reviewed above in 3.2.S.2.5 Process Validation and/or Evaluation.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

Refer to the aforementioned sections above.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

Defer to PO.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Defer to PO and DBSQC.

3.2.P.4.4 Justification of Specifications

Defer to PO.

3.2.P.4.5 Excipients of Human or Animal Origin

Defer to PO.

3.2.P.4.6 Novel Excipient

Defer to PO.

Overall Reviewer's Assessment of Section 3.2.P.4:

Defer to PO.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Sterility, mycoplasma, and endotoxin testing for DP release is performed on (b) (4) medium and is reviewed above in 3.2.S.4 Control of Drug Substance above.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

UPDATE: Update of this section duplicates that of section 3.2.S.4. Please see above.

For review of specifications within DMPQ purview please refer to the aforementioned section above.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Defer to PO.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

Defer to PO.

3.2.P.5.4 Batch Analyses

Batch analysis of PV lots manufactured in 2018 and 2019 was provided in this section. The applicant stated that all acceptance criteria were met except donor screening. Endotoxin acceptance criterion of (b) (4) was applied. Results for PV lots were reviewed above in 3.2.S.2.5 *Process Validation*.

3.2.P.5.5 Characterization of Impurities

Defer to PO.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

UPDATE: These sections were not updated.

Based on the batch analyses, the applicant can consistently manufacture sterile product, free of mycoplasma.

Based on the information provided in eCTD 3.2.S.4.3, endotoxin acceptance criteria should be (b) (4) instead of (b) (4) applied by the applicant to PV lots. Endotoxin levels in (b) (4) clinical lots manufactured in the (b) (4) facility in 2016-2017 (see 3.2.S.4.4 *Batch Analyses* above) and PV lots (b) (4) were within the specification (b) (4) PV lot (b) (4) tested (b) (4) at Day 21 and as such failed release endotoxin specification.

As the actual specification is set in (b) (4), and the DP dose is in mm²/m² of body surface area, recalculation of endotoxin into (b) (4) includes multiple assumptions, which are inconsistent throughout the submission (e.g. worst case patient body surface area is (b) (4) per 3.2.S.4.3 and (b) (4) per 3.2.S.4.4 and 3.2.P.5.4), which would affect the endotoxin acceptance criteria in (b) (4). Furthermore, an (b) (4) of endotoxin levels was observed between Day 12 (b) (4) and Day 21 (b) (4) which was not the case for other (b) (4) batches. It is unclear whether this is due to an undetermined source of endotoxin or method variability. Clarification was requested in IR on 06/24/2019. The response was received on 7/17/2019 in eCTD seq 0014 (amendment STN 125685/0.15) and is reviewed below:

Q.13: Regarding the DP endotoxin levels:

- a. You applied an acceptance criterion of (b) (4) to endotoxin levels in PV batches. As per Section 3.3 of eCTD 3.2.S.4.3 *Validation of Analytical Procedures*, it was calculated based on maximum dose of (b) (4), whereas the maximum dose in the DP specifications (eCTD 3.2.P.5.1) is 22,000 mm²/m². As such, your worst case endotoxin levels should be (b) (4). This criterion was not met at Day 21 for PV lot (b) (4). We also noticed an (b) (4) of endotoxin levels between Day 12 and Day 21 for this lot. Please

justify using this lot to support your process validation and provide a root cause analysis for (b) (4) endotoxin level in lot (b) (4) .

Enzyvant explained the lot is acceptable based on the following:

- The upper limit of the dose specification was reduced to (b) (4) since the PV protocol has been approved and executed.
- The endotoxin specification for PV lots was theoretical based on the worst-case patient weight of (b) (4) whereas during regular manufacture the limit (and the maximum valid dilution) is calculated based on the actual weight of the patient prior to testing.
- The apparent (b) (4) in endotoxin over the course of manufacture is “an artifact from testing” because the first tests was deemed to be invalid and re-test had to be performed at (b) (4) dilution. Testing at this dilution would not have been used “had the maximum valid dilution been smaller due to a decreased endotoxin limit”.

Reviewer Comment: I reached out to the DBSQC reviewer, Simleen Kaur, for the feedback regarding the applicant’s “testing artifact” claim. She reviewed the IR response and the batch analysis data for all (b) (4) PV lots and concluded that the (b) (4) in endotoxin is either due to (b) (4) . I defer the final decision about the validity of PV lot (b) (4) to the PO.

b. Please clarify the total amount of endotoxin units over the full volume of the (b) (4) culture medium.

Enzyvant explained that the total amount is dependent on the media volume and measured concentration of endotoxin. The volume depends on the size of the lot, up to approximately (b) (4) endotoxin concentrations measured to date were less than LOD for every lot.

Reviewer Comment: The response is acceptable.

c. We notice that your endotoxin data looks different between the (b) (4) clinical lots manufactured in 2016-2017 (all batches tested were (b) (4) and process validation lots (most results were (b) (4) Please clarify if there were any differences in the culturing conditions, such as media volume or number of slices per dish, testing method, or anything else that could have resulted in such differences between clinical and PV lots.

Enzyvant explained that the difference was due to (b) (4) to increase method sensitivity, which was implemented prior to method validation. Sensitivity of the current test cartridge is the same as the one used for testing of previous clinical lots manufactured at the (b) (4) facility.

Reviewer Comment: This response is acceptable.

3.2.P.6 Reference Standards or Materials

Defer to PO and DBSQC.

3.2.P.7 Container Closure System

Primary container closure is a 100 mL transparent polypropylene container with a leakproof orange high density polyethylene cap. Size of the container is 2.050 in diameter and 2.550 in height. It is manufactured by (b) (4) and the firm indicated it is supplied sterile, unlabeled, and individually wrapped.

The container is (b) (4) sterilized by the supplier to (b) (4). Certificate of sterilization is provided and confirmed upon receipt. Additionally, 100% visual inspection upon receipt confirms that containers meet the following description: (b) (4)

” Each lot of containers is tested for endotoxin.

Evaluation of container suitability and E&L is deferred to the PO. CCIT was evaluated within APV and is reviewed above in 3.2.S.2.5 Process Validation and/or Evaluation.

Up to (b) (4) filled and labeled primary DP containers are placed in (b) (4)

UPDATE: Final container closure system is the same cell culture dish with lid that is used for the (b) (4). The containers are placed in a sealable polycarbonate box (b) (4) which is placed inside an insulated shipping box for transport to OR.

Primary container: polystyrene (b) (4) culture dish described in Section 3.2.S.6. The dishes are sterilized by (b) (4) by the supplier to (b) (4). Each lot of containers will be tested for endotoxin before use. Upon receipt, each sleeve of culture dishes is visually inspected to ensure integrity of the sleeve plastic (ex. no holes or tears), and that there are no visible cracks on the plates inside each sleeve.

Secondary container: single-use polycarbonate (b) (4) Container System supplied by (b) (4) product number (b) (4)), can hold up to (b) (4) dishes in (b) (4) separate stacks. The (b) (4) Container System consists of the following components:

- Container tray, cover and (b) (4) latch assemblies (b) (4) on each long side) attached to the container tray, all composed of natural clear polycarbonate
- (b) (4) fitted into container lid

Shipping container: reusable shipping of (b) (4) capacity.

Refer to Section 3.2.S.2.5 for the transportation studies of the (b) (4) culture dish in the (b) (4).

Overall Reviewer’s Assessment of Section 3.2.P.7:

UPDATE: Issues regarding sterility assurance of the product contact supplies identified during the PLI (refer to EIR and 483 Observation 8) still apply. No information regarding material controls applied to the secondary container was

provided. The applicant did not perform cleaning or sterilization validation of (b) (4). I recommend a comment be sent to the firm (refer to Item 6 in Remaining Deficiencies section below).

Overall limited information was provided. DMPQ discussed container closure system with the applicant during Type B meeting on 01/19/2018, where (b) (4) of the container justified by a short hold time (b) (4) was accepted by the Agency.

The container might allow for excessive movement of the product during shipping (discussed above). Mechanical protection was evaluated for the shipping configuration (b) (4) as a part of shipping validation and was acceptable.

I noted during the review of the summary of all product deviations at (b) (4) facility (submitted on 6/17/2019 in response to Q3.c of the IR dated 5/24/2019 in eCTD seq 0009, amendment STN125685/0.9), that black particulate was noted (inside the pouch, but outside the containers) during inspection of (b) (4) containers upon receipt. The issue was investigated but the origin of the particulate was not determined, and the applicant has resorted to wiping the cups before use in manufacture. This issue was followed up during PLI. No product quality issues related to the deviation were identified during the inspection. Additionally, the applicant will visually inspect DP in the final container for the presence of foreign particles (see response to IR of 08/30/2019 below). I consider this issue to be resolved.

Clarification regarding DP testing was requested by PO in IR on 08/30/2019. The response was received on 09/13/2019 in eCTD se 0030 (amendment STN 125685/0.28) and is reviewed below (DMPQ-pertinent responses only):

Q.1: Acceptance criteria for Drug Substance and Drug Product testing:

- e. Visual inspection of the final product in the final container should include an evaluation of the appropriate color and clarity of medium and evaluate for the presence of foreign particles.***

Enzyvant updated (b) (4)-SOP-031 and (b) (4)-SOP-031 FRM14 to instruct operators to perform a visual inspection of the medium in the drug product container, in addition to the visual inspection of the thymus tissue and container integrity. Visual examples of acceptable media (b) (4) will be provided for reference in the batch record. The acceptance criteria for visual inspection of the drug product was modified to indicate that the media should be of appropriate (b) (4).

Reviewer Comment: The response is acceptable.

Clarification of issues noticed during the review was requested in IR on 06/24/2019. The response was received on 7/17/2019 in eCTD seq 0014 (amendment STN125685/0.15) and is reviewed below:

Q.12: Regarding your new DP container implemented in 2018:

d. Please provide (b) (4) validation for sterilization of your primary DP container and studies done to determine highest achievable sterility assurance level.

Enzyvant explained that there was no formal study performed to evaluate highest achievable (b) (4) for the container. Instead, the vendor (b) (4) to achieve (b) (4) and sent a sample container to (b) (4) for assessment. The container was (b) (4) comparing to the containers sterilized under the current cycle, which was deemed unacceptable. The sterilization cycle was not changed.

The firm provided a final validation report for (b) (4) sterilization of (b) (4) container. The study # 949836-S01 was sponsored by (b) (4) . and performed by (b) (4) . The contract (b) (4) was (b) (4)

(b) (4)

Reviewer Comment: The response is not adequate. Container used in (b) (4) validation study is different from DP container and no information was provided to support that the container used in the study is equivalent or worse case comparing to DP container with respect to bioburden and sterilization challenge it presents. It was not specified whether the load was packaged in a manner and with materials used for the actual product being sterilized and (b) (4) was not performed. Sterility assurance of the (b) (4) container was further assessed during PLI. Please refer to EIR and 483 Observation 8. I recommend a Complete Response be sent to the firm (refer to Item 1 in Remaining Deficiencies section).

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Defer to PO.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Defer to PO.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Facilities Table

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
(b) (4)				
Manufacturing of DS and DP. Release testing of (b) (4) DP (identity, visual inspection, dose, endotoxin, sterility). DP packaging and labeling	Inspection	Yes	Yes	N/A

(b) (4)				
DS release testing for final product release (b) (4)	Not Required	Yes	Yes	N/A
(b) (4)				
Source material and DS Release testing for final release (b) (4)	Inspection	Yes	Yes	N/A
(b) (4)				
DS release testing for final release and testing of intermediates (b) (4)	Waiver	Yes	Yes	

Facility and Flows. The (b) (4) facility is a multi-product facility that was designed for GMP aseptic process operations and currently manufactures several cell and tissue products under INDs. (b) (4) is located in (b) (4) building on the (b) (4) (b) (4) is an (b) (4) building, which houses mainly (b) (4) clinics. Based on the floor plans and room descriptions provided, the following production rooms, laboratory space, and storage space were identified:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

appropriate corrective actions prior to conducting a new study demonstrating that the final DP container adequately maintains a sterile environment. Please submit the summary reports.

3. Adopting the (b) (4) culture dish as your primary DP container changed your DP packaging and configuration of the shipping container used for DP transport to the OR. Therefore, the validation of this shipping container to maintain the appropriate temperature is no longer valid. Please revalidate and provide the summary report.
4. Regarding your (b) (4) system:
 - a. Qualification of (b) (4) system is deficient in scope and duration. Specifically, it did not include monitoring of (b) (4) quality over a period of time and only a limited number of locations were sampled. (b) (4) sampling did not demonstrate (b) (4) particulate is within ISO (b) (4) acceptance limits.
 - b. Your strategy and schedule for routine (b) (4) sampling is unclear as not all testing is performed quarterly, and locations vary for different dates and types of tests. The sampling procedure description is inconsistent (e.g. use of (b) (4) and vague about (b) (4) use during sampling, which could interfere with bioburden testing.

Please provide the necessary information and/or data to address these issues.

5. The personnel flows at your multi-product facility create an increased risk of product contamination and cross-contamination. Specifically,
 - You allow (b) (4) of your facility. This allows simultaneous presence of personnel working on different products in (b) (4).
 - Additionally, personnel enter Gown-In Room (b) (4) and exit Gown-Out Room (b) (4) of the facility through the same Receiving/Supply Room (b) (4). This allows simultaneous presence of personnel entering and exiting the manufacturing areas in Room (b) (4).

Please provide a description of procedural and/or engineering controls in place that ensure correct personnel flows, prevent exceedance of maximum number of allowed personnel in Rooms (b) (4), and mitigate risk of product contamination and cross-contamination due to personnel flows described above.

6. Due to the nature of your primary DP container, the environment inside your secondary (b) (4) container becomes more critical to ensure microbial protection of the product. We recommend cleaning and/or sterilization validation of the secondary container and packing of the

(b) (4) container in the ISO (b) (4) environment. Additionally, please implement and provide procedures and lot disposition for spill incidents in transport.

Inspectional Follow-Up:

1. During the PLI the inspection team noted that (b) (4) does not use (b) (4) DP container for tissue transfer during (b) (4) and for its (b) (4) storage as described in the BLA and follow-up IRs responses. I recommend inspectional follow up for the (b) (4) storage container. Unless (b) (4) specimen cup is used, qualification of the container (including sterilization validation) should be verified.
2. (b) (4) made multiple changes to DP manufacturing process and EM during manufacture, such as implementation of (b) (4) tissue dish as the final DP container and of (b) (4) monitoring using (b) (4). I recommend inspectional follow up to ensure the (b) (4) e studies were expanded to cover the new process as well as the new (b) (4) set up.

3.2.A.2 Adventitious Agents Safety Evaluation

Defer to PO.

❑ Viral Clearance Studies

3.2.A.3 Novel Excipients

Defer to PO

3.2.R Regional Information (USA)

❑ Executed Batch Records

Reviewed within the relevant sections above (APV, PV, shipping validation).

❑ Method Validation Package

Defer to DBSQC and PO.

❑ Combination Products

NA

❑ Comparability Protocols

NA

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

A claim for categorical exclusion under 21 CFR 25.31 (a) and 25.31 (c) was submitted on 12/20/2018 in an amendment STN 125685/0.2. The applicant states that to their

knowledge no extraordinary circumstances exist. Approval of this product derived from a naturally occurring substance is not expected to significantly increase the use of the active moiety or alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

The categorical exclusion claim is accepted.

B. Labeling Review

Full Prescribing Information (PI):

Defer to PO

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Defer to PO.