



Our STN: BLA 125685/0

**MID-CYCLE COMMUNICATION  
SUMMARY**

August 9, 2019

Enzyvant Therapeutics Inc.  
Attention: Dr. Kevin Healy  
c/o 324 Blackwell Street, Suite 1220  
Durham, NC 27701

Dear Dr. Healy:

Attached is a copy of the summary of your July 18, 2019 Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to BLA 125685/0 in your future submissions related to Allogeneic processed thymus tissue.

If you have any questions, please contact Jean Gildner at (240) 402-8296.

Sincerely,

Raj K. Puri, MD PhD  
Director  
Division of Cellular and Gene Therapies  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

## Mid-Cycle Communication Teleconference Summary

**Application type and number: BLA 125685/0**  
**Product name: Allogeneic processed thymus tissue**  
**Proposed Indication: Treatment of DiGeorge Disease**  
**Applicant: Enzyvant Therapeutics**  
**Meeting date & time: July 18, 2019 1300 – 1400 EST**  
**Committee Chair: Dr. Thomas Finn**  
**RPM: Jean Gildner**

### **FDA Attendees:**

Qiao Bobo, PhD, CBER/OCBQ/DMPQ  
Wilson Bryan, MD, CBER/OTAT  
Dennis Cato, PhD, CBER/OCBQ/DIS  
Christine Drabick, MS, CBER/OCBQ/DIS  
Melanie Eacho, PhD, CBER/OTAT/DCGT  
Thomas Finn, PhD, CBER/OTAT/DCGT  
Jean Gildner, MSHS, MT (ASCP), CBER/OTAT/DRPM  
Elizabeth Hart, MD, CBER/OTAT/DCEPT  
Ellen Huang, CBER/OCBQ/DMPQ  
Sukhanya Jayachandra, PhD, CBER/OTAT/DCGT  
Alyssa Kitchel, PhD, CDRH/ODE/DSD  
Randa Melhem, PhD, CBER/OCBQ/DMPQ  
Steven Oh, PhD, CBER/OTAT/DCGT  
Raj Puri, MD, PhD, CBER/OTAT/DCGT  
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT  
Lisa Stockbridge, CBER/OCBQ/DCM/APLB  
Winson Tang, MD, CBER/OTAT/DCEPT  
Irina Tiper, PhD, CBER/OTAT/DCGT  
Cong Wang, PhD, CBER/OBE/DB

### **Enzyvant Therapeutics Attendees:**

Alan Kimura, MD, PhD, Chief Medical Officer, Enzyvant Therapeutics, Inc.  
Alex Tracy, PhD, Vice President, Pharmaceutical Development & Manufacturing,  
Enzyvant Therapeutics, Inc.  
Kristin Marks, Senior Process Engineer, Enzyvant Therapeutics, Inc.  
Allison Lim, Medical Director, Clinical Development, Enzyvant Therapeutics, Inc.  
Erin Fleig, Aseptic Scientist, Enzyvant Therapeutics, Inc.  
Nicole Baker, PhD, Manager, Regulatory Affairs and Quality, Enzyvant Therapeutics,  
Inc.  
Karin Pihel, PhD, Director, CMC Regulatory Affairs, Enzyvant Therapeutics, Inc.  
Kevin Healy, PhD, Vice President, Regulatory Affairs, Enzyvant Therapeutics, Inc.  
Beverly Orozco, Head of Quality, Enzyvant Therapeutics, Inc  
(b) (4) , PhD, Director of Regulatory Affairs and Quality, (b) (4)

### **Agenda:**

**Discussion Summary:**

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.
  - a. We have some concern about the proposed tissue slice sampling time points and harvest time points. We are still performing our review and evaluating all relevant sources of information, including product development data, batch history, process validation data, and clinical data. It is not clear at this point that the (b) (4) sampling time points for histology is justified, and it is not clear that Day 21 represents the same level of product quality as Day 12:

- i. Supplied images of Day (b) (4) histology sections both indicate healthy looking tissue, but Day (b) (4) typically contains (b) (4) than Day (b) (4). While Day (b) (4) sampling consistently demonstrates a significant (b) (4) within the tissue, and thus serves as a useful measure of a unit operation, it is not necessarily reflective of final product quality. Although there are significant differences between images of different product lots at any one culture stage, in general later stages show a more consistent (b) (4) present in the tissue that is likely to be more representative of what would be expected in the DP. It also appears the slices may change over time in culture beyond just a (b) (4) from Day (b) (4). From information you provided on clinical lots to support safety and efficacy, patients received product that was sampled histologically between Day (b) (4) and (b) (4) with the majority of testing done on Day (b) (4). You have proposed to change from a strategy of testing by histology (b) (4) days before transplant to sampling at Days (b) (4) regardless of the final harvest time point. As reported in your (b) (4) histology analysis, newer lots manufactured in (b) (4) were sampled between Day (b) (4). If it is the intention to treat a patient with product harvested from Day 21 cultures it is unclear why it is necessary to sample as early as Day (b) (4) or to limit histological samples to Day (b) (4). Testing product at Day (b) (4) (about (b) (4) of the way through manufacturing) for release at Day 21 may not be warranted.

Testing should be performed as close as is feasible to drug product preparation to verify the quality of the product lot. Please indicate the histology sampling time point and the culture harvest time point for lot (b) (4) and newer.

**Meeting Discussion:** The applicant agreed that some changes in the tissue slices occur over time, but felt that sufficient quality is still present in the Day 21 product. FDA

appreciated that flexibility in the manufacturing schedule may be needed to coordinate with patient scheduling but was unsure if such a long interval between testing and final product release was appropriate. FDA expressed concern that if a deviation occurred during processing, such as an incubator malfunction at Day (b) (4), that it would be hard to evaluate the impact of the deviation because potency, identity, and overall quality had already been assessed as early as Day (b) (4). The applicant understood FDA's concern about testing (b) (4) on the drug substance as a measure of final drug product quality, but felt this strategy was needed for this particular patient population. FDA noted that the BLA does not contain a lot of information on the rationale for the timing of histology-based release testing. FDA recommended an amendment be submitted with more detail on the coordination of the patient scheduling with product manufacturing and testing, and to better justify the time points selected. FDA noted that as intended Day (b) (4) the tissue is significantly reduced of thymocytes. However, while Day 12 and Day 21 tissue still maintain hallmarks of thymus tissue, the histological properties and (b) (4) appear to change over the course of time in culture. FDA recommended to further support the applicant's justification for the testing time points they also consider ways to mitigate the risk of testing (b) (4), such as potentially retesting the product after a significant deviation.

- ii. Though it appears that thymus tissue is remarkably resilient to ex-vivo cell culture, it is not clear that Day 21 represents the same level of tissue quality as earlier harvest time points. Some subjects treated with Day 21 tissue did have a positive outcome; however, most subjects received tissue collected for drug product formulation between Day (b) (4) and Day (b) (4). The process validation data, biomarker analysis, and (b) (4) histology provided appear partially supportive, but the sensitivity of the assays is limited. We note that the (b) (4) seen at Day (b) (4) appears to change over time in culture. It is not clear whether the change represents an improvement or a reduction in product quality. There are also differences in (b) (4) over time in culture. While it is sometimes the case that a level of flexibility is designed into a manufacturing process to allow for manufacturing or patient treatment to be more feasible, established ranges must be justified. A manufacturing range of Day 12 through Day 21 represents a large manufacturing window, and little justification has been given for why the full range is needed or how timing of product manufacturing, product testing, and patient treatment are coordinated. Given the historical clinical data and the observed changes over time in culture, it might be preferable if some target were implemented to harvest tissue slices earlier, or to better coordinate tissue testing with tissue harvest.

**Meeting Discussion:** Applicant stated that the donor supply is unpredictable and they are very limited in the number of lots they can manufacture and the patients they can treat. Not allowing Day 21 age thymus slice cultures to be used could reduce the number

of patients that might benefit from this therapy. Some patients who had positive clinical outcome received Day 21 tissue. FDA acknowledged that fact, and could not say as yet that Day 21 tissue does not represent the same level of tissue quality as earlier harvest time points, only that Day 21 tissue appears histologically different from Day 12 tissue and it is not clear what that means in terms of product quality. Further, a preliminary FDA analysis found that more patients that didn't benefit from the product received tissue slices that had been incubated longer in culture or received fewer slices, compared to those that did benefit. The applicant proposed to look more carefully at the relationship between time in culture and clinical outcome. The Applicant pointed out that product manufacturing is closely tied with the clinical schedule. Atypical DiGeorge patients that are part of the intended target population require treatment with immunosuppressants prior to treatment with the thymus product that must be weaned off 3 days prior to transplant. It is not possible to treat Atypical patients with Day 12 product. FDA requested the Applicant submit additional information about the timing of product harvest and patient treatment.

Additional discussion was held on the minimum criterion of (b) (4) of source material thymus tissue. FDA had expressed concerns in a recent information request that (b) (4) may not be sufficient in all cases. The Applicant agreed that (b) (4) would not necessarily be sufficient for every lot, but that this was a business risk. Given the scarcity of surgically resected thymus tissue, the applicant plans on processing any tissue that meets the minimum (b) (4) criterion, even if some lots ultimately fail.

- b. The histology assays appear to have no minimum threshold in place. All assays should have a minimum threshold to distinguish a quality lot from one not acceptable for commercial distribution. We can appreciate that your studies to date may not have identified a clear threshold, but your substantial experience and your more recent efforts with forced degradation studies should be able to identify representative images that would distinguish acceptable quality.

**Meeting Discussion:** The Applicant discussed the challenges with developing a (b) (4) assay and expressed concerns that developing a more (b) (4) test with a specific threshold would be difficult. FDA explained a (b) (4) test is not necessarily required, but even (b) (4) measures should have some reference that helps define what is and is not acceptable. FDA used (b) (4) visual inspections of final container quality as an example, where reference photographs can be used to indicate what would not be considered adequate or out of range. FDA stated that the Applicant should use their experience to develop reference examples and integrate them into their SOPs. The Applicant indicated they have examples they use in their histology training guide. FDA recommended that such references be more fully established.

- c. Identity assays for all critical reagents is a regulatory requirement. It is not clear you have identity assays in place for (b) (4) culture medium components.

**Meeting Discussion:** The Applicant will investigate this issue. Complying with this requirement may take time and they have limited experience or equipment to perform such tests. The Applicant expressed concerns about how developing such tests might impact the BLA review timeline. FDA advised that identity tests on media components are fairly common and that they reach out to 3<sup>rd</sup> parties with more experience who might be able to help. FDA suggested one option might be to address full implementation as a post-marketing commitment if a detailed plan was in place at the time of licensure. FDA would consider possible options going forward.

- d. Validation of the (b) (4) is limited. The method allows use of (b) (4), but data was provided on the product using only one method, and does not appear to have included (b) (4) medium.

**Meeting Discussion:** The Applicant is in the process of preparing a response to an Information Request that was sent prior to the Mid-Cycle Meeting. They will provide validation data on the (b) (4) method.

- e. Stability studies not fully tested under worst case conditions: Normally, stability studies are conducted on a minimum of 3 lots all tested under worst case conditions. Your stability studies were incorporated into the process validation studies (which is acceptable), but none of the (b) (4) process validation lots were exposed to full extent of all hold and step times. It is also not clear how the holding and step times proposed compare with your clinical experience

**Meeting Discussion:** The Applicant explained that they did not conduct a separate stability study, and the process validation study was not designed as a stability study, as they did not feel that stability pertains to this product. FDA explained that it was acceptable to integrate expiry in their hold times as part of the process validation studies considering how integrated manufacturing steps are with planning the surgical transplant. However, all products need to be stable for the proposed hold times, including shelf-life. FDA noted that the studies did include those hold times, so some stability data is available. Since only (b) (4) lot was held to the full extent of the desired shelf life and that product lot was not manufactured under worst case conditions, it makes analysis more difficult.

- f. The impact of the new container closure is still being evaluated by FDA.

**Meeting Discussion:** The Applicant described how the product was handled when the culture dish is used as the final container. Under those conditions the cell culture dishes containing the drug substance are collected from the incubator, (b) (4) culture medium is collected for release testing, and then (b) (4) medium is replaced as excipients. The culture dishes were transported directly to the operating room in a shipping container. The new container requires different logistics with a longer hold time.

- g. It does not appear that a shipping container label will be on the shipping container. FDA is reviewing whether the documentation that accompanies the shipping container would be adequate, but a container label is generally expected.

**Meeting Discussion:** The Applicant has provided the information that will accompany the (b) (4) cooler. No label will be on the shipping container. The shipping container is handled by GMP facility staff and directly brought to the operating room. FDA will discuss with FDA labeling experts if any additional identifiers will be needed.

- h. We have concerns about the environmental controls in your facility. Specifically, Environmental Monitoring Performance Qualification performed in 2017 after HVAC modifications is limited in scope (only (b) (4) monitoring of ISO (b) (4) ISO (b) (4) and CNC areas), has a short duration (b) (4) and did not establish worst case sampling locations. Additionally, your routine monitoring data is collected under (b) (4) conditions only; the number of sampling locations appears limited. (b) (4) sampling was performed in ISO (b) (4) only and in case of (b) (4) monitoring, it appears to consist of only (b) (4) sample collected at the (b) (4) of open manipulations.

**Meeting Discussion:** The Applicant agreed and stated that routine environmental monitoring under (b) (4) conditions are planned for the ISO (b) (4) cleanrooms. FDA will discuss the Environmental Monitoring program, qualification and routine monitoring during the scheduled inspection.

- i. You have not established effectiveness of your disinfectants. Furthermore, the source material can potentially introduce contaminants to your facility as it is processed at risk before donor screening results are available. This is particularly a concern due to the immunocompromised status of the recipient, high prevalence of some viruses in the population, and lack of controls of potential viral contamination at later stages of production.

**Meeting Discussion:** The Applicant stated that they are in the process of locating an external provider who will conduct this study. The Applicant agreed that additional testing is needed and will provide this information February 2020. FDA will discuss this during the scheduled inspection.

- j. Qualification of your (b) (4) system is limited in scope [only (b) (4) POU tested (none in the (b) (4) particulate data not collected], duration (b) (4) is short, and does not provide assurance that the (b) (4) at the POU in (b) (4) will continuously match ISO (b) (4) air quality level.

**Meeting Discussion:** The Applicant will provide additional testing. This topic will be discussed further during the inspection.

- k. You do not control endotoxin levels in your product contact supplies

except for media components, final containers, and tissue culture implements supplied endotoxin free. We are particularly concerned about the support filters that are included into your final formulation, (b) (4) where (b) (4) were recovered during endotoxin risk assessment.

**Meeting Discussion:** The Applicant stated that the product is tested on day of release. This topic will be discussed further during the inspection.

2. Information regarding major safety concerns.

The review team has not identified any major safety concerns.

3. Preliminary Review Committee thinking regarding risk management. Enzyvant's general approach to risk management appears appropriate. The most significant changes reported in the BLA from how product was manufactured for the clinical studies conducted under IND is a change in container closure to better conform to container closure integrity testing, and a change in manufacturing facility from that used to supply clinical data on safety and efficacy. The impact of that change is still being reviewed. The tissue slicer is a critical piece of equipment and has not been fully qualified to demonstrate acceptable operating ranges. Enzyvant is conducting additional testing on the tissue slicer as part of an information request.

**Meeting Discussion:** No discussion on this issue.

4. Any information requests sent and responses not received. Sponsor has provided an updated schedule for when FDA can expect responses to CMC information request sent thus far. Enzyvant is working on responses to 4 separate information requests.

**Meeting Discussion:** No discussion on this issue.

5. Any new information requests to be communicated.

Additional CMC information requests may be needed depending on the responses FDA receives from previous requests. A new CMC information request will be sent shortly.

**Meeting Discussion:** No discussion on this issue.

6. Proposed date(s) for the Late-Cycle meeting (LCM).

Late-Cycle Internal Meeting September 6 1000-1100

Late-Cycle Applicant Meeting September 19 1100-1200