

## Late-Cycle Internal Meeting Summary

**Application type and number:** BLA 125694/0  
**Product name:** onasemnogene abeparvovec-xioi  
**Proposed Indication:** Treatment of Infantile Spinal Muscular Atrophy  
**Applicant:** AveXis, Inc.  
**Meeting date & time:** March 7, 2019, 11:00 AM- 12:00 PM  
**Date of LCM with Applicant:** **March 28, 2019, 1:00 PM- 2:00 PM**  
**Committee Chair:** Andrew Byrnes, PhD  
**RPM:** Candace Jarvis

Link to submission:

(b) (4)

Link to sharepoint site: (b) (4)

### Attendees:

| Discipline   | Name [with credentials (not title)] | Attended meeting? |
|--|-------------------------------------|-------------------|
| Regulatory Project Manager (RPM)                     | Candace Jarvis                      | X                 |
| Chair/ CMC Reviewer / Inspector                      | Andrew Byrnes, PhD                  | X                 |
| Clinical Reviewer                                    | Mike Singer, MD                     | X                 |
| CMC Reviewer   | Angela Whatley, PhD                 | X                 |
| Toxicology Reviewer                                  | Feorillo Galivo, MD                 | X                 |
| OCBQ/DMPQ RPM  | Amanda Trayer                       |                   |
| OCBQ/DMPQ Reviewer                                   | Wei Wang, PhD                       | X                 |
| OCBQ/DMPQ/PRB Reviewer                               | Cheryl Hulme                        |                   |
| Statistical Reviewer of clinical data                | Xue (Mary) Lin, PhD                 | X                 |
| Postmarketing Safety Epidemiological Reviewer        | Deborah Thompson, MD, MSPH, FACPM   | X                 |
| OCBQ/APLB Reviewer                                   | Sonny Saini, PhD                    |                   |
| OCBQ/BIMO Reviewer                                   | Erin McDowell                       | X                 |
| OCBQ/DBSQC Reviewer                                  | Hyesuk Kong, PhD                    | X                 |
| OCBQ/DBSQC Reviewer                                  | Varsha Garnepudi, PhD               | X                 |
| Consult Reviewer(s)                                  | Rainer Paine, MD, CDER/OND/ODEI/DNP |                   |
| OCBQ/DMPQ/Lead Inspector/Consult Reviewer, Team Lead | Deborah Trout, PhD                  | X                 |
| Labeling Reviewer                                    | Oluchi Elekwachi                    |                   |
| Other Attendee(s)                                    |                                     |                   |
| OTAT/DRPM  | Ramani Sista, PhD                   | X                 |

|                    |  |                          |
|--------------------|--|--------------------------|
| OTAT               | Kimberly Benton, PhD                       | X                        |
| OTAT               | Wilson Bryan, MD                           | X                        |
| OTAT/DCEPT         | Lei Xu, MD                                 | X                        |
| <b>Discipline</b>  | <b>Name [with credentials (not title)]</b> | <b>Attended meeting?</b> |
| OTAT/DCGT          | Denise Gavin, PhD                          | X                        |
| OTAT/DCEPT         | Iwen Wu                                    | X                        |
| OBE/DB             | Min (Annie) Lin, PhD                       | X                        |
| OTAT               | Rachel Anatol, PhD                         | X                        |
| OCBQ/DBSQC/QAB     | Suzanne Carter                             | X                        |
| OCBQ/APLB Reviewer | Alpita Popat                               | X                        |
| OCBQ/APLB Reviewer | Carolyn Renshaw                            | X                        |
| OCBQ/APLB Reviewer | John Eltermann                             | X                        |
| OTAT/DCEPT         | Ilan Irony                                 | X                        |
| OTAT/DCEPT         | Tejashri Purohit-Sheth                     | X                        |
| OTAT/DCGT          | Steven Oh                                  | X                        |
| OTAT/DCGT          | Raj Puri                                   | X                        |
|                    |  |                          |

### **Late-cycle internal meeting agenda:**

#### **1. Short summary of the submission.**

BLA 125694 was received on October 1, 2018 and filed on November 28, 2018, with a PDUFA priority review action due date of May 31, 2019. The mid-cycle communication was held on January 29, 2019. The 120 day safety and efficacy updates were received on February 4 and 6, respectively. An advisory committee meeting will not be held.

#### **2. Substantive issues raised during review.**

##### **a. DCGT**

Andrew Byrnes and Angela Whatley

##### **i. Substantive issues to report (major and minor)**

### **Major issues**

- Only a few months of stability information have been submitted for the DS and for the DP commercial presentation. We acknowledge your plans to submit additional stability data by March 31, 2019. We may decide to approve a shorter shelf life than the (b) (4) that you have requested. A PMC will be necessary to provide (b) (4) of stability data in order to support the requested (b) (4) shelf life for (b) (4) DP. You will also need to provide evidence that DP is stable for (b) (4) following manufacture from (b) (4) that has been held for (b) (4).

2. On February 14, 2019, FDA inspectors noted that primary reference standard RS002 had not been extensively bridged to interim reference standard AAV9SMN0613, leading to uncertainty about the (b) (4) of RS-002 and AAV9SMN0613. For (b) (4), there is currently just one data point evaluating the (b) (4) of AAV9SMN0613 relative to RS-002. For (b) (4), there are only a few data points characterizing the (b) (4) of AAV9SMN0613 and RS-002, and some of the data may have been affected by (b) (4) of AAV9SMN0613 and RS-002. You agreed to perform additional assays comparing AAV9SMN0613 and RS-002 using (b) (4) of AAV9SMN0613. Please submit the resulting data to the BLA.
3. The acceptance criteria are not agreed for the following lot release assays:
- a. (b) (4): You are currently revising the (b) (4) assay and will propose a new acceptance criterion, as described in submission number 43 (February 26, 2019). Please submit the revised SOP263, the proposed acceptance criterion, and justification for the proposed acceptance criterion.
  - b. (b) (4) The (b) (4) assay is currently under investigation and is suspected of producing inaccurate results. Please provide the investigation report, CAPA, the proposed acceptance criterion, and justification for the proposed acceptance criterion.
  - c. Total protein: In IR #23 (January 7, 2019) and our mid-cycle communication, we listed multiple concerns with the DP total protein concentration that have not been resolved. You informed us in submission number 40 (February 25, 2019) that the total protein assay is currently under investigation. The investigation will determine whether the variability in total protein is due to variability in the assay or the product, and you may take other actions as the result of the investigation. Please provide the investigation report, the proposed acceptance criterion, and justification for the proposed acceptance criterion.
  - d. (b) (4): We tentatively agree with your plan in submission number 43 (February 26, 2019) to set acceptance criteria for these (b) (4) assays at (b) (4) in conjunction with an alert limit that will trigger a nonconformance and investigation if exceeded. Please submit clarification to the BLA that the alert limit for these assays will be (b) (4) and that any such nonconformance investigation will be closed before release of lots.

4. On February 8, 2019, you agreed with FDA inspectors that you will modify the MBRs for DP manufacturing to remove the option for an (b) (4) step. You also agreed that you will provide data from additional lots that have been (b) (4) a (b) (4) time, with the goal of demonstrating that there has been adequate qualification of the (b) (4) sterile filtration process. Please submit the updated MBRs and the (b) (4) process qualification data to the BLA.
5. The (b) (4) assay (SOP-137) has not been adequately validated for specificity. In discussion with FDA inspectors on February 7, 2019, you agreed to validate specificity by demonstrating a negative result when the (b) (4) in SOP-137. Please provide this additional validation report to the BLA.
6. The process for labeling of frozen DP vials has not been validated. Please validate the labeling process and submit the validation report to the BLA.
7. On February 6, 2019, you informed FDA inspectors that a single DP lot may be (b) (4) for different markets. FDA inspectors informed the applicant that (b) (4) of DP intended for the US market must be tested for identity after completion of labeling operations, to comply with 21 CFR 610.14. Please confirm that you will perform identity testing in this manner. Please provide an updated labeling MBR.
8. Based on discussion between FDA inspectors and the firm on February 7, 2019, our current understanding is that the secondary packaging will consist of a carton that can hold between 2 and 9 vials. Please submit shipping validation reports for this new configuration, updated variable labels for the kit, and an updated package insert.
9. Regarding control and qualification of reference materials used in assays, you agreed in submission number 38 (February 19, 2019) to implement an SOP by March 15, 2019 to control inventory and lot-to-lot variability of reference materials. Please submit this SOP to the BLA, and list which reference materials this SOP will apply to.

#### **Minor issues**

- a. The (b) (4) assay (SOP-137) lacks a positive control for (b) (4) activity. In submission number 36 (February 15, 2019), you provided a plan to develop an appropriate positive control method and to add this control method to SOP-137. Please provide the method development report and the updated SOP-137 to the BLA.

- b. The (b) (4) assay (SOP-328) does not include an assay validity criterion for each run to ensure that the (b) (4) of the reference standard falls within an appropriate range. In submission number 28 (January 25, 2019), you agreed to update SOP-328 to incorporate this assay validity criterion and to update the BLA. Please provide the updated SOP-328 to the BLA.
- c. In information request number 21, sent on January 7, 2019, we asked you to provide data demonstrating the robustness of (b) (4) lot release assays. In submission number 38 (February 19, 2019), you replied that you will evaluate the robustness of the (b) (4) assay and that you will submit the additional validation data for this assay to the BLA. You also stated that it is not necessary to evaluate robustness of the (b) (4) assay or the (b) (4) assay. We disagree that it is not necessary to validate the robustness of the (b) (4) assay and (b) (4) assay. Please provide data demonstrating the robustness of the following assays:
- i. (b) (4)
  - ii. (b) (4)
  - iii. (b) (4)
- d. We acknowledge the data in submission number 40 (February 25, 2019) that demonstrates clearance of (b) (4) and undetectable concentrations of (b) (4) in (b) (4). You agreed in submission number 40 to provide an additional process validation report to support that the manufacturing process has sufficient clearance capacity to remove (b) (4) to a safe level for humans. Please provide this additional validation report and more detailed information on the (b) (4) assay procedure and assay qualification.
- e. On February 14, 2019, FDA inspectors asked the firm to develop procedures to ensure that managed documents are promptly updated in regulatory submissions, when needed. The firm agreed to update their procedures and to submit the updated procedures to the BLA, along with any managed documents that need to be updated in the BLA. Please update the BLA accordingly.
- f. On February 7, 2019, FDA inspectors noted that frozen materials are not physically separated in freezers. The firm agreed to separate frozen materials by adding (b) (4) on freezer shelves. The firm agreed to implement these (b) (4) by March 31, 2019 and to submit confirmation to the BLA. When this change has been implemented, please provide confirmation to the BLA that frozen materials are physically separated in freezers.
- g. The acceptance criterion for (b) (4) testing of (b) (4) is “tested.” In submission number 38 (February 19, 2019), you indicated that all parent lots of (b) (4) that have been used in manufacturing have tested negative for (b) (4) and that the parent lots

must test negative before they are used in manufacturing. Please update the acceptance criteria for the (b) (4) test to “negative.”

- h. We agree with the addition of (b) (4) as a (b) (4) supplier. However, we do not agree that PLAN-296 is sufficient, on its own, to qualify additional new (b) (4) suppliers. Please confirm that any future (b) (4) suppliers will be submitted as a PAS.

ii. Review update

All assigned sections of the BLA have been reviewed. The applicant has communicated their plans for resolving each of the major CMC issues that were listed in the mid-cycle communication. For some issues, the applicant has promised resolution at a future date, and as a result certain CMC issues cannot be completely reviewed until we receive further information from the applicant. A number of new issues were discovered during the facility inspections, and we have not yet received responses to these new issues.

Amendments # 37 and 42 (received on February 25 and 26, 2019) are still being reviewed. These amendments contain large amounts of new information about manufacturing process control and recent changes to the manufacturing process. We will communicate with the firm by March 18 if we require additional information.

iii. Review completion date

The primary discipline review is ready for supervisor review, except for:

- Information requests that the applicant has not completely resolved.
- New issues that arose during the inspection of the AveXis (b) (4) and AveXis (b) (4) facilities, which require responses from the applicant.

b. DMPQ

Wei Wang

i. Substantive issues to report (major and minor)

Major issues to report.

- a. Regarding the sterile filtration (b) (4), the firm has not yet provided a written procedure for (b) (4) and a summary report to include (b) (4) validation data.
- b. The firm has not provide a summary report of the Drug Product vial labeling validation.

Minor Issues to report (See IR with issues identified during the pre-license inspection):

- a. (b) (4) storage had not been equipped with refrigerators or freezers for the storage of (b) (4) .
- b. Lack of shipping validation for Drug Product dosed for patients' weight range between 8.5 kg – 13.5 kg.
- c. (b) (4)
- d. A same set of data of impurities in the (b) (4) PPQ lots were reported differently in two sections of BLA submission.

ii. Review update

Primary discipline review memo preparation is mostly finished but need to include summary of the sponsor's responses to the FDA 483 observations.

Establishment Inspection Report (EIR) for the pre-license inspection (PLI) of the (b) (4) manufacturing facility (FEI# (b) (4) , conducted (b) (4) is WIP.

iii. Review completion date

Primary discipline review memo preparation is mostly finished but need to include summary of the sponsor's responses to the FDA 483 observations.

c. DBSQC

Varsha Garnepudi

- i. Substantive issues to report (major and minor)

No substantive issues to report.

ii. Review update

Lot Release Protocol Template received in 125694/0.24 is under review, The LRP template will be updated once the specifications are finalized. Product Testing Plan –draft testing plan in progress.

iii. Review completion date

The review of the lot release protocol is in progress

The testing plan will be finalized once the lot release protocol templates and labeling impacting the testing plan has been finalized

*Hyseuk Kong*

i. Substantive issues to report (major and minor)

Qualification for mycoplasma (b) (4) method will be reviewed for the memo.

ii. Review update

The mycoplasma (b) (4) has not reviewed, as second IR was submitted and AveXis committed to submit an additional qualification report to CBER by 29 March, 2019.

iii. Review completion date

Review memo will be completed within weeks after receiving AveXis's submission. Mid April, tentative.

d. Pharmacology/Toxicology

Feorillo Galivo

i. Substantive issues to report (major and minor)

No substantive issues to report.

ii. Review update

Review of nonclinical studies have been completed.

iii. Review completion date

Review memo has been submitted to the Branch Chief for review

e. Clinical

Mike Singer

i. Substantive issues to report(major and minor)

- One subject in the European study died after a prolonged hospital course which began with onset of respiratory insufficiency about two weeks after receiving the treatment. That subject also experienced seizures and leukoencephalopathy. We have requested the autopsy report for this subject, to help clarify whether a possible association may exist linking the product and these events.

- Use of flat dose for patients weighing (b) (4) kg or higher  
Dosing of product, flat dose for larger patients

\*\* Major issues\*\*\*



ii. Review update

- Reviewing 120-day efficacy and safety updates and financial disclosure information.
- Package insert (label) review and modifications are ongoing.

iii. Review completion date

Mid-April

f. Statistics

Xue (Mary) Lin

i. Substantive issues to report (major and minor)

No substantive issues to report

ii. Review update

All reviews have been completed

iii. Review completion date

Review has been completed, target date mid April

g. BiMO

Erin McDowell

i. Substantive issues to report (major and minor)

No substantive issues to report

ii. Review update

A BiMO inspection is currently in progress at Nationwide Children's Hospital. Inspections at the other sites are complete. No FDA Form 483 have been issued to date. All Establishment Inspection Reports (EIRs) are pending receipt, review, and final classification.

iii. Review completion date

The primary discipline review will be completed after all EIRs are received and reviewed.

iv. Inspectional Findings

| Site | Study   | #<br>Subjects | Location  | Inspection<br>Status                      |
|------|---|---------------|---|---|
| 001  | AVXS-101-CL-101<br>AVXS-101-CL-303<br>AVXS-101-LT-001 | 15<br>3<br>11 | Nationwide Children's<br>Hospital Columbus, Ohio                | Inspection in<br>progress/ EIR<br>pending |
| 005  | AVXS-101-CL-303                                       | 2             | Boston Children's Hospital<br>Boston,                           | Inspection<br>complete EIR                |
| 008  | AVXS-101-CL-303                                       | 4             | Stanford Neuroscience<br>Health Center Palo Alto,<br>California | Inspection<br>complete EIR                |
| 010  | AVXS-101-CL-303                                       | 2             | Nemours<br>Hospital   | Inspection<br>complete EIR                |

h. Epidemiology  
Deborah Thompson

i. Substantive issues to report (major and minor)

No substantive issues to report

ii. Review update

Review of the information received to date is complete

**Current assessment of risk management issues:**

The sponsor's proposed routine pharmacovigilance (PV) activities, routine risk communication, and routine risk minimization measures are adequate and appropriate based on the available safety data. The important identified risks (elevated transaminases and transient thrombocytopenia), important potential risks (cardiac adverse events), and missing information (off-label use and longterm effects of Zolgensma therapy) are adequately addressed by the ongoing and proposed long-term follow-up safety studies.

iii. Review completion date

Review is complete

i. APLB

Sonny Saini

i. Review update

No Review issues at this time. Review is ongoing

ii. Review completion date

Review expected to be complete by the end of March.

3. Review of upcoming timeline/deadlines.

|  |                    |
|--|--------------------|
| Late-Cycle Meeting Internal                    | 07-Mar-2019        |
| Late-Cycle Meeting materials sent to Applicant | 18-Mar-2019        |
| Late-Cycle Meeting with Applicant              | 28-Mar-2019        |
| PMC Study Target                               | 18-Apr-2019        |
| Labeling Target                                | 18-Apr-2019        |
| <b>Action Due Date</b>                         | <b>17-May-2019</b> |

4. Assess status of the review including plans for completing outstanding discipline reviews and any remaining outstanding issues.
5. Reach agreement on Late-Cycle Meeting Materials that will be sent to the Applicant.
6. Come to agreement on the issues to be included on the agenda for the LCM with the Applicant. The timeframes for each agenda item should also be agreed to.
7. **Concurrence:** RPM, Chair, Division Director of the product office

## **Late-Cycle Meeting Agenda to Applicant**

1. Introductory Comments – 3 minutes (RPM/Chair)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 27 minutes. Each issue will be introduced by FDA and followed by a discussion. **Major issues – CMC**

- a. Only a few months of stability information have been submitted for the DS and for the DP commercial presentation. We acknowledge your plans to submit additional stability data by March 31, 2019. We may decide to approve a shorter shelf life than the (b) (4) that you have requested. A PMC will be necessary to provide (b) (4) of stability data in order to support the requested (b) (4) shelf life for DS and DP. You will also need to provide evidence that DP is stable for (b) (4) following manufacture from (b) (4) that has been held for (b) (4).
- b. On February 14, 2019, FDA inspectors noted that primary reference standard RS-002 had not been extensively bridged to interim reference standard AAV9SMN0613, leading to uncertainty about the (b) (4)

(b) (4) of RS-002 and AAV9SMN0613. For (b) (4), there is currently just one data point evaluating the (b) (4) of AAV9SMN0613 relative to RS-002. For (b) (4), there are only a few data points characterizing the (b) (4) of AAV9SMN0613 and RS-002, and some of the data may have been affected by (b) (4) of AAV9SMN0613 and RS-002. You agreed to perform additional assays comparing AAV9SMN0613 and RS-002 using (b) (4) of AAV9SMN0613. Please submit the resulting data to the BLA.

c. The acceptance criteria are not agreed for the following lot release assays:

- i. (b) (4): You are currently revising the (b) (4) assay and will propose a new acceptance criterion, as described in submission number 43 (February 26, 2019). Please submit the revised SOP263, the proposed acceptance criterion, and justification for the proposed acceptance criterion.
- ii. (b) (4) The (b) (4) assay is currently under investigation and is suspected of producing inaccurate results. Please provide the investigation report, CAPA, the proposed acceptance criterion, and justification for the proposed acceptance criterion.
- iii. Total protein: In IR #23 (January 7, 2019) and our mid-cycle communication, we listed multiple concerns with the DP total protein concentration that have not been resolved. You informed us in submission number 40 (February 25, 2019) that the total protein assay is currently under investigation. The investigation will determine whether the variability in total protein is due to variability in the assay or the product, and you may take other actions as the result of the investigation. Please provide the investigation report, the proposed acceptance criterion, and justification for the proposed acceptance criterion.
- iv. (b) (4): We tentatively agree with your plan in submission number 43 (February 26, 2019) to set acceptance criteria for these three assays at (b) (4) in conjunction with an alert limit that will trigger a nonconformance and investigation if exceeded. Please submit clarification to the BLA that the alert limit for these assays will be (b) (4) and that any such nonconformance investigation will be closed before release of lots.

d. On February 8, 2019, you informed the FDA inspectors that, after the Sterile Filtration (b) (4) step, you will no longer need to perform an optional (b) (4) and will modify the MBRs for DP manufacturing

accordingly. You also stated that the (b) (4) (i.e. (b) (4) the Sterile Filtration (b) (4) step (b) (4) is needed and has been performed to manufacture additional Drug Product lots due to deviations (e.g. (b) (4) by (b) (4) outside of action limit). Please submit the updated MBRs and provide a summary report of (b) (4) validation data based on the data from the manufacturing of (b) (4) Drug Product lots to the BLA. Please submit a (b) (4) SOP to the BLA.

- e. The (b) (4) assay (SOP-137) has not been adequately validated for specificity. In discussion with FDA inspectors on February 7, 2019, you agreed to validate specificity by demonstrating a negative result when the (b) (4) in SOP-137. Please provide this additional validation report to the BLA.
- f. The process for labeling of frozen DP vials has not been validated. Please validate the labeling process and submit the validation report to the BLA.
- g. On February 6, 2019, you informed FDA inspectors that a single DP lot may be (b) (4) for different markets. FDA inspectors informed the applicant that (b) (4) of DP intended for the US market must be tested for identity after completion of labeling operations, to comply with 21 CFR 610.14. Please confirm that you will perform identity testing in this manner. Please submit to the BLA an updated labeling MBR.
- h. Based on discussion between FDA inspectors and the firm on February 7, 2019, our current understanding is that the secondary packaging will consist of a carton that can hold between 2 and 9 vials. Please submit shipping validation reports for this new configuration, updated variable labels for the kit, and an updated package insert.
- i. Regarding control and qualification of reference materials used in assays, you agreed in submission number 38 (February 19, 2019) to implement an SOP by March 15, 2019 to control inventory and lot-to-lot variability of reference materials. Please submit this SOP to the BLA, and list which reference materials this SOP will apply to.

### **Clinical**

- j. Please submit the final autopsy report and other relevant results of the subject who died in Study AVXS-101-CL-302 as soon as they become available.

### **3. Discussion of Minor Review Issues – 15 minutes**

## Minor Issues – CMC

- a. In information request number 38, sent on March 6, 2019, we asked you to provide data demonstrating the amount of time required to thaw the 9-vial kit. In submission number 43, received on March 11, 2019, you agreed to perform a study to determine the thaw time of the 9 × 8.3 mL vial kit at both room temperature and refrigerated temperature, and to update the thaw times in the package insert accordingly. Please submit the study report and the updated package insert to the BLA.
- b. The (b) (4) assay (SOP-137) lacks a positive control for (b) (4) activity. In submission number 36 (February 15, 2019), you provided a plan to develop an appropriate positive control method and to add this control method to SOP-137. Please provide the method development report and the updated SOP-137 to the BLA.
- c. The (b) (4) assay (SOP-328) does not include an assay validity criterion for each run to ensure that the (b) (4) of the reference standard falls within an appropriate range. In submission number 28 (January 25, 2019), you agreed to update SOP-328 to incorporate this assay validity criterion and to update the BLA. Please provide the updated SOP-328 to the BLA.
- d. In information request number 21, sent on January 7, 2019, we asked you to provide data demonstrating the robustness of (b) (4) lot release assays. In submission number 38 (February 19, 2019), you replied that you will evaluate the robustness of the (b) (4) assay and that you will submit the additional validation data for this assay to the BLA. You also stated that it is not necessary to evaluate robustness of the (b) (4) assay or the (b) (4) assay. We disagree that it is not necessary to validate the robustness of the (b) (4) assay and (b) (4) assay. Please provide data demonstrating the robustness of the following assays: iv. (b) (4)
  - v. (b) (4)
  - vi. (b) (4)
- e. We acknowledge the data in submission number 40 (February 25, 2019) that demonstrates clearance of (b) (4) and undetectable concentrations of (b) (4) in (b) (4). You agreed in submission number 40 to provide an additional process validation report to support that the manufacturing process has sufficient clearance capacity to remove (b) (4) to a safe level for humans. Please provide this additional validation report and more detailed information on the (b) (4) assay procedure and assay qualification.
- f. On February 14, 2019, FDA inspectors asked the firm to develop procedures to ensure that managed documents are promptly updated in regulatory submissions, when needed. The firm agreed to update their procedures and to submit the

updated procedures to the BLA, along with any managed documents that need to be updated in the BLA. Please update the BLA accordingly.

- g. On February 7, 2019, FDA inspectors noted that frozen materials are not physically separated in freezers. The firm agreed to separate frozen materials by adding (b) (4) on freezer shelves. The firm agreed to implement these (b) (4) by March 31, 2019 and to submit confirmation to the BLA. When this change has been implemented, please provide confirmation to the BLA that frozen materials are physically separated in freezers.
- h. The acceptance criterion for (b) (4) testing of (b) (4) is “tested.” In submission number 38 (February 19, 2019), you indicated that all parent lots of (b) (4) that have been used in manufacturing have tested negative for (b) (4) and that the parent lots must test negative before they are used in manufacturing. Please update the acceptance criteria for the (b) (4) test to “negative.”
- i. We agree with the addition of (b) (4) as a (b) (4) supplier. However, we do not agree that PLAN-296 is sufficient, on its own, to qualify additional new (b) (4) suppliers. Please acknowledge that any future (b) (4) suppliers will be submitted as a PAS.
- j. In information request #29, sent on January 17, 2019, we asked you to qualify the mycoplasma (b) (4) method for the (b) (4). In submission number 26, received on January 23, 2019, you agreed to perform this qualification and to submit the qualification report by March 29, 2019. Please submit this qualification report to the BLA.

#### 4. Additional Applicant Data – 10 minutes (Applicant)

#### 5. Information Requests – 3 minutes

Information Request # 39 due March 22, 2019

Information Request # 40 due March 18, 2019

Information Request # 42 due March 28, 2019

Information Request # 43 due March 21, 2019

- 6. Current assessment of risk management activities, e.g, REMS We have not identified any issues related to risk management. We do not believe that a risk management action (e.g., REMS) is needed at this time.

#### 7. Postmarketing Requirements/Postmarketing Commitments – 2 minutes

As indicated in section 2 comment a, a PMC will be necessary to provide additional DS and DP stability data.

Based on currently-available information, we do not anticipate a need for a PMR.

8. Major labeling issues – 15 minutes

- a. Dosage and Administration section: We do not agree with the proposed weight limit on dosing. We strongly recommend that the dose should be  $1.1 \times 10^{14}$  vg/kg without weight restriction. However, we recommend including the following:
  - i. Administration of ZOLGENSMA to premature neonates before reaching full term may adversely affect neurological development, due to the concomitant treatment with corticosteroids. Therefore, delay administration of ZOLGENSMA until the corresponding full term age is reached..
- b. Following the Indication Statement: Limitation of Use: The benefit / risk profile of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanently ventilator-dependent) is not established.

9. Review Plans – 2 minutes

Review is ongoing based on information received. The final determination will be made after receipt of outstanding information. Responses to all review issues listed in this late cycle meeting agenda should be submitted to the BLA no later than **Wednesday April 10, 2019.**

10. Applicant Questions –10 minutes

11. Wrap-up and Action Items – 3 minutes