

From: Morris, Nevitt
To: jim.wang@Sparktx.com
Cc: Morris, Nevitt
Subject: BLA 125610 Information Request (DMPQ) dated 7/31/17 #2
Date: Monday, July 31, 2017 5:02:30 PM
Attachments:
(File Attachment comment)
image001.png

Hi Jim:

Please respond to the following Information Request for DMPQ no later than August 15, 2017.

DMPQ INFORMATION REQUEST (to be submitted by August 15, 2017 in an amendment to the BLA 125610 file):

1.

Please provide a summary of deviations occurred during Drug Substance (DS), Drug Product (DP) and Diluent PPQ runs. This summary should include a summary of incidents, investigations, results of root-cause analyses and implemented CAPAs (where applicable)

2. Regarding DS manufacturing at Spark Therapeutics Inc.:

2.1. Please provide the following information regarding environmental monitoring

(EM):

2.1.1. Risk assessment for EM

2.1.2. EM frequency for ISO ^(b)₍₄₎ and ^(b)₍₄₎ areas

2.1.3. It is unclear from the information provided in the BLA submission whether

non-viable particulate monitoring is performed during dynamic conditions in Biological

Safety Cabinets (BSCs). Please comment. If not performed, please provide a

justification/rationale for not performing non-viable particulate monitoring during dynamic conditions.

2.2. Please provide cleaning frequency for BSCs and ISO ^(b)₍₄₎ and ^(b)₍₄₎ areas.

2.3. Please provide a summary of cleaning validation (including protocol and data)

for TFF^(b)₍₄₎ system, homogenizer, chromatography system and ^(b)₍₄₎ centrifuge/rotor. Please

ensure that acceptance limits are provided for cleaning parameters evaluated during

validation such as for ^(b)₍₄₎

that you indicated

in the BLA submission. Please also indicate frequency of equipment cleaning and whether

there is any qualified pre-use flushing procedure (e.g., with either WFI or buffer as

appropriate) for TFF systems (to remove storage solution for TFF (b) (4) and potential extractables/leachables).

2.4. We note from the information provided in Section 3.2.a.1 (on page 12) that glassware washer and steam sterilizer have been qualified, but associated qualification reports are not included in the submission. Please provide a copy of those qualification reports.

2.5. Please provide a summary of OQ (or PQ if applicable) for incubators (CO2 and roller bottle incubators), TFF systems (TFF (b) (4)) and (b) (4) chromatography system. Alternatively, you may submit a copy of actual qualification reports (that contain protocol and data).

(Unsigned signature field (Click to sign)) Signature field is unsigned

2.6. Please indicate filter type (e.g., cartridge, capsule), membrane area and manufacturer for TFF and (b) (4) filters used in PPQ run.

2.7. Please describe how you decontaminate and dispose viral biological waste.

Please provide a copy of decontamination validation report. If not validated, please provide a justification/rationale.

2.8. Please provide a qualification report demonstrating effectiveness of facility cleaning/sanitization procedures.

3. Regarding DP manufacturing at (b) (4) :

3.1. Please provide SOP (s) or a detailed description of procedures for the following:

- Segregation, labeling and tracking procedures in shared (multi-product) areas and

- equipment to prevent mix-ups and cross contamination

- voretigene neparvovec 100% DP visual inspection and labeling procedures

- Change over procedures for shared (multi-product) areas and equipment

3.2. Please provide a copy of cleaning and decontamination validation reports for

(b) (4) used in voretigene neparvovec DP and Diluent manufacturing.

3.3. Please provide a floor plan/diagram of equipment/items in the (b) (4) .

3.4. Please provide a copy of a (b) (4) total particle qualification of the (b) (4) at rest and in operation.

3.5. Please provide a copy of decontamination validation report for viral biological waste. If there is no validation, please provide a justification/rationale.

3.6. Please provide a copy of actual microbial retention study report(s) for sterilizing grade/(b) (4) filters - used in voretigene neparvovec DP and Diluent manufacturing.

3.7. Please provide a qualification report for mixing to ensure DP homogeneity

(performed prior to sterilizing grade/(b) (4) filtration). If DP mixing process is not qualified, please provide a justification/ rationale.

3.8. It is unclear from the information provided in your BLA submission whether

there is AQL sampling for DP 100% visual inspection. Please comment and provide

associated acceptance limits. If there is no AQL sampling, please provide a

justification/rationale. Please also indicate the total qualified time for DP visual inspection and labeling.

3.9. We note from the information provided in the certificate of analysis (COA) for

(b) (4) 13 mm stoppers (COA-NO. (b) (4) for 13 mm Serum (b) (4) Stopper attached

to Section 3.2.P.7 Container Closure System) that these stoppers are indicated as

(b) (4) - sterilized (ready to use). We also note that (b) (4) stoppers are (b) (4)

(b) (4) at (b) (4) prior to use in the filling of voretigene neparovvec DP in (b) (4)

(b) (4) (Section 3.2.P.7 Container Closure System and pages 69-71 /228 of (b) (4)

Batch Record submitted with the BLA submission). Therefore, it is unclear why steam

sterilized stoppers are sterilized again ((b) (4) at (b) (4)). Please

comment and provide a rationale/justification for the additional sterilization of the stoppers

prior to use in DP and Diluent manufacturing.

3.10. It is also unclear from the information provided in the BLA submission whether

sterility test result on the COA of the (b) (4) stoppers (b) (4) at (b) (4)

has been verified for the use in voretigene neparovvec DP manufacturing. Please

comment. If not verified, please provide a justification/rationale.

3.11. Please provide a copy of the study performed at (b) (4) to demonstrate that

(b) (4) does not penetrate the closed DP container closure system during (b) (4).

4. Diluent Manufacturing at (b) (4):

4.1. Please provide your qualification report for mixing to ensure diluent homogeneity.

If diluent mixing process is not qualified, please provide a justification/ rationale.

4.2. It is unclear from the information provided in the BLA submission whether there is AQL sampling for diluent 100% visual inspection. Please comment and provide associated acceptance limits. If there is no AQL sampling, please provide a justification/rationale. Please also indicate the total qualified time for diluent visual inspection and labeling.

Thanks, and please acknowledge receipt of this Information Request email.

Nevitt

Nevitt Morris

Nevitt
Morris,
RN,
BSN,
BS
Consumer
Safety
Officer
Office
of
Tissues
and
Advanced
Therapies
Center
for
Biologics
Evaluation
and
Research
(CBER)

U.S.
Food
and
Drug

Administration
Building
71,
Room
4207
10903
New
Hampshire
Avenue
Silver
Spring,
MD 20993
Phone: (240)
402-8269
Fax: (301)
595-1303
Nevitt.Morris@fda.hhs.gov

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED
AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND
PROTECTED
FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person
authorized to deliver
the document to the addressee, you are hereby notified that any review,
disclosure,
dissemination, copying, or other action based on the content of this
communication is not
authorized. If you have received this document in error, please
immediately notify the sender
immediately by e-mail or phone.