

From: Jim Wang
To: Morris, Nevitt
Subject: RE: BLA 125610 Information Request CMC 9/1/17
Date: Friday, September 01, 2017 10:45:02 AM
Attachments: image001.png

(File Attachment comment)

Good morning Nevitt. Got it and will pass it along.
Will you also let me know if you can share any information about topics to be discussed at our mid-

cycle review meeting as well as general focus area/issues to be addressed at the FDA advisory committee meeting.
Thank you and Have a great Labor Day weekend!
Jim

From: Morris, Nevitt [mailto:Nevitt.Morris@fda.hhs.gov]
Sent: Friday, September 01, 2017 10:37 AM
To: Jim Wang <jim.wang@sparktx.com>
Cc: Morris, Nevitt <Nevitt.Morris@fda.hhs.gov>
Subject: BLA 125610 Information Request CMC 9/1/17
Importance: High

Hi Jim:

We have the following Information Request for Spark Therapeutics. Please address the items below by Friday, September 8, 2017.

CMC information request:

a.
Please indicate where in the BLA you describe how voretigene neparvovec will be stored and distributed following secondary packaging at (b) (4)

. If this information is not in the BLA, please submit this information to the BLA.

b.
In accordance with 21 CFR 211.84, you must test components used for voretigene neparvovec manufacturing prior to approval or rejection for use. To comply with this requirement, you should perform the following tests at a minimum for qualification of components:

i.
You should conduct identity testing of incoming lots of the HEK 293 Master Cell Bank prior to release for use. Please provide a testing plan for confirmatory identity testing on the HEK 293 Master Cell Bank conducted

at Spark. If other tests are required to confirm conformity with written specifications for purity, strength, and quality (see 21 CFR 211.84(d), please add these tests.

ii.

We note that in your response (Amendment 13 received August 11, 2017) to our previous IR dated July 21, 2017, you state that "The FBS is tested as (Unsigned signature field (Click to sign)) Signature field is unsigned

outlined in the MSS (MSS 10015 - FBS) prior to its use in Manufacturing. Samples of the lot being considered for purchase are obtained from the vendor prior to acceptance of the lot and are tested to evaluate (b) (4). However, MSS10015 does not indicate that confirmatory (b) (4) testing are part of the sampling plan for FBS. Please clarify if this confirmatory testing is completed by Spark or a contract lab, and update MSS 10015 to reflect all confirmatory testing completed on FBS lots prior to use in manufacturing. Alternatively, if this testing has not been performed in the past, you should conduct the proposed testing on future lots of FBS prior to use in GMP manufacturing at Spark. Please provide SOPs for the confirmatory assays performed to qualify FBS lots. Samples of the lot being considered for purchase are obtained from the vendor prior to acceptance of the lot and are tested to evaluate (b) (4). However, MSS10015 does not indicate that confirmatory (b) (4) testing are part of the sampling plan for FBS. Please clarify if this confirmatory testing is completed by Spark or a contract lab, and update MSS 10015 to reflect all confirmatory testing completed on FBS lots prior to use in manufacturing. Alternatively, if this testing has not been performed in the past, you should conduct the proposed testing on future lots of FBS prior to use in GMP manufacturing at Spark. Please provide SOPs for the confirmatory assays performed to qualify FBS lots.

c.
In the original BLA submission you stated "Based on the intermediate (b) (4) result, the (b) (4) ". In your response (submitted on August 11, 2017) to FDA information request (sent on July 21, 2017), you stated "(b) (4) step at Spark are listed in the Module 3.2.S.2.3.2". We recommend that you change the naming "(b) (4) " for this (b) (4) buffer used in those Drug Substance manufacturing steps, to differentiate it from the Drug Product Diluent.

d.

In your BLA submission, the label for Drug Substance storage was written as

"Store (b) (4)", which is not consistent with the proposed storage condition

"(b) (4)". Please provide an updated label to BLA.

e.

In response to the recommendation to measure (b) (4) after shipping of the drug product, you responded that the drug product is shipped frozen at

=-65°C and available stability data indicates that product is not altered when

maintained at =-65°C. Please provide the data that supports the conclusion

that (b) (4) when the product is frozen, shipped, and

thawed. For the PPQ DP lot, you determine purity by (b) (4).

Please

clarify if this test is sufficiently sensitive to detect the (b) (4).

f.

We do not agree that you do not need to test the Drug Product as part of shipping validation. Please submit a revised shipping validation plan.

g.

Your proposal (in Response#1 to the Information Request dated July 21 2017)

to set the acceptance limits for Drug Product particulate matter to a level that

is (b) (4)-fold higher ((b) (4))

than that in (b) (4) is acceptable, provided that all DP lots are diluted prior

to administration. Since your rationale for setting the acceptance criteria for

(b) (4) Drug Product is based on your plan to dilute the Drug Product (b) (4)-fold with Diluent at the pharmacy, please set the acceptance

criteria

for particulate matter for the Diluent to (b) (4) levels; i.e., to (b) (4)

(b) (4).

h.

We do not agree with your current practice of pooling crude harvest samples

((b) (4) harvest sample for each sub-lot) for (b) (4)

(b) (4) testing. Please test the harvests prior to pooling. We refer you to the following guidance: 'Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (2010)', which is applicable to viral vectors used in gene therapy. The guidance states that "If multiple harvests are performed for a single lot, testing should be performed on each individual harvest (rather than the pooled harvest) in order to avoid dilution of a potentially contaminated harvest with uncontaminated harvests."

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

Nevitt

Nevitt Morris

Nevitt
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BSN,
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Officer
Office
of
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and
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