

From: Morris, Nevitt
To: jim.wang@sparktx.com; paul.gil@sparktx.com
Cc: Morris, Nevitt
Subject: BLA 125610 Information Request CMC 9.15.17
Date: Friday, September 15, 2017 10:04:46 AM
Attachments:
(File Attachment comment)
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Hi Paul and Jim:

Below is an Information Request from CMC. Please respond to the following Information

Request by Friday, September 22, 2017:

1.

Please reset the acceptance criteria for the following specifications:

a.

pH of (b) (4) Drug Product to (b) (4) There is no clinical/scientific/manufacturing data to support rounding down the pH from

(b) (4) .

b.

(b) (4) , considering the (b) (4) data from all lots manufactured to date.

c.

In vitro relative potency of (b) (4) by (b) (4) assay to (b) (4) , considering the (b) (4) data from Spark lots manufactured to date.

d.

Residual Cs levels to (b) (4) , considering the (b) (4) data from all Spark lots manufactured to date, and the residual Cs levels in the two AAV2hRPE65v2

clinical lots (Lot (b) (4)

) .

2.

Assay Validation and Verification:

a.

Please provide the Verification report for the 'Appearance by Visual Inspection' test by (b) (4) .

b.

Please provide comprehensive validation data for the (b) (4) test to show that the method is suitable and sensitive for

detection of (b) (4) in the test article. Specifically, please provide

information on product-specific qualification; i.e., side-by-side assessment of

the detection limits of positive control (b) (4)

) alone, and when spiked in (b) (4) samples (from AAV2-hRPE65 manufacturing) under the assay conditions used for routine testing.

c.

Please provide validation data for the in vitro assay for (b) (4)

by 9CFR testing to show that the method is suitable and sensitive for detection of (b) (4) in the test article.

Specifically, please provide information on product-specific qualification: side-by-

side assessment of the detection limits of positive control viruses ((b) (4)) alone and when spiked in (b) (4) samples (from AAV2-hRPE65 manufacturing) under the assay conditions used for routine testing.

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d. Please clarify why instrument-to-instrument variability was not assessed as one of the robustness criteria in the Vector Genome Concentration Assay, particularly if the Quality Control Laboratory has (b) (4) (as noted during PLI).

e. For the (b) (4) Assay: We do not agree with the high RSD

((b) (4)) acceptance criteria that were set for precision (repeatability and intermediate) parameter in the validation study. The validation is not suitable

for release and stability testing of a licensed product. Please describe the

variables in the assay that were assessed as part of assay qualification/prevalidation studies, and the assay controls put in place for validation.

f. Please explain the low sensitivity of the validated (b) (4) assay (lowest at (b) (4)

, highest at (b) (4)). Please describe the variables in the assay that were assessed as part of assay qualification/prevalidation studies, and the assay controls put in place for validation.

g. Please report the residual plasmid DNA levels in consistent units. In the

validation study residual plasmid DNA levels is reported as (b) (4) but in

the (b) (4) release testing plan it is reported as (b) (4). In the (b) (4)

release plan, please report the residual plasmid levels as both, (b) (4) and the

(b) (4).

h. Please clarify: SPK-RPE65 Lot (b) (4) is listed as the test sample/test article

in several validation reports (Residual Bovine Albumin by (b) (4), Concentration of Pluronic, Residual (b) (4)).

However, this lot is absent from the Spark Lot History list provided under the

BLA submission (Table 1 in Response to FDA Request for Information dated June 2, 2017 and in the updated copy provided during PLI). If this is a typo,

please identify the lot that was used for the aforementioned validation studies.

i. Please clarify the Limit of Quantitation (LOQ) and the Limit of Detection

(LOD) of the Assay for Concentration of Pluronic by (b) (4). Please note:

The validation report has LOQ listed as (b) (4) in the summary section and in Section 10 [Confirmation of Working Limit of Quantitation (LOQ) and Calculation of Limit of Detection (LOD)], but under Section 11 (Accuracy) the LOQ is reported as (b) (4).

During review of the Deviation Investigation Report DI17-138 during

PLI, it was noted that the LOQ of the assay was being reassessed at the current LOD levels (which is noted as (b) (4) in the validation report). Please update the information in the BLA submission if the LOQ of the assay is now changed to (b) (4), with related details.

3.

Please use at least three or more replicates for each test that measures a CQA of the product in the Qualification Plan for Reference Standards.

4.

Lot (b) (4) selected as the Primary Reference Standard, was reported to have an unusually higher (b) (4) compared to the Interim Reference

Standard and to the other lots made at Spark (b) (4). Please justify qualifying

Lot (b) (4) as the Primary Reference Standard considering that (b) (4) is a

CQA assessed for lot release testing and in stability testing.

Lot (b) (4) as the Primary Reference Standard considering that (b) (4) is a

CQA assessed for lot release testing and in stability testing.

5.

Please provide a comprehensive stability plan for the Primary Reference Standard.

Please include all the planned testing, acceptance criteria and time points.

6.

Please clarify:

a. The upper specification limit for residual Cs that was set for IND studies.

The value listed in Table 1 (last row) in the FDA Request for Information of 05

July 2017 is (b) (4) (which amounts to (b) (4)). Based on

the lot release data for the (b) (4) CHOP lots (reported in Table 1 FDA Request for

Information of 05 July 2017), all lots would have failed this specification as

they were vialled at (b) (4) and reportedly contained between (b) (4) of Cs.

b.

The AAV2-RPE65 lot used in the device compatibility study titled

'Recovery

of AAV vector genomes and functional activity using Bausch & Lomb Storz 39G clinical administration device for use with AAV2-hRPE65v2' authored by

Wright and Zeleniaia, dated 31 Oct 2007 (in Section 3.2R).

The Lot listed in the report (on page 3 of the report under Materials Section:

AAV2-hRPE65v2 Lot (b) (4) is absent from the Spark Lot History list provided under the BLA submission (Table 1 in Response to FDA

Request for Information dated June 2, 2017 and in the updated copy provided

during PLI). Were retains of AAV2-hRPE65v2 Lot (b) (4) tested for Pluronic content using the (b) (4) validated assay? Please report on

the Pluronic content for this lot.

7.

In BLA submission 3.2.S.2.2.2 Description of Manufacturing Process, "Step (b) (4): Buffer

Exchange by (b) (4), Formulation and (b) (4) Filtration": you states that

"Following (b) (4) P188 is added to the (b) (4) to achieve a final concentration of 0.001%". Please describe how the (b) (4) P188 is added to reach the accurate final concentration of 0.001%. Please provide a SOP for this manufacturing step.
Thanks, and please acknowledge receipt of this Information Request via email reply.

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

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