

(File Attachment comment)

From: Paul Gil

To: Morris, Nevitt

Subject: Re: BLA 125610 Spark Therapeutics/CMC Information Request 11.17.17

Date: Friday, November 17, 2017 4:41:47 PM

Attachments: image001.png

Hi Nevitt,

I acknowledge receipt. Have a nice weekend.

Paul

----- Original Message -----From:

"Morris, Nevitt" <Nevitt.Morris@fda.hhs.gov>

Date: Fri, November 17, 2017 4:29 PM -0500

To: Paul Gil <Paul.gil@sparktx.com>, Jim Wang <jim.wang@sparktx.com>

CC: "Morris, Nevitt" <Nevitt.Morris@fda.hhs.gov>

Subject: BLA 125610 Spark Therapeutics/CMC Information Request 11.17.17

Hi Jim and Paul:

Below is the CMC Information Request that includes issues discussed at the

November 16, 2017 CMC Telecon between Spark Therapeutics and the FDA.

Also

included, in section 4, are additional Information Requests that were not discussed at

the telecon. Please provide a response to all the Information Request items

by Close of Business on Monday, November 20, 2017. Please also acknowledge this email Information Request.

CMC issues discussed with Spark at the Telecon of Nov. 16, 2017:

1.

Regarding the (b) (4) DP lot release specifications:

a.

Given that there is no clinical data to support the proposed broad acceptance

criteria for the three potency assays, the acceptance criteria should be tightened. If a (b) (4) DP tests at the lower limit for each of these parameters, it

will pass your lot release criteria, but provide no assurance of potency. We have

the following recommendations based on the data presented in the BLA for the

clinical and PPQ lots:

(1) We recommend that the In Vitro Relative Potency of (b) (4) by (b) (4) Assay (b) (4) have an acceptance criterion of between (b) (4)

as this is reflected by the data submitted in the BLA for the PPQ lots ((b) (4) (b) (4)), and this also reflects the data from the

clinical

lot tested with this assay in the comparability study. However, due to the

limited amount of lot release data available, we would accept a lower limit of (b) (4) and the upper limit that you have suggested ((b) (4)).

(2) We accept the revised acceptance criteria for the In Vitro Relative Potency of (b) (4) Assay of (b) (4), which is based on the

(b) (4). While, the clinical lot was within this range (1.06), the lower limit you are proposing is (b) (4) of the clinical lot, so this criterion could be tightened as you acquire more data.

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(3) We have recommended that the acceptance criteria for the (b) (4) be revised to more closely reflect the PPQ and clinical lots

(i.e., in line with the (b) (4) see Nov 3 IR). However, as you have limited lot release data, we are willing to consider the stability data (as presented in Table 1 and Table 2 in the response to the

Nov3 IR submitted on Nov 11). We discussed the following at our Nov 16, teleconference:

(a) We do not agree that the data for the clinical and PPQ lots supports the (b) (4) ratio generated using addition assay data presented in the Nov 11 response to our Nov3 IR.

(b) We acknowledge that the variability in the assay reflects on the (b) (4) that is reported as (b) (4).

With this in mind, we would consider a specification for (b) (4) that is based on the (b) (4) as a stand-alone test, rather than a ratio of vg/IU. Accordingly, please convert the (b) (4) data for the lots reported in the BLA to justify the specification, and submit for review. As discussed, we would be concerned if the variability was greater than  $\pm 0.5$  log.

(c) If you revise the specification to report (b) (4) as (b) (4), rather than

as the (b) (4), the (b) (4) should still be reported for each lot to gain additional data for the purpose of product characterization.

b.

Considering the variability in the (b) (4) assay, and the wide acceptance criteria set for the in vitro relative potency of (b) (4)

by

(b) (4) assay, the (b) (4) Release Plan should include an additional relevant measure of potency; i.e., the (b) (4) potency assay, to assure the agency

that a relevant high quality (b) (4) will be released for the manufacture of every DP lot.

c.

Please confirm that the revised acceptance criteria for pH, (b) (4) set for

Drug Product also apply to the Diluent.

d.

Please submit a revised Lot Release Protocol based on the revised acceptance criteria for lot release specifications.

e.

Please revise specifications in all relevant sections of the BLA.

2.

Expiration date and post-approval stability protocol:

a.

We agree with your proposed shelf life as (b) (4) and

18 months for the Drug product.

b.

The revised post marketing stability protocol should include revised acceptance criteria in accordance with lot release specifications.

c.

Please submit a revised post marketing stability protocol in the BLA to include:

i)

Stability testing on the DS and DP on the next (b) (4) lots, then on one lot every (b) (4) or as use dictates as proposed in the original BLA. As discussed, the stability studies may be performed at (b) (4) only.

ii) Please include additional potency tests in the stability protocol specifications, including the In Vitro Relative Potency of (b) (4)

by (b) (4) Assay (b) (4); the In Vitro Relative Potency of (b) (4) Assay, and the (b) (4); in addition to the assays proposed in the original BLA submission on the stability for both drug substance and drug product.

3.

Please commit to the following post marketing commitments (CMC). Please provide proposed dates to complete:

a.

Perform shipping validation studies for the DP from the distributor to a clinical site, using a worst-case scenario. This should be completed within 3 months of approval, if the BLA is approved.

b.

Complete and submit data for the verification studies for the (b) (4)

(b) (4) tests for particulate matter for Drug Product and Diluent. We note that the study reports are expected in late December, please submit the data when it is available as supplements to the BLA, if approved.

c.

Collect additional assay performance and lot release data to revise the acceptance criteria for DP (b) (4) lot release specifications to tighten specifications if the BLA is approved, for the following tests:

i. in vitro relative potency of (b) (4) assay

ii. in vitro relative potency of (b) (4) by (b) (4)

iii. (b) (4)

iv. (b) (4)

v. (b) (4)

4.

Additional information requests not discussed on Nov 16th:

a.

Please provide a plan to the BLA for how and when you will submit the Continued Process Verification (CPV) study reports for your CPV studies on drug substance and drug product manufacturing.

b.

Please provide data to support your proposal to extend the hold time for the

(b) (4) to the BLA. If this data

is not available, please revise the hold time to (b) (4) to reflect the supporting data submitted to the BLA.

C.

Please send a brief description of the (b) (4) assay referenced on the updated MSS 00179 submitted in amendment 41. In the description please define the reagents (such as (b) (4)) that contribute to the (b) (4) identity.

d.

The plasmids used to make your product are critical components for manufacturing, and stability is important to continued manufacture of a quality product. You should plan to conduct stability studies on the

(b) (4)

Master Cell Banks (MCB) used for plasmid manufacture. Please submit a stability testing plan to the BLA, which will ensure the MCBs are suitable for

their intended use for the duration they are used in manufacturing.

Thanks,

Nevitt

Nevitt Morris

Nevitt Morris, RN, BSN, BS

Consumer Safety Officer

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