

Hithe, Darlene

From: Hithe, Darlene
Sent: Thursday, March 12, 2009 1:03 PM
To: 'Pakulski, John'
Cc: Miller, Daryll L; Gemignani, Helen S
Subject: Request for more information regarding testing

Dear John,

Your BLA is under review by CBER and we have the following comments in regard to testing. Please submit your response as an amendment to the BLA by April 10, 2009, in order to avoid an extension of the reveiw clock.

- 1. Mycoplasma testing of control cell fluids is required by 21CFR 610.30. According to the BLA Section 3.2.S.2. Manufacture, Subsection 4.1 “Bulk Virus Production Controls”, it seems the spent media from Production control cells is not tested for Mycoplasma. Please comment.
- 2. Water (Residual Moisture) was tested by –(b)(4)-- - MTH-729 for the Lyophilized Intermediate Raw Material and MTH-732 for the Finished Product, Adenovirus tablets, Type 4 and Type 7.

Please indicate the number of sample extractions performed and the number of titrations performed on each extract along with the procedure in which these are averaged to report the analytical result for the test material. A minimum of -----(b)(4)----- from each extract is suggested.

Please submit information establishing the qualification of the described procedures for the determination of water content of raw material and finished product. Although the general test procedure is described in --(b)(4)---, the suitability of this procedure for this specific non-compendial test article needs to be established. At a minimum, data supporting accuracy and repeatability at the specification level should be submitted.

- 3. Residual Solvents -----(b)(4)-----

Please indicate the number of sample extractions performed and the number of -----(b)(4)----- obtained from each extract along with the procedure in which these are averaged to report the analytical result for the test material. A minimum of -----(b)(4)----- from each extracted sample preparation is suggested.

Please submit information establishing the qualification of the described procedures for the determination of -----(b)(4)----- in the finished product. Although the procedure described in MTH-732 Section 8 is generally consistent with the -----(b)(4)----- the suitability of this procedure for this specific non-compendial test article needs to be established. At a minimum, data supporting accuracy and repeatability at the specification levels should be submitted.

- 4. Microbial Limits Testing - Summary Report for the Validation of Harmonized Microbial Limits Testing for Adenovirus Tablets, Type 7, -----(b)(4)----- Number: Ns-04944589, Page 111 of Section “Control of Drug Product”.
Details of sample preparation were not provided. It was mentioned in the report that the -----(b)(4)----- Since the product is a tablet, please provide details of sample preparation for this study and for testing samples for the Microbial Limits test with details on the number of tablets tested. Please also provide the number of lots tested in this study.
The method was qualified for Type 7 tablets only. Please provide an explanation for not validating

this procedure for Type 4 tablets.

5. -----(b)(4)----- Test - Analytical Method Validation Report Adenovirus Tablets, Type 4 Type 7, -----(b)(4)----- Test, Doc ID ARD_RPT-1849, version 3.0, Page 73 of Section 3.2.P.5. "Control of Drug Product". The purpose of this -----(b)(4)----- test based on -----(b)(4)----- present in tablets is not clear. Specifications of -----(b)(4)----- Test for Drug Product are based on the --(b)(4)-- assay. Please clarify if the -----(b)(4)----- test is performed by the ---(b)(4)-- assay or by -----(b)(4)----- . If the ----(b)(4)----- is evaluated by -----(b)(4)----- -----, how are data translated into infectivity?

6. Infectivity Test (TCID₅₀ Assay) - Summary Report for Validation of a TCID₅₀ Assay used to measure Adenovirus Infectivity, Document No. KVPO0083.R00, Page 40, Section 3.2.P.5. "Control of Drug Product".

Validation was performed using only (b)(4) of type 7 tablets. It is mentioned in the report that the validation of the method using type 4 tablets would be performed later, if necessary. Please comment on the use of only (b)(4) of type 7 tablets to validate a biological assay for a biological product, live virus vaccine. Also provide information on the plans for validation of this method for type 4 tablets.

Precision of the infectivity assays based on virus titration by TCID₅₀ is usually accepted as – (b)(4) when data are used from a single test. Please justify evaluation of precision of this assay using a

(b)(4) standard deviation of log values.

The intra-assay precision specifications on page 7 are shown in standard deviation, whereas results on page 18 are discussed with regard to standard error. As discussed above, evaluation of precision of such assay should be evaluated from -----

----- (b)(4) -----
----- Please re-evaluate data according to this criterion and also evaluate ----- (b)(4) -----

Section 11.2, accuracy studies by ----(b)(4)----- does not demonstrate accuracy of the method. Accuracy of this type of method is relative depending upon the type of cell line used, conditions/passage of the cell line and conditions of the test, such as incubation time. In this case, it should be demonstrated that the method has not changed with regard to cell line, cell passages allowed for titration and conditions of the test from the original test performed on the product used in clinical trials or when it was previously licensed by Wyeth. Alternatively, such assays can be validated for accuracy if a standard and control preparation with known titer is available. Testing the preparation by the method to be validated and getting results within ---(b)(4)-- of claimed titer demonstrate accuracy.

Page 30 of the Report discussed the choice of incubation time. The incubation time of the test should be the same as used in the original test performed on the product used in the clinical trials or when it was previously licensed by Wyeth.

1 Disintegration Test – You perform the Disintegration Test on the finished product. Please justify why you chose the -(b)(4)- Disintegration Test rather than the -(b)(4)- Dissolution Test for the finished product. Please provide actual results in minutes for the disintegration test for simulated gastric fluid TS and simulated intestinal fluid TS disintegrations.

2 Specifications for -----(b)(4)----- - Specifications for -----(b)(4)----- for an individual tablet should be the same as the specification for the assay. Please comment.

3 Please provide the following SOPs, Worksheets, Standards and Reagents to enable us to perform testing-in-support of this BLA.

a. SOPs and Worksheets:

- 1) SOP BPBT0600, Maintenance of (b)(4) Cells
- 2) SOP BPBT0841, Virus Titer Calculations and Statistical Evaluation for Virus Validation Studies
- 3) EPBT00082, Use of -----(b)(4)----- Excel Spreadsheets
- 4) --(b)(4)--- calculation spreadsheets
- 5) Information on release criteria used, such as number of tests per sample, test format etc. in the SOP KPBT0627.R05: Titration of Sponsor's Adenovirus using (b)(4) cells.

b. Standards and Reagents: (Please provide sufficient quantities to perform at least 25 tests for each type).

- 1) Adenovirus 4 and Adenovirus 7 standards for TCID 50 assay.
- 2) Adenovirus 4-Specific Primers and Probe:
 - i. (b)(4)
 - ii. (b)(4)
 - iii. (b)(4)
- 3) Adenovirus 7-Specific Primers and Probe
 - i. (b)(4)
 - ii. (b)(4)
 - iii. (b)(4)
- 4) Primers and Probe for internal standard:
 - i. Forward primer -(b)(4)-
 - ii. Reverse Primer -(b)(4)-
 - iii. Probe -(b)(4)- 5)
 Adenovirus standards:
 - i. -----(b)(4)-----
 - ii. -----(b)(4)-----
 - iii. -----(b)(4)-----

c. Test Samples: 1) Adenovirus 4 Tablet – 50 tablets
 from each of 3 lots 2) Adenovirus 7 Tablet – 50 tablets
 from each of 3 lots

Please consider this e-mail as a formal request for information. No fax or letter will be sent separately.

Best Regards,

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