

**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Product Quality
Division of Manufacturing and Product Quality
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Record of Telephone Conference Call

Date of call: May 13, 2013
Industry: Dynavax Technologies Corporation (Dynavax)
STN: 125428 -HEPLISAV

SUBJECT: Dynavax requested clarification of selected items in the CR Letter issued on February 22, 2013.

Participants:

CBER

Richard Daemer Regulatory Project Officer, Regulatory / DVRPA / CMC2
Marian Major Research Microbiologist / CBER / OMPT / OVRR / DVP /LHV
Priscilla Pastrana Consumer Safety Officer / OMPT / OCBQ / DMPQ / BII
Destry Sullivan Senior Supervisory Regulatory Officer / OMPT / OCBQ / DMPQ / BII

Industry

Elaine Alambra Director, Regulatory Affairs
Jeanne Bonelle Consultant, Acting Senior Director, Quality
Patrick Giljum CMC Consultant
David Novack Senior VP, Operations and Quality
Edie Smith Executive Director, Project Management
William Turner VP, Regulatory Affairs and Corporate Quality Systems

CBER representatives held a teleconference with Dynavax on **May 13, 2013**, to discuss the file and to request clarification regarding the CR Letter items below. The CR Letter comment is in bold font followed by the discussion points. The following items were discussed:

Item 5

Please provide, or have your contract manufacturer, Rentschler Biotechnologie GmbH provide, via an appropriate regulatory mechanism, a complete list of products filled in Building ^(b), Room ^{(b) (4)}, for the Laupheim, Germany facility.

Dynavax noted that this question had been previously discussed between Destry Sullivan

and William Turner. Dynavax further stated that Rentscher, owner of the contract fill/finish facility in Laupheim Germany, would provide a complete list of products filled in their facility directly to FDA/CBER.

Mr. Sullivan stated that this response was acceptable.

(b) (4)



(b) (4)

Item 6

The container closure integrity tests performed in support of the final drug product (DP) container is inadequate, as follows:

- a) The (b) (4) test was not performed under extremes of pressure to simulate worst case conditions.
- b) Positive controls employed as part of the (b) (4) test are not appropriate, in that they do not approach a worst case leak, and do not define an aperture size, or utilize an aperture/defect.
- c) The (b) (4) test does not provide qualification data to demonstrate that it can reliably detect a (b) (4) within test vials that would approach the amount that would migrate into a defective vial with a defect size approaching a critical threshold (i.e., (b) (4)) under your chosen test conditions. Additionally, you have not provided any information regarding positive controls incorporated into the test.

Therefore, please submit results from a container closure integrity test that is performed under worst case conditions and that utilizes appropriate positive controls.

Dynavax stated that CCIT for the vials which store Drug Product will be repeated using the (b) (4) method. The following test conditions are proposed:

(b) (4)

(b) (4)

The (b) (4) for the positive control is (b) (4), and this would also determine the limit of sensitivity using this test method. The (b) (4) represents the (b) (4) during development of the test parameters (b) (4). Multiple positive controls with the (b) (4) will be included during each chamber test.

Dynavax requested the following feedback:

1. The (b) (4) test described for (b) (4). Does the agency agree that (b) (4) represents extreme pressure exposure to simulate worst case conditions?
2. (b) (4) with a certified variance of not greater than (b) (4). Extensive development work with the (b) (4) did not result in (b) (4) using any combination of test parameters (b) (4). This result is also supported by research documented in scientific literature. (b) (4) was attained using the (b) (4) using the proposed test conditions.

Therefore, does the agency accept the use of the (b) (4) as acceptable sensitivity for testing, and confirmation as a positive control result for (b) (4) using this method?

Mr. Sullivan stated that although (b) (4) is not optimal and not consistent with published literature, it appears that Dynavax has done extensive development work to demonstrate that this is the limit of this test as designed. Dynavax should further investigate why you have not observed (b) (4) below this (b) (4), and should investigate other types of defects for use as positive controls. However, given the scope of the development work you have completed, we will accept this for use as a positive control for CCIT for final product vials.