

**APPROVED**

By Katherine Berkhausen at 3:15 pm, Apr 19, 2017

**From:** [Elaine Alambra](#)  
**To:** [Berkhausen, Katherine](#)  
**Cc:** [Agnihothram, Sudhakar](#); [Daemer, Richard J.](#); [Major, Marian](#)  
**Subject:** RE: Telecon Request reg Endotoxin support testing of conformance lots / Preliminary thoughts  
**Date:** Tuesday, April 18, 2017 5:26:43 PM  
**Attachments:** [image001.png](#)

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Dear Katherine,

Acknowledge receipt - thank you for your response. This will help us with our discussions at the telecom on Thursday.

Kind regards,

*Elaine*

Elaine Alambra • Senior Director, Regulatory Affairs • Dynavax Technologies Corporation ☎ Tel: 510-665-0474 ✉ email: [ealambra@dynavax.com](mailto:ealambra@dynavax.com)

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**From:** Berkhausen, Katherine [mailto:[Katherine.Berkhausen@fda.hhs.gov](mailto:Katherine.Berkhausen@fda.hhs.gov)]  
**Sent:** Tuesday, April 18, 2017 1:21 PM  
**To:** Elaine Alambra  
**Cc:** Agnihothram, Sudhakar; Daemer, Richard J.; Major, Marian  
**Subject:** RE: Telecon Request reg Endotoxin support testing of conformance lots / Preliminary thoughts

Dear Elaine,

Thank you for providing the information below. Our reviewers have looked at the information and the questions you provided in preparation of our discussion this Thursday. We have the following responses, followed by some questions.

(b) (4)

[Redacted]

[Redacted]						
[Redacted]						
[Redacted]						
[Redacted]						

[Redacted]

[Redacted]

(b) (4)									

[Redacted]

[Redacted]

[Redacted]


[Redacted]

[Redacted]

[Redacted]

							(b) (4)

Prior information:

- 1) CBER used (b) (4) instead of (b) (4) for testing;
- 2) The product was not adjusted for (b) (4) as this was not indicated as necessary in your SOP;
- 3) CBER’s analyst who ran these results has years of ISO 17025 proficiency reports comparing manufacturer results with those from our (b) (4) testing laboratory, indicating equipment and software differences do not significantly impact results of this compendial assay;
  - a. These proficiency results also indicate (b) (4) use instead of (b) (4) has a minimal impact compared to the use of different (b) (4) reagents; and
- 4) The \* and \*\* on the table previously provided are (b) (4) and (b) (4) recovery specification’, respectively.

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CBER is interested in knowing:

- 1) the dilution scheme used to reach (b) (4);
- 2) if the product was adjusted for (b) (4) in the results provided;
- 3) if an endotoxin specific buffer was used in the determination of the results provided;
- 4) potential reasons for the outlying PPC % recoveries for the 'end' measurements of lot number 1033385 and 1017099; and
- 5) potential reasons to explain CBER's observed greater PPC % recovery for lot number 1033385 than the other two lots whose results were submitted (i.e., 1017099 and 1017100)?

Kind regards,  
-Katherine

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**From:** Elaine Alambra [<mailto:EAlambra@dynavax.com>]  
**Sent:** Friday, April 14, 2017 10:52 AM  
**To:** Berkhausen, Katherine  
**Cc:** Agnihothram, Sudhakar; Daemer, Richard J.  
**Subject:** RE: Telecon Request reg Endotoxin support testing of conformance lots / Preliminary thoughts  
**Importance:** High

Dear Katherine,

So we can all best prepare for our telecom on Thursday (20 Apr 2017), we would like to share some of our preliminary thoughts.

Starting with some very basic assumptions:

1. The FDA followed the Rentschler SOPs.
2. All of the reagents used including the (b) (4) were (b) (4) materials.
3. A (b) (4) was used.
4. The data were analyzed using (b) (4) software.
5. The samples (b) (4) was between (b) (4) before testing.
6. The assays were run at (b) (4)
7. All sample preparation was performed using (b) (4)

Some potential causes we can discuss for the discrepancies in the spike recovery could be:

- Variation in pipetting between labs/operators

- Variable factors including temperature (was the (b) (4) used (b) (4) [redacted] [redacted])
- Variation in (b) (4) the standard and samples (timeframe, solvent or any other kind of buffer used, eg, (b) (4) )
- What was the standard used for spiking? How was the spike done?
- Variations in the dilution range (standard curve prepared from initial (b) (4) [redacted] in the range from (b) (4) [redacted] ?)
- Variation between test kit lots
- (b) (4) - instrument/module variability or software version - different instruments may give different results. Different Reader cause different temperatures e.g.

It would also be very helpful if the Agency could provide the following information before the telecom:

- a) Standard curve; endotoxin concentrations, mean onset times and %CV, R-value, Intercept and slope
- b) Mean onset time for PPC and %CV
- c) The description of the asterisks (\*) used in the table in the email from the Agency dated 06Apr2017 (b) (4) [redacted] \* above the result table, and \*\* %Spike Recovery within the table)

Lastly, based on your own experience with this assay we would appreciate it if you could share whether you have seen similar issues in the past, and your thoughts on what could be causing the difference.

We look forward to a productive discussion.

Sincerely,

*Elaine*

**Elaine Alambra** • Senior Director, Regulatory Affairs • Dynavax Technologies Corporation ☎ Tel: 510-665-0474 ✉ email: [ealambra@dynavax.com](mailto:ealambra@dynavax.com)

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**From:** Berkhausen, Katherine [<mailto:Katherine.Berkhausen@fda.hhs.gov>]  
**Sent:** Thursday, April 06, 2017 11:51 AM  
**To:** Elaine Alambra  
**Cc:** Berkhausen, Katherine; Agnihothram, Sudhakar; Daemer, Richard J.  
**Subject:** Telecon Request reg Endotoxin support testing of conformance lots

Dear Elaine,

CBER performed (b) (4) endotoxin licensing support testing of the Heplisav conformance lots submitted in support of your license application. The samples were tested per your (b) (4) method validation/qualification report at a (b) (4) sample dilution using the same (b) (4) reagent kit. CBER experienced more product enhancement of the positive product control than reported in your laboratory. This disparity in method qualification criteria could delay or prevent the release of product lots post licensing. Therefore, CBER requests a teleconference with those who performed sample testing for the (b) (4) method validation report to determine if there are subtle difference between our methods that could explain the observed differences in positive product control recovery.

Below are the results for comparison. On average, CBER is getting 50% more product enhancement of the PPC. Of the lots tested, Lot 1033385 was the most recent lot produced and provided the most product enhancement. The second table below provides results tested at the maximum valid testing dilution (i.e., (b) (4)) and even though lot 1033385 passed, our PPC % recovery ((b) (4)) was still higher than yours ((b) (4)) tested at (b) (4). Indicating there is a possibility CBER could reject a lot for release, even though it passed your lot release testing. Thus, the main reason for this teleconference request.

(b) (4) test results at sample dilution of (b) (4)

Lot Number	Test Dilution	CBER		Dynavax <sup>†</sup>	
		% Spike Recovery**	Results (b) (4)	% Spike Recovery	Results (b) (4)
1033385	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
1017099					
1017100					

<sup>†</sup> Amendment 125428/0/74 dated February 7, 2017

(b) (4) test results at sample dilution of (b) (4) (CBER's additional data)

Lot Number	Test Dilution	% Spike Recovery**	Results (b) (4)

1033385
1017099
1017100

(b) (4)

We request a telecon with Dynavax to further discuss. We would be available next Wed April 12<sup>th</sup> at 11:00 EST.

Kind regards,

*Katherine*

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