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FDA-CBER-2021-5683-1149588

The review team has the below three question for you regarding the measurement of endotoxins using the (b) (4) LAL procedures. They have requested a response as soon as possible and no later than Friday, August 13, 2021.

QUERY 1

Your procedure for measuring endotoxin in Drug Product (DP) includes a (b) (4) (b) (4) step. While you provide data demonstrating the (b) (4) does not impact the activity of endotoxin that is (b) (4) you have not provided data to evaluate the potential endotoxin-like activity of the (b) (4) (b) (4) Please provide data to address potential endotoxin-like activity of (b) (4) .

RESPONSE 1

(b) (4)

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FDA-CBER-2021-5683-1149589

Literature References

"The Bacterial Endotoxins Test: A Practical Approach" by Karen Zink McCullough 2011 PDA, available upon request

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

None

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QUERY 2

You state that the (b) (4) step is performed to (b) (4) (b) (4) is the usual approach to (b) (4). Please provide data from a (b) (4) (b) (4)

RESPONSE 2

(b) (4)

Literature References

"The Bacterial Endotoxins Test: A Practical Approach" by Karen Zink McCullough 2011 PDA, available upon request

"Pre-clinical immunotoxicity studies of nanotechnology-formulated drugs: Challenges, considerations and strategy" Marina A. Dobrovolskaia Journal of Controlled Release Vol. 220 (2015), pages 571-583, available upon request

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SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

None

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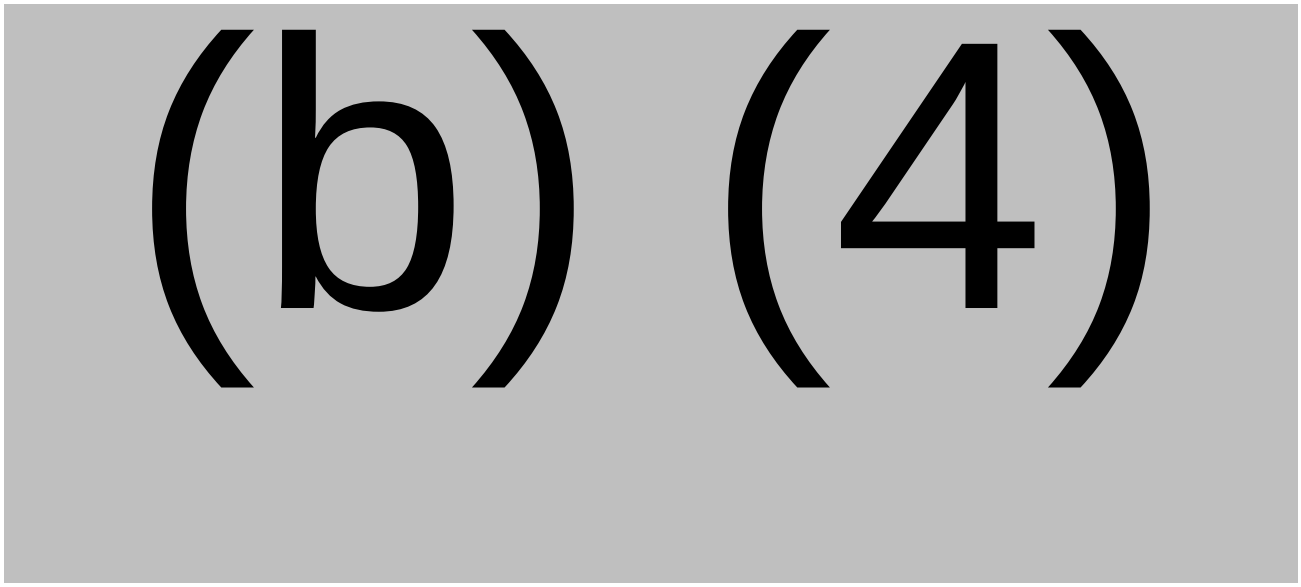
QUERY 3

From the data generated in the preceding request, we ask that you identify a (b) (4) for testing DP within the (b) (4). Please use this information to establish the endotoxin limit and establish a specification for DP endotoxin activity levels for samples that are (b) (4). Please comment and provide a date by which results from the test using (b) (4) samples can be included for DP lot release, together with the endotoxin results for samples (b) (4).

RESPONSE 3



Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

None

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