DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

1401 Rockville Pike
Rockville MD 20852-1448

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Division of Vaccines and
Related Products Applications
Telephone: (301) 827-3070

Dear

The Center for Biologics Evaluation and Research (CBER) is issuing this letter to inform manufacturers of viral vaccine products, being investigated for human use, of recent advancements in testing for adventitious retroviruses and policies developed by CBER to utilize these state-of-the-art tests. For manufacturers of products produced in mammalian cell substrates, the test(s) described below are being requested. For manufacturers of products produced in cell substrates derived from avian species (e.g., hen's eggs, chick embryo fibroblasts, chick embryo dermal cells), the test(s) described below are being requested; however, it is possible that the results will be positive, which may require further characterization of the source of the positive activity. In the latter case, IND sponsors are recommended to contact CBER for further guidance in this regard, prior to undertaking any additional testing. Viral vaccines manufactured in insect, yeast, or prokaryotic cells would not be expected to be contaminated with adventitious retroviruses and would not be subject to the testing described below, unless the culture methods (e.g., medium) or processing introduced animal-derived materials.

Over the last few years, several different PCR-based assays were developed that detect the enzymatic activity of reverse transcriptase (RT) or other polymerases possessing reverse transcriptase-like activity. These PCR-based reverse transcriptase (PBRT) assays have been described in the literature (Silver et al., Nucleic Acids Research, 21:3593-3594, 1993; Pyra, Böni, and Schüpbach, Proceedings of the National Academy of

Sciences, USA, 91:1544-48, 1994; Heneine et al., Journal of Infectious Diseases, 171:1210-6, 1995; Maudru, Cooperating Units, and Peden, Journal of Clinical Virology, 11:19-28, 1998). It is known that polymerases other than retroviral RTs can result in positive test results by these tests. However, methods to minimize "false" positive signals have been introduced (Lugert et al., BioTechniques, 20:210-17, 1996; Chang et al., Journal of Virological Methods, 65:45-54, 1997; and Maudru and Peden, Journal of Virological Methods, 66:247-261, 1997). Additionally, CBER can provide further guidance, upon request.

Whichever PBRT test you choose to employ, its performance should be validated, especially with regards to the lower limit of detection, the specificity (generality for retroviral RTs, negative for non-retroviral polymerases with RT activity), and the reproducibility of the assay. The lower limit of detection ("sensitivity") should be comparable with the published literature.

If positive results are obtained, infectivity studies may be requested to demonstrate that the source of the positive activity is not an infectious retrovirus. It is known that preparations (e.g., allantoic fluid) from chicken cells will give a low positive signal, which is authentic, by these assays. Available data suggest that these positive signals are produced by an expressed endogenous retroviral RT that is not associated with an infectious agent. However, each source of chicken cells may require characterization to demonstrate the lack of an infectious agent associated with the positive activity. CBER can provide further guidance on infectivity studies, upon request.

The stage of manufacture at which you should perform the PBRT test is dependent on the manufacture of your product. For example, products manufactured from primary cells might need to be assessed on a lot-by-lot basis. Whereas, for products manufactured from an established cell bank and viral seed, it may be sufficient to test the cell bank(s) and viral seed(s); you may not be requested to test lot-by-lot. At whatever stage of manufacture you currently perform the conventional RT assay, you should perform a PBRT assay instead. The recommendation to perform a PBRT assay will not otherwise eliminate the need for other testing currently recommended (e.g., transmission electron microscopy of a cell bank).

To facilitate the transition for implementation of this new policy, we recommend the following:

a. For products that are currently in the pre-IND stage of product development, for which the IND will be submitted to CBER subsequent to the date six months from the date of this letter, you will be requested to submit PBRT test results with the original submission of the IND.

b. For products that are currently in the Phase I stage of product/clinical development, and will enter Phase II testing subsequent to the date six months from the date of this letter, you will be requested to submit PBRT test results with the lot release for clinical lots to be tested in Phase II.

c. For products that are currently in the Phases II and III stages of product/clinical development and you intend to submit a PLA/BLA subsequent to the date six months from the date of this letter, you will be requested to submit PBRT test results with the original submission of the PLA/BLA.

d. For products for which a PLA/BLA is submitted prior to six months from the date of this letter, you will be requested to submit PBRT test results as soon as possible, but prior to licensure.

CBER recommends that information regarding retrovirus testing be obtained and submitted to all pertinent applications for investigational products. If you do not currently manufacture a viral vaccine in mammalian or avian cells, this letter is being sent to you for your information. If you do currently manufacture a viral vaccine in mammalian or avian cells, please respond to all corresponding IND(s).

Detailed guidance on requested testing will be provided by CBER, upon request. If you have any questions, please contact Dr. Rebecca Sheets at the above telephone number.

Sincerely yours,

M. Carolyn Hardegree

M. Carolyn Hardegree, M.D.
Director
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