DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

MAR 12 2001

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 the following interim recommendations pertaining to viral vaccine products that are produced in Vero cells and investigated for human use. These recommendations are based on extensive internal discussions, consultation with outside experts, and comments received from the Vaccines and Related Biological Products Advisory Committee (VRBPAC) during the meeting held on May 12, 2000. In general, CBER currently views Vero cells as an acceptable cell substrate for viral vaccines, but has residual concerns sponsors should attempt to address.

CBER recommends that all products derived from Vero cells be free of residual intact Vero cells. If your manufacturing process does not include a validated filtration step or other validated procedure to clear residual intact Vero cells from the product, please incorporate such a procedure into your manufacturing process and submit the appropriate changes to your IND or MF.

Internal discussions and comments from the VRBPAC suggest the need for continued concern about the level of residual Vero cell DNA in products manufactured in these cells. Although the World Health Organization (WHO) currently accepts a limit of residual DNA from continuous cell lines of 10 ng per dose for these products when administered parenterally, CBER wishes to continue considering the level of risk posed by residual Vero cell DNA on a case-by-case basis for viral vaccines. Consideration will also be given to the method of vaccine administration, e.g.,

parenteral, mucosal, or other route. Based on this concern, CBER recommends that you:

a. Measure the amount and size distribution of residual cellular DNA in your final product if you have not done so already. Please submit these results to your IND or MF and describe them in terms of the amount of residual cellular DNA per human dose of final formulated vaccine.

b. Consider various methods (e.g., DNAse treatment) by which the amount and size of residual cellular DNA might be further reduced. Please comment on what you have done or intend to do to consider the introduction of additional DNA reducing methods into your process, as well as the potential impact of such changes on the performance (e.g., immunogenicity) of the product.

Internal discussions and preliminary comments of the VRBPAC also suggest the need for tumorigenicity testing of each manufacturer's Vero master cell bank and the end-of-production-passage-level-cells (EOPC) derived from this cell bank. The term "EOPC" is meant to include cells at the end of a production run, as well as cells cultured from the master or working cell bank to a population doubling level comparable to or beyond cells at the end of production. EOPC should preferably be described in terms of population doublings from your Vero master cell bank. The preferred model for this test is the immunosuppressed newborn Wistar rat, which should be followed for a period of at least five months. Alternative tumorigenicity models may also be appropriate in certain circumstances and their use should be discussed with CBER. If any evidence of tumorigenic potential is demonstrated in these tests, or if the results are inconclusive, the need for additional tumorigenicity testing with cell lysates and/or DNA will also need to be discussed with CBER.

Please submit your responses to your IND(s) or MF(s) within six months from the date of issuance of this letter. Please direct any questions in the interim to Dr. Rebecca Sheets at the telephone number above.

Sincerely yours,

Karen Midthun

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