DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

March 19, 1999

CBER-99-015

BY FACSIMILE AND CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Miles D. White
Chief Executive Officer
Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

WARNING LETTER

Dear Mr. White:

This letter concerns Abbott Laboratories' (Abbott) "Dear Abbokinase Customer" letter pertaining to the supply of Abbokinase, which Abbott disseminated via Western Union Mailgram on March 16, 1999. The Food and Drug Administration (FDA) has reviewed this letter, which constitutes labeling within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(m). We have concluded that the letter violates the Act and applicable regulations as set forth below.

Because your March 16, 1999, "Dear Abbokinase Customer" letter is labeling as defined in 21 U.S.C. § 321(m), you were required to include the full prescribing information for the product [21 C.F.R. § 201.100]. Since the approved product labeling for Abbokinase was not included with the letter, the product is misbranded within the meaning of 21 U.S.C. § 352(f). In view of the current compliance status of your product, the inclusion of the approved product labeling with the letter was critically important. Among other important prescribing information, the approved labeling contains an amended warning statement, with agreed upon, bolded risk assessment information for physicians to consider in deciding whether to use Abbokinase for particular patients. As you are well aware, this information was added to the labeling for Abbokinase to reflect the significant, numerous, deviations from Current Good Manufacturing Practice (CGMP) observed during FDA's recent inspections of Abbott and its supplier of Human Neonatal Kidney (HNK) cells.

In addition, the "Dear Abbokinase Customer" letter contains representations and suggestions that are false or misleading within the meaning of 21 U.S.C. § 352(a), particularly in the absence of the product labeling, which contains the warning statement referenced above. The FDA objects to the following representations and suggestions of the safety of your product in your letter.

a. Your letter states that "Abbott has expanded its manufacturing procedures to include additional testing and validation...." This sentence is misleading. Rather than expanding its procedures, Abbott, in fact, *initiated efforts to rectify deficiencies in* its manufacturing procedures in order to correct the numerous, significant deviations from CGMP observed during FDA's inspection of Abbott last fall.

b. Your letter states that "Abbott has always employed a viral inactivation process (heat treatment) to help ensure that Abbokinase is free of viral contamination." This claim is false or misleading, particularly in light of the letter's claim of full validation of the viral inactivation process, because it suggests that no viruses remain in the product after viral inactivation and hence there is no risk associated with the use of this product. In fact, a heat treatment viral inactivation process does not remove any virus present in the product and therefore does not render the product "free" of viruses. Rather, such a process renders some or all of those viruses that may be present in the product inactive.

c. Your letter states, "Further, during a process characterization study...." The detection of reovirus was found during Abbott's initial in-process control study to test for the presence of viruses, not during process characterization. Abbott implemented this in-process control testing in response to a Form FDA 483 observation which noted that no such procedures for testing in-process product for the presence of adventitious agents were in place, nor had ever been performed. Stating that reovirus was detected during process characterization incorrectly suggests to the reader that the testing was routine and had always been in place, rather than an action recently employed to correct a manufacturing deficiency.

d. With regard to reovirus, your letter states, "...and all test results have been negative, in both cells and finished product." The reovirus was detected in three lots of in-process product (unprocessed bulk harvest). The statement in your letter is misleading because only two lots of HNK cells have been tested for reovirus to date. In addition, while Abbott has informed FDA that those lots of final product currently on the market and lots pending at the Center for Biologics Evaluation and Research (CBER) were tested and found to be negative for reovirus, the polymerase chain reaction (PCR) test used by Abbott has not been validated.

The foregoing constitute the most significant violations and are not intended to be an all-inclusive list of the deficient language in your labeling.

In light of the above-mentioned violations, FDA requests that you provide all recipients of the original letter with amended correspondence that includes as part of the text the full warning statement as it now appears in the approved labeling, along with a copy of the full prescribing information, as well as corrections to the statements in the letter that fully

address the points outlined above. The amended correspondence should be prominently marked and worded to enable a physician to immediately recognize that the letter is a corrected version and not simply a duplicate copy of the March 16th letter with the approved labeling. In addition, we request that you post the amended correspondence on your company's website.

Please submit in writing, within five (5) working days of receipt of this letter, your responses to the violations identified in this letter, including your corrective action plan. Failure to promptly correct these deviations may result in regulatory action, such as seizure or injunction, without further notice.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, you may contact me at (301) 827-6190.

Sincerely,

Steven A. Masiello
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research