DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

JUL 14 1999

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

Robert L. Parkinson, Jr.
President and Chief Operating Officer
Abbott Laboratories
100 Abbott Park Road
Dept. 392, AP6D
Abbott Park, Illinois 60064-6020

Dear Mr. White and Mr. Parkinson:

The Food and Drug Administration (FDA) conducted inspections of Abbott Laboratories' facility at 1401 Sheridan Road, North Chicago, Illinois between October 22 and November 10, 1998 (water for injection) and October 26 and November 20, 1998 (Abbokinase-Urokinase). FDA also conducted inspections of Abbott's supplier of the human neonatal kidney (HNK) cells used in the manufacture of Abbokinase, BioWhittaker, Inc. (BioWhittaker), 8830 Biggs Ford Road, Walkersville, Maryland, between July 14 and 23, 1998, on August 3, 1998, and between October 1 and 20, 1998. Each of these inspections revealed numerous significant deviations from the current good manufacturing practice (CGMP) regulations as well as the Federal Food, Drug, and Cosmetic Act, many of which were outlined in the FDA's January 13, 1999 letter to you.

In January 1999, in order to address public health needs resulting from the shortage of Abbokinase, and because the FDA believed at that time that there may have been a medical need for Abbokinase for the treatment of some patients, the Agency exercised its enforcement discretion regarding Abbott's distribution of Abbokinase for use by physicians in critical care situations. FDA's decision on whether to take enforcement action regarding Abbott's distribution of Abbokinase took into account the results of additional testing of samples of Abbokinase for hepatitis B virus (HBV), hepatitis C virus (HCV), and the human immunodeficiency virus (HIV) using polymerase chain reaction (PCR) methodologies; the FDA's reviews of relevant manufacturing records and procedures; Abbott's willingness to provide healthcare providers with clear notice of the

potential risks associated with the use of Abbokinase; and Abbott's commitment to undertake, within specified time frames, appropriate intermediate and long-term corrective actions on the numerous significant deviations from CGMP identified at Abbott and to ensure prompt correction of the deviations identified at its supplier, BioWhittaker.

On January 25, 1999, the FDA issued an Important Drug Warning to inform healthcare providers of important safety information regarding the use of Abbokinase. Concurrently, as agreed, Abbott updated the labeling for Abbokinase to include information regarding the potential risk for transmission of infectious diseases. Abbott then commenced distribution of nine lots of Abbokinase. Abbott and the FDA also discussed the expectation that Abbott would complete full validation of its heat inactivation process and its newly-implemented PCR testing for HIV, HBV, and HCV before Abbott would distribute additional lots of Abbokinase.

There have been a number of developments since January 1999, which are discussed in greater detail below. Two are most significant. First, the FDA received new information that heightened the Agency's concerns about the deficiencies in the screening of the donors of the HNK cells used to manufacture Abbokinase. Second, on three different occasions between February and May 1999, your staff reported to the FDA that six lots of in-process bulk harvest were found to contain three separate strains of reovirus and a seventh lot was found to contain mycoplasma. The presence of reovirus and mycoplasma in the in-process bulk harvest was discovered as a result of bioburden testing begun by Abbott in December 1998 at the FDA's request to correct deficiencies noted during the FDA's November 1998 inspection.

Since January 1999, the FDA has received 21 letters from Abbott regarding corrective plans or corrective actions in response to the FDA Form 483 issued in November 1998, the reovirus investigation, and the implementation of additional testing of finished lots of Abbokinase for HBV, HCV, HIV, and reovirus using PCR methodologies. In addition, the FDA has met with Abbott representatives on several occasions and participated in numerous telephone conference calls with Abbott concerning the CGMP issues and Abbott's corrective action plan. The Agency has also met with BioWhittaker.

Based on our review of the events that have occurred since January 1999 and Abbott's numerous submissions, the Agency has a number of significant, ongoing concerns regarding the manufacture of Abbokinase that directly impact on the Agency's assessment of the safety of the product. The FDA has concluded that Abbott must take additional action with respect to the following important issues before your corrective actions can be deemed adequate.

I. Heat Inactivation Studies

We have reviewed your April 28, 1999 letter in which you responded to our concerns that the materials used in the viral heat inactivation studies were not representative of the in-process material that undergoes the heat inactivation step during routine manufacturing of Abbokinase. As set forth in our April 8, 1999 letter, the FDA is concerned about whether additional processing of samples prior to the heat inactivation study (" ——————— .) could potentially alter the samples, and whether the material used in the heat inactivation study is comparable to that used during routine manufacturing. As you know, neither Abbott nor the Agency can assess whether Abbott's heat inactivation process can consistently and reliably inactivate viral agents if the material used in the validation study is not comparable to the material used during the actual manufacturing process. The reliability of Abbott's heat inactivation process is of particular importance in light of Abbott's findings of contamination of in-process bulk harvest Abbokinase with reovirus and mycoplasma.

Our continuing concerns and requests for further information with respect to these two issues are listed below.

Process Differences
Samples used in the viral heat inactivation study underwent filtration through a —
— filter and storage at 2-8°C for up to ——— , whereas samples from routine manufacturing are heat inactivated ———————————

1. Please identify the filters used to prepare the samples used for the heat inactivation studies.

2. The recovery of urokinase activity after filtration should be calculated based on the total activity (IU) recovered, not on potency (IU/ml). Please recalculate the percent recovery based on the total activity (IU) recovered.

3. Please provide the percentage of protein recovered following filtration through the ———filters, including all calculations and methods used to determine the amount of protein.

4. Analysis of the filter retains should include an attempt to elute proteins and other components that might bind to the filter. Any protein or other material retained on the filter should be quantitated and identified, if possible.

5. The study used to determine the comparability of the pre-filtrate and post-filtrate was incomplete in that it did not include an analysis of pH, conductance, or non-protein components.

6. The study used to determine the presence of particulates was incomplete in that:

   a. The methods used in the study were not described in detail. For example, it is unclear whether the entire filter was screened.
   b. No assurance was provided that the microscopic method used was an acceptable method for determination of particulates. We note that the method used did not follow USP ——— .
   c. The observed particulates were not definitively identified.
   d. The size of the observed particles was not described.

7. You have provided the SDS-PAGE profiles as assessed by ——— staining of in-process material used in the heat inactivation study after storage at 2-8° C. However, you have failed to provide the SDS-PAGE profile of this material when it was fresh. Please provide a direct comparison of the SDS-PAGE profiles between ——— samples when newly isolated and when stored at 2-8° C for prolonged periods.

Comparability of Materials

In the FDA's April 8, 1999 letter concerning Abbott's heat inactivation studies, we asked Abbott to provide data regarding the comparability of bulk product used in drug manufacturing to the bulk product purified from in-process material that was used as source material in the heat inactivation studies. We stated that analytical testing should include both chemical and physical assays with side-by-side comparisons and that tests should be sensitive to the full range of differences in bulk product that might be observed during the manufacture of Abbokinase. In response, Abbott provided SDS-PAGE profiles from 29 samples of final bulk urokinase.

8. The potency value for ——— samples from lots 48-798-N2 and 48-778-N was estimated at 199,000 IU/mL and 161,000 IU/mL, respectively. However, you failed to indicate whether these values for the ——— samples are representative of, or comparable to, those obtained from production samples. Please provide a characterization of ——— material over an extended manufacturing period in relation to total protein content, potency, specific activity, and other relevant parameters.

9. The comparison of SDS-PAGE profiles from bulk lots of Abbokinase does not support the comparability of bulk product used in drug manufacturing to the bulk product purified from in-process material that was used as source material in the heat inactivation studies because:

   a. SDS-PAGE profiles are not sufficient to establish comparability among lots of bulk Abbokinase. Analytical testing should include both chemical and physical

assays with side-by-side comparisons. Tests should be sensitive to the full range of differences in bulk product that might be observed during manufacture of Abbokinase.

b. Despite the poor resolution of the ——— stained SDS-PAGE profiles from 29 samples of bulk drug, distinct qualitative and quantitative differences in the SDS-PAGE profiles are observed among lots used in the heat inactivation studies and routine lots of bulk drug.

c. No data were provided to assess the significance of differences in the "impurity" profiles with regard to the ability of heat treatment step to inactivate viruses.

10. In addressing the issue of product comparability used to support the heat inactivation studies, particular attention should be placed in assessing product heterogeneity. We believe that the limited amount of data from the SDS-PAGE profiles of the Abbokinase bulk lots indicates that there is significant lot-to-lot variation in the type and level of impurities. Abbott should determine the identity and quantity of the impurities and urokinase fragments, and appropriate specifications should be set.

II. Viral and Bacterial Contamination of In-process Bulk Harvest Material

In February 1999, Abbott reported to the FDA that three lots of in-process bulk harvest were found to contain two different strains of reovirus. The presence of reovirus in the in-process bulk harvest was discovered as a result of bioburden testing begun by Abbott in December 1998 at the FDA's request to correct deficiencies noted during the FDA's November 1998 inspection. During an April 23, 1999 telephone conversation and a subsequent letter dated April 27, 1999, your staff reported that Abbott had again detected reovirus in two additional lots of in-process bulk harvest material. The two newly discovered contaminated lots contained the same two strains of reovirus as those identified in February. In Abbott's May 19, 1999 letter, your staff reported the discovery of a sixth lot of in-process bulk harvest that contained reovirus and one lot contaminated with mycoplasma. The report of the sixth lot contaminated with reovirus is particularly significant because this lot was manufactured in a facility (building M6) separate from the facility where the other five contaminated lots were manufactured (building M3B), and the reovirus strain identified was different than those detected in the other five lots.

On April 13, 1999, in response to Abbott's letters dated February 25 and 26, March 1, 2, 3, 11, 23, and 26, and April 5, 1999, the FDA provided Abbott with an outline of the Agency's general areas of concern regarding Abbott's reovirus investigation.

Following issuance of the FDA's letter, a meeting was held between representatives of Abbott and the FDA on April 19, 1999, to further discuss the unresolved issues.

In the letters dated April 27 and 28, and May 19, 1999, Abbott provided updated information regarding the status of the overall investigation of the reovirus findings. These letters also included information about the newly discovered contaminated lots of in-process bulk harvest material (the 4th, 5th, and 6th lots discussed above). Your conclusion that the reovirus contamination was a "low level" contamination incident confined to a few roller bottles needs to be reevaluated in light of the three new bulk harvest lots, making a total of six lots, found to contain reovirus. At the time of Abbott's May 19, 1999 report on the reovirus contamination, no specific source of the reovirus contamination had been identified.

Reovirus is an adventitious agent that should not be present in the production of Abbokinase. The FDA is very concerned that, since adventitious virus testing began in December 1998, of approximately 35 lots of in-process bulk harvest Abbokinase that have been tested, *six* lots have been found to contain a total of three different strains of reovirus. Despite the FDA's request that Abbott perform neutralization and/or immunofluorescence studies to determine whether additional viruses are present in in-process bulk harvest lots found to be contaminated with reovirus, your staff has declined to perform these studies. In an April 28, 1999 letter, Abbott stated that "neutralization studies do not appear to be warranted" or necessary, and that the data do not justify the need for the studies. Additionally, the FDA has requested that Abbott quantitate the number of viral particles in the contaminated in-process bulk harvest lots. However, Abbott has failed to report these data.

In addition to the new finding of additional lots of unprocessed bulk harvest that contained reovirus, Abbott also reported that one lot of the material, lot 51-728-CY, tested positive for mycoplasma. The positive mycoplasma result has been confirmed by PCR testing by Abbott, and we understand that additional testing is planned. —

———————————————————————————

——————————— Abbott has notified the Agency that, upon completion of the investigation, Abbott intends to destroy all intermediate and final products associated with 51-728-CY and decontaminate the — facility.

Additionally, data obtained by the FDA's Chicago District Office during the inspection that concluded on May 26, 1999, reveals that six of 21 in-process bulk harvest lots contained 200 cfu/10 ml or greater in Abbott's initial bioburden testing. We note, however, that you have not yet established microbial alert and action limits for in-process bulk harvest lots of urokinase, nor have you described any corrective actions taken with respect to the six in-process bulk harvest lots containing high levels of bacteria.

In summary, your testing to evaluate the bioburden in each lot of unprocessed bulk harvest urokinase, initiated in December 1998 in response to FDA's November 1998 inspection, has revealed numerous examples of bacteria, mycoplasma, and adventitious virus contamination. Moreover, your investigation into the sources of the reovirus and mycoplasma contamination has been inadequate in that Abbott has failed to adequately determine the sensitivity of the RT-PCR test; assure that the bulk harvest lots found to contain reovirus are free of additional viruses; and take adequate steps to identify the source of the reovirus contamination. As we explained in our May 27, 1999 meeting, the failure to discover the sources of these repeated instances of contamination is a significant impediment to Abbott's preventing their recurrence. All of these findings provide little assurance that adequate controls are in place to prevent microbiological contamination of Abbokinase, a sterile drug product.

III. PCR Testing of Abbokinase for Reovirus

Please submit the complete results of studies performed to establish the specificity and sensitivity of the RT-PCR assay for reovirus. Based on the information you provided in the summary report, we calculated the level of sensitivity of the RT-PCR assay for final product Abbokinase as 0.4 particles per reaction. This level of sensitivity appears inadequate to ensure a consistently positive signal.

IV. PCR Testing of Abbokinase for HIV, HBV, and HCV

As noted above, in response to the inspectional findings, Abbott committed to conduct HIV, HBV, and HCV testing on finished lots of Abbokinase and to validate those tests. In a letter dated May 25, 1999, the FDA informed Abbott of its conclusion that the overall qualification program for finished product testing using PCR-based testing for HIV, HBV, and HCV is incomplete. The FDA communicated a number of comments and requests for further clarification in that letter. To date, we have not received a written response from Abbott.

V. Future Use of Existing Inventory of HNK Cells

The FDA has carefully reviewed the two options presented in Abbott's February 24, 1999 letter regarding future manufacture of Abbokinase using HNK cells in storage at Abbott that were obtained from BioWhittaker during or before December 1998. Under "Option One," Abbott would [redacted]

[redacted] "Option Two" [redacted]

to a recombinant product.

With regard to Option One, since the close of the inspection of BioWhittaker's facility conducted between July 14 and August 3, 1998, the Agency has on numerous occasions communicated to Abbott and BioWhittaker the Agency's expectations with regard to donor suitability and selection. As of the writing of this letter, however, the significant deviations from good manufacturing practice that FDA has observed still have not been adequately corrected. In any event, during a telephone call on June 25, 1999, your attorney notified the Agency

With regard to Option Two, as you know, in January 1999 the FDA communicated to Abbott its serious concerns about the numerous significant deviations from CGMP regarding the manner in which the HNK cells currently in storage at Abbott were procured, processed, and stored by BioWhittaker and its supplier. Since January, the FDA has received additional information from BioWhittaker that strongly reinforces the Agency's belief that the screening and testing of the mothers and neonates were not consistently or reliably performed. The Agency's concerns were also heightened by a report that Abbott's testing found that five additional lots of HNK cells that met BioWhittaker's specifications failed Abbott's testing. Two lots exhibited abnormal karyotypes (trisomy 18 and 21) and three lots contained virus.

As a result of these and other findings, the Agency has concluded that HNK cells that have been procured by BioWhittaker under its current practices and procedures are adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Accordingly, we have concluded that, based on the information available to the Agency, the HNK cells in Abbott's possession are not suitable for use in manufacturing Abbokinase or any other injectable human drug products. During our July 1, 1999 meeting, we discussed methods by which Abbott could attempt to requalify these HNK cells. These methods include identification, direct questioning, physical examination, and laboratory testing of the mothers of the neonate donors. Additionally, requalification would require obtaining autopsy reports and laboratory test results from the neonate donors.

as we discussed in our May 27, 1999 meeting, the FDA recommends that you identify and qualify an alternative source of HNK cells.

VI. Additional Unresolved Form FDA 483 Issues

Observation 1 – We acknowledge receipt of your May 19, 1999 report from the scale-down study for the chromatography step in the Abbokinase manufacturing process. This report is currently under review by the FDA. We note

that you have not yet submitted the reports from the three remaining virus removal/reduction studies that you agreed to perform in response to observation 1. According to your February 24, 1999 letter, these three reports were to be available to FDA by June 30, 1999.

Observation 5 – You stated that all HNK cells in inventory that were procured from donors who were not tested for anti-HIV and anti-HTLV-I antibodies, and all in-process materials from these HNK cell lots were destroyed on February 12, 1999. Please submit a detailed list of all material destroyed.

Observation 7 – In your February 1999 letter, you enclosed the revised purchased material specification ————————————————————

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Observation 9 – We acknowledge receipt of your May 19, 1999 letter which contains the report of the study performed to determine the lifetime of the ——————— ——————— This report is currently under review by the FDA.

Observation 10 – Please provide the results of your study to evaluate the levels of bacteria, endotoxin, and mycoplasma in each lot of in-process bulk harvest material. Please include the limits that you have established for bacteria, endotoxin, and mycoplasma based on this study.

Observation 14 – In your February 24, 1999 letter, you committed to conducting a study to evaluate the consistency of the Abbokinase bulk drug. The study involved a biochemical comparison of 10 lots of urokinase tested using nine methodologies listed in Appendix Q of your letter. Please submit the results of this study as well as the new testing specifications developed.

Observation 17 – In your February 1999 letter, you stated that your procedures and batch records would be revised to require that filling of the upper chamber of the univials be completed within ——— of lyophilizer unloading. This change would decrease the maximum hold period during which lyophilized, sterile Abbokinase Open-Cath remains unstoppered ———————————————————— You also stated that procedures for media fills would be updated by April 1, 1999 to require that Abbokinase Open-Cath media fills be held in the ——————— for a period supporting the new maximum hold time of ——— We note that, during a recent inspection that concluded May 26, 1999, the FDA's Chicago District office documented, that as of

May 20, 1999, media fills that incorporate the —— hold time in ——— have not been completed.

As discussed in detail above, in January 1999, in order to address public health needs resulting from the shortage of Abbokinase, and because the FDA believed that there may have been a medical need for Abbokinase for the treatment of some patients, the Agency exercised its enforcement discretion regarding Abbott's distribution of Abbokinase for use by physicians in critical care situations. The FDA's willingness to exercise its enforcement discretion took into account not only Abbott's commitment to correct the CGMP deficiencies observed at Abbott and its supplier of HNK cells and its willingness to provide notice to physicians about the risks associated with the use of Abbokinase, but also the Agency's analysis of the risks associated with the lots of Abbokinase to be distributed.

However, as detailed above, since January 1999, the Agency has received additional information that has had an impact on the Agency's determination of the safety of Abbokinase, including, but not limited to, the seven instances of lots of in-process bulk harvest being found to be contaminated with reovirus and mycoplasma; further evidence of the inadequate screening and testing of the mothers and neonates from whom the HNK cells are obtained; as well as the other important unresolved manufacturing deficiency issues outlined above. Current good manufacturing practice for products like Abbokinase that are derived from human source material requires the presence of a number of important, overlapping safeguards in the production process, including adequate donor screening and testing, adequate manufacturing controls, and adequate processes to remove or inactivate transmissible agents. The new information the FDA has received, together with the information the Agency had already obtained through its inspections of Abbott and BioWhittaker, establishes that there are significant and serious deficiencies in each of these layers of protection. Based on the Agency's careful review of the information currently available, we have concluded that at this time the Agency is not prepared to exercise its enforcement discretion regarding Abbott's distribution of Abbokinase unless and until Abbott does the following:

1. Manufactures Abbokinase using HNK cells from an alternate source that have been shown to be obtained, processed, and tested through adequate methods. For HNK cells currently in Abbott's possession, Abbott requalifies the HNK cells;

2. Completes a thorough and adequate investigation of the reovirus and mycoplasma contamination events;

3. Fully validates the methods for detection of HIV, HBV, and HCV in Abbokinase finished product using PCR-based testing; and

4. Fully validates all drug product manufacturing processes for Abbokinase, including heat treatment, viral removal steps, and other testing methods.

Additionally, we note that your ability to address the issues raised in this letter is significantly impaired by the fact that product characterization and manufacturing controls for Abbokinase do not meet levels that are readily and commonly achieved. Therefore, we also believe it is critical that you review and redesign where necessary the manufacturing process for Abbokinase in order to comply with current manufacturing standards. In this regard, Abbott should address the following issues:

1. Abbokinase has not been sufficiently characterized. Currently, a potency test and an immunodiffusion assay are _____.

2. Process and product-related impurities appear to be abundant and have not been identified. Additionally, there is considerable lot-to-lot variation in impurities.

3. The in-process manufacturing controls appear to be inadequate to maintain the consistency of the product.

Please send your reply to Mr. Steven A. Masiello, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Attn: HFM-600. If you have questions about this letter, Mr. Masiello may be reached at (301) 827-6190.

Sincerely,

Kathryn C. Zoon, Ph.D.
Director
Center for Biologics Evaluation
and Research