#1473

ABBOKINASE

Public Citizen

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

February 10, 1999

Dr. Jane Henney, Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Henney:

The purpose of this letter is to strongly urge you to recall immediately all lots of Abbokinase, a widely-used clot-busting drug--$250 million in sales in 1998 for Abbott Laboratories of Abbokinase[1]--and to seize all raw materials and in-process precursors used to make Abbokinase, as recommended by FDA field officials, because of possible contamination with infectious agents. In addition, you must launch an immediate investigation into the extremely suspicious circumstances in which the kidney tissue, from which the drug is made, has been obtained in Colombia. I also urge you to investigate whether charges should be brought against the companies involved for violation of the prohibition against bringing human body parts or tissue into this country identified as "Noninfectious Biological Materials for Medical Research and Use" when, in fact, they are to be used to produce an FDA-regulated product. As FDA personnel have concluded, the law requires them to be identified as "potentially infectious." In addition, there are other apparent violations of Federal law.

From FDA inspection reports and import documents and from interviews with many FDA officials, I have learned the following:

1. Abbokinase has been derived from kidneys taken from deceased newborn babies or aborted fetuses in a hospital in Cali, Colombia (South America) without evidence of adequate informed consent from the parents (no "**verification that the parents of the neonates signed the consent forms for the use of neonatal tissue.**"--this and other bolded quotations in this paragraph are from an FDA inspection report) and without adequate screening and testing of babies or their mothers for infections ("**....no documentation of a questionnaire evaluating the suitability of the mother, nor documentation of an appropriate physical exam of the mother or**

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[1] Abbott *Abbokinase* Use Should Be Limited Due to Infection Risks From Donors. *Food Drug and Cosmetic Reports*, February 1, 1999, page 6.

neonate.") The kidney tissue is then shipped to BioWhittaker, a company in Walkersville, MD for further processing of the material. **("BioWhittaker did not provide a description of the precautions taken to prevent adventitious contamination and cross contamination during the processing of the neonatal tissues and cells--kidney, liver, lung, central nervous system cells are harvested simultaneously-- in the South American facilities.")** Furthermore, the materials were then imported by BioWhittaker into the United States for further processing without being declared through customs as an FDA-regulated commodity and without being identified as "Treat as Potentially Infectious." Both of these omissions violate U.S. law.The material processed by BioWhittaker is then sent to Abbott.

2. After a July 1998 FDA inspection of BioWhittaker, which revealed the above violations in procuring kidneys in Colombia and shipping the kidney cells into the United States, [2] the FDA placed an import ban on the neonatal kidney tissue from Colombia.[3] According to FDA officials, that ban is still in effect. A September 18, 1998 FDA warning letter to BioWhittaker stated that, in violation of FDA law, **"The labeling for shipments of _____states, 'These cells are NON-HAZARDOUS, NON-INFECTIOUS, and NON-RESTRICTED,' when, in fact, this material is potentially infectious."** FDA investigators of BioWhittaker recommended seizure of existing in-process tissue at BioWhittaker, a recommendation which was ultimately overturned by FDA's Washington office.

3. As a result of the findings at BioWhittaker and the recommendation for seizure, the FDA conducted an inspection in October-November, 1998 of Abbott Laboratories itself, in Abbott Park, Illinois, which produces Abbokinase from the kidney tissue partially processed by BioWhittaker. At the Abbott facility, FDA inspectors found serious breaches in the testing and production of Abbokinase such as : **"Supplier's [BioWhittaker] Certificate of Analysis for Human Neonatal Kidney Cells (HNK) indicated cell lot numbers...passed the tests for Hepatitis B surface Antigen ....similar tests [on the same lot] performed by Abbott...was positive for HbsAg (Hepatitis B surface Antigen). No documentation can be located to assure the supplier was contacted [by Abbott] to determine the cause of the non-conformance and to assure corrective actions will prevent future occurrence."** Referring to separation/purification column resins that are part of Abbott's manufacturing process, the investigators found that**: "No validation studies have been conducted to assure that any virus (or other contaminant) potentially retained on the resin or column, would be adequately removed or destroyed prior**

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[2] FDA Form 483: Summary of Inspection of BioWhittaker, Walkersville MD, July 14-16, 21-23 and August 3, 1998. Issued August 3, 1998.

[3] FDA Import Alert: 8/11/98 (IA # 57-B10).

to reuse, preventing cross-contamination between lots."[4]

4. Because of the risk of infection to people using the product, FDA's investigators of Abbott recommended seizure of $100 million worth of raw materials, in-process products and finished products relating to Abbokinase that were located at Abbott facilities in Abbott Park, Illinois.

However, due to pressure on the FDA from radiologists who use the drug in procedures to break up blood clots in the peripheral arteries and veins (a use not approved by the FDA), who alleged that there is no suitable substitute for Abbokinase for this use, the FDA, without doing its own thorough, independent investigation into the suitability of alternative drugs, reversed the recommendations of its own field office and neither seized the potentially contaminated products nor recalled those already in the channels of commerce. A recognized international expert in the use of these drugs, whom I consulted, stated that urokinase (Abbokinase) and tPA, another drug for treating peripheral blood clots, were equally as safe and effective. For other conditions for which Abbokinase is approved, such as treatment of heart attacks or blood clots to the lungs (pulmonary embolism), there is not any dispute that equally safe and effective alternatives exist.

5. Instead of a recall, FDA's CBER (the Center for Biologic Evaluation and Research) Director Dr. Kathryn Zoon sent a letter on January 25th of this year to healthcare providers coincident with the resumption of Abbokinase shipments that had been on hold since December 1998. Her letter stated that:

> "recent manufacturing inspections revealed deficiencies in some of the procedures used by Abbott and its supplier of the human neonatal kidney cells that could increase the risk of transmitting infectious agents...The FDA is not aware of any cases of infectious diseases that can be attributed to the use of Abbokinase. However, **the likelihood that cases of infectious diseases caused by Abbokinase, if any, would have been recognized as such and reported to the FDA is probably very low. Therefore, the actual risk to patients of developing an infectious disease as a result of using Abbokinase is unknown**.(emphasis added). The FDA is recommending that Abbokinase be reserved for only those situations where a physician has considered the alternatives and has determined that the use of Abbokinase is critical to the care of a specific patient in a specific situation..."[5]

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[4] FDA Form 483: Summary of Inspection of Abbott Laboratories, Abbott Park, IL. 10/26-11/20/98. Issued 11/20/98.

[5] Letter from Dr. Kathryn Zoon, Director of CBER in FDA, 1/25/99 to Health Professionals. "Important Drug Warning."

6. Abbott and the FDA are making a travesty of public health by their solution to this serious problem. Instead of seizing the product made from the Colombian kidneys, Abbokinase has been relabeled with, among other information, the following statements:

> **"The procedures used in the manufacture of currently available ABBOKINASE raise concerns regarding the risk of transmission of infectious agents....The kidney cells used in the manufacture of this product were obtained from populations at high risk of a variety of infectious diseases, including tropical diseases....While Abbott has recently instituted a test for HCV [hepatitis C virus] in kidney cells used in the manufacture of currently available lots of ABBOKINASE, this test has not been validated."[6]**

The following is a more detailed review of each of the steps leading to the present situation:

1. <u>FDA Inspection of BioWhittaker in July/August 1998 (7/14-16/98; 7/21-23 and 8/3/98)</u>

(FDA Form 483 inspection summary, dated 8/3/98 is the source)

This suburban Washington facility was inspected in July and August, 1998. FDA inspectors made, in addition to others, the following findings:

"Audits...are not sufficient to assess safety issues in that they do not include:

> **-evidence that the facilities, equipment, personnel, and procedures used in the harvesting of neonatal kidneys in the South American hospital have ever been audited;**
>
> **-verification that the parents of the neonates signed the consent forms for the use of neonatal tissue;**
>
> **-verification into the cause of the termination of pregnancy and the causes of the neonates deaths;**
>
> **-verification of the clinical history (e.g. medical records) of the mother and neonate used to evaluate the potential occurrence of infectious disease and evidence of genetic defects;"**

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[6] Current FDA-approved labeling of Abbokinase.

"....there is no documentation of a questionnaire evaluating the suitability of the mother, nor documentation of an appropriate physical exam of the mother or neonate."

"BioWhittaker was unable to provide documentation of autopsies performed on the neonates despite the fact that the Human Neonatal Kidney Cells Specimen Form 0643 states the date of the autopsy."

"There is no assurance that orphans with unknown mothers are not used as a source of Human Neonatal Kidney Cells."

"BioWhittaker does not segregate Human Neonatal Kidney Cells intended for production of pharmaceutical Urokinase from the following: untested Human Neonatal Kidney Cells from potentially infectious material of human and animal origins (human tumorigenic cell lines, African Green Monkey, Buffalo Green Monkey, Rhesus Monkey, Cynomolgus Monkey, Canine, and Rabbit sources)."

"BioWhittaker failed to verify that the deficiencies noted in the audit report of 1993 for the Human Neonatal Kidney Cells supplier were corrected..."

"BioWhittaker did not provide a description of the precautions taken to prevent adventitious contamination and cross contamination during the processing of the neonatal tissues and cells (kidney, liver, lung , central nervous system cells are harvested simultaneously) in the South American facilities."

"BioWhittaker is receiving Human Neonatal Kidney Cells in the United States that are not being declared [through customs] as an FDA regulated commodity."

"BioWhittaker's shipping containers used to ship Human Neonatal Kidney Cells to _____are not labeled as: 'HUMAN SOURCE MATERIAL: TREAT AS POTENTIALLY INFECTIOUS...' according to their master file."

2. <u>Import Bulletin [Hold] of August, 1998;</u> Following the FDA inspection of BioWhittaker

(I have learned from FDA officials that a hold was then placed on the import into the U.S. of the Human Neonatal Kidney Cells from Colombia which is still in effect)

"Baltimore district has learned through establishment inspection that human neonatal kidney cells (HNK cells) are being imported to the United States for use in the manufacture of an FDA approved drug. Available information indicates the HNK cells are represented during importation

as "Noninfectious Biological Material For Medical Research and Use."

The statement appears on records accompanying the shipments, but not on the product container labels. The product container label states "WARNING: Human Source Material. Treat as Potentially Infectio[u]s."

"Serious safety issues per Section 361 of the Public Health Service Act were raised during Baltimore's inspection which cause concern for the following reasons:

* **Inadequate medical history exists for the mother.**
* **Virology testing procedures have not been validated.**
* **Inadequate testing and documentation exists to demonstrate adherence to the Drug Master File.**
* **Audits of the foreign firm are not adequate to ensure compliance with all Drug Master File requirements."**

3. <u>FDA Warning letter to BioWhittaker September 18, 1998</u>

Following the inspection described above, a recommendation for seizure was made by the Baltimore FDA Office but it was not implemented. A Warning Letter from the FDA to BioWhittaker was sent on September 18, 1998. Included in the letter were the following:

"Investigation of Quality Control InitialTest Failures" is not followed in that, for at least___ lots of ____that initially failed sterility testing, there was no investigation into the cause of the contamination..."

"The labeling for shipments of _____states, 'These cells are NON-HAZARDOUS- NON-INFECTIOUS, and NON-RESTRICTED,' when, in fact, this material is potentially infectious."

"....labeling which routinely accompanies shipments of _____ from your supplier was found by the agency to contain false and misleading statements."

4. <u>FDA Inspection of Abbott in October/November 1998</u>

Following the BioWhittaker inspection, the FDA conducted an inspection of Abbott in the Chicago area. This inspection was done from 10/26 to 11/20/98: Excerpts from FDA form 483 are listed below:

"Human Neonatal Kidney Cells used for the production of urokinase during 1997 and 1998 manufacturing campaigns...have not been tested for the presence

of Hepatitis C virus".

"Human Neonatal Kidney Cell culture supernatant is harvested daily and placed into a chilled tank where it is stored for up to one week prior to further processing. There are no tests performed to evaluate the level of bacteria, endotoxin, mycoplasma or adventitious virus in the in-process bulk at the end of this hold period."

Referring to separation/purification column resins which are part of Abbott's manufacturing process, the investigators found that: **"No validation studies have been conducted to assure that any virus (or other contaminant) potentially retained on the resin or column, would be adequately removed or destroyed prior to reuse, preventing cross-contamination between lots."**

"Supplier's [BioWhittaker] Certificate of Analysis for Human Neonatal Kidney Cells (HNK) indicated cell lot numbers...passed the tests for Hepatitis B surface Antigen....similar tests [on the same lot] performed by Abbott...was positive for HbsAg (Hepatitis B surface Antigen). No documentation can be located to assure the supplier was contacted [by Abbott] to determine the cause of the non-conformance and to assure corrective actions will prevent future occurrence."

Based on the findings of this inspection, FDA's Chicago office recommended seizure of $100 million worth of raw materials, in-process products and finished products relating to Abbokinase that were located at Abbott facilities in Abbott Park, IL. This recommendation was overturned by the FDA in Washington.

5. **FDA Statement of December 11, 1998**

Two days following an Abbott 12/9/98 letter to doctors concerning the shortage of Abbokinase, the FDA released a statement concerning what was to be a temporary hold (not a seizure) of Abbokinase.

"FDA Center for Biologics Evaluation and Research (CBER) will not release lots of Abbokinase until CBER's review of the inspectional findings and information recently submitted by Abbott is complete. During inspections of Abbott, the FDA observed significant deviations from Current Good Manufacturing Practices."

6. Letter of January 25, 1999 from CBER Director, Dr. Kathryn Zoon to Health Professionals.

Instead of acting on the recommendations of FDA's field office in Chicago and seizing Abbokinase finished and in-process products, the FDA was persuaded by

physicians who use Abbokinase that it has unique advantages for the treatment of peripheral (leg) clots, even though it is not approved for this purpose and there is no scientific evidence of its superiority over other thrombolytic (clot-busting) drugs for this purpose. Thus, instead of seizure and recall, the company changed the labeling of the drug and the FDA sent a letter to physicians and other health care providers:

> **" recent manufacturing inspections revealed deficiencies in some of the procedures increasing the risk of transmitting infectious agents....The FDA is not aware of any cases of infectious diseases that can be attributed to the use of Abbokinase. However, the likelihood that cases of infectious diseases caused by Abbokinase, if any, would have been recognized as such and reported to the FDA is probably very low. Therefore, the actual risk to patients of developing an infectious disease as a result of using Abbokinase is unknown. The FDA is recommending that Abbokinase be reserved for only those situations where a physician has considered the alternatives and has determined that the use of Abbokinase is critical to the care of a specific patient in a specific situation...."**

7. Lack of Scientific Evidence that Abbokinase is Safer or More Effective Than Other Thrombolytic (clot-busting) Drugs

The FDA did not actively seek opinions from independent experts on the evidence for the relative benefits of various thrombolytic agents for the treatment of blood clots. Instead, the FDA listened to radiologists who like the drug despite the absence of objective data that it is superior in safety or effectiveness to other drugs. The FDA contacted the professional organizations representing doctors who use the drug for breaking up blood clots in the legs, all of which are likely to have strong ties with Abbott and who similarly liked the drug. Apparently, no effort was made to seek out experts who are not so strongly affiliated with the product.

I wrote to Dr. Victor Marder, a noted hematologist at the University of Rochester, who has published more than 200 medical journal articles, mostly concerning treatments for blood clots, and who has written a chapter on the use of these thrombolytic (clot-busting) agents soon to be published in Hoffman's textbook, *Hematology,* which reviews 230 papers on the use of drugs for clot-busting purposes. I asked him to comment on whether or not there was any scientific basis to support the alleged superiority of Abbokinase, even if it were not possibly contaminated, for the treatment of peripheral blood vessel clots. He replied that in the only published large head-to-head study of Abbokinase vs. tPA, the other clot-busting drug used for peripheral arterial occlusion,[7] "both were equally safe and effective." In his response to

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[7] *Annals of Surgery* 1994; 220:251-268.

me, he also pointed out that "any plasminogen activator [clot-busting drugs such as urokinase, tPA and streptokinase] is equivalent to another until proven otherwise by direct comparison in a properly-performed randomized and blinded trial."[8] The list of alternative drugs for all of the uses of Abbokinase, including peripheral blood clots, is included in Dr. Zoon's letter.

Summary

Given the extraordinary number of gross breaches from the collection and processing of kidneys, and in Good Manufacturing regulations governing the manufacture of Abbokinase, there is a significant likelihood that these products are contaminated. If cases of infection have occurred, the likelihood that they would have been reported to the FDA is, according to the agency, "probably very low." In the absence of evidence of the superiority of Abbokinase over other available products, there is no excuse for these products to stay on the market.

If the FDA does not recall these products, considering the unknown risk of infection and the knowledge that equally effective products exist for treating all of the diseases for which Abbokinase is approved and the unapproved uses as well, what assurance do Americans have for the safety of many other FDA-regulated biologics, such as the blood supply? If blood were collected and processed in the extraordinarily dangerous and sloppy process which has been found to characterize the production of Abbokinase from kidneys obtained under highly suspicious circumstances from infants at high risk of Hepatitis C and other diseases including tropical diseases, and processed in the dangerous way Abbokinase has been, there would be a massive outcry. If the FDA waits until the first documented case of Abbokinase-induced infection occurs to act, it will be making a mockery out of the notion of preventive public health action.

A double standard seems to be operating in this case. The questions raised about the kidney tissue taken from deceased babies in Colombia were serious enough to merit a now six-month hold on importing this tissue. Yet patients are being exposed to potentially contaminated Abbokinase manufactured from kidney tissue imported before the hold which was collected and processed under equally questionable and dangerous methods. It is difficult to come up with a more dangerous scenario for an FDA-regulated biologic.

However, the recent record number of non-biologic drugs which have been recalled in the past two years because of serious safety problems (Duract, Posicor, Redux and Seldane) demonstrates that the problem of inadequate--too late--regulatory action is not limited to biologics.

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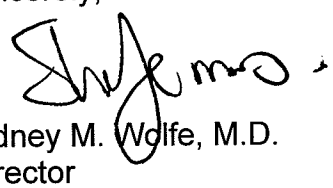
[8] Letter from Victor Marder, M.D. to Sidney M. Wolfe, M.D., February 5, 1999.

An immediate recall of all Abbokinase products should be instituted and prosecution of the companies involved for violation of federal laws should be immediately undertaken.

I look forward to a prompt response to this letter.

Sincerely,



Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 900 Madison Avenue Baltimore, MD 21201 Phone: (410) 962-3396	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Noel L. Buterbaugh	PERIOD OF INSPECTION 7/14-16, 21-23/98 & 8/3/98	C. F. NUMBER 1114298
TITLE OF INDIVIDUAL President of BioWhittaker, Inc	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer	
FIRM NAME BioWhittaker, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 8830 Biggs Ford Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Walkersville, Maryland 21793	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

THE OBSERVATIONS NOTED IN THIS FDA-483 ARE NOT AN EXHAUSTIVE LISTING OF OBJECTIONABLE CONDITIONS. UNDER THE LAW, YOUR FIRM IS RESPONSIBLE FOR CONDUCTING INTERNAL SELF-AUDITS TO IDENTIFY AND CORRECT ANY AND ALL VIOLATIONS OF THE GMP REGULATION.

Human Neonatal Kidney (HNK) Cells

1. Although selection criteria for the mother and neonate are defined as stringent (SOP Human Neonatal Kidney Cells-1.00, page 3), there is no documentation of a questionnaire evaluating suitability of the mother, nor documentation of an appropriate physical exam of the mother or neonate.

2. BioWhittaker failed to identify the actual cause for termination of pregnancy for lots 1722, 1736, 1842, 1860, 1865, and 2018 as specified on the Human Neonatal Kidney Cells Specimen Form 0642. In these cases, the cause for termination of pregnancy was listed as being premature delivery.

3. The cause of the neonatal death was not identified in some cases (e.g. lot 2036 identified the cause of death as prematurity), or it was identified as prematurity and hyaline membrane (lots 1736, 1842 and 1870). Prematurity and hyaline membrane are not causes of death. Furthermore, BioWhittaker was unable to provide documentation of autopsies performed on the neonates despite the fact that the Human Neonatal Kidney Cells Specimen Form 0642 states the date of autopsy.

4. According to the Human Neonatal Kidney Cells Specimen Form 0642, guardian consent may be given for collection of the kidney tissue. However, in a letter to FDA dated November 3, 1989, BioWhittaker stated that cells will be utilized only if written parental consent is obtained. No explanation for the continued use of guardian consent was provided.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Lynette P. Salisbury Barry Cherney	Lynette P. Salisbury, CSO Dr. Barry Cherney, Biologist, CBER	8/3/98

[redacted]

FDA INSPECTION OF BIOWHITTAKER

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

5. Human Neonatal Kidney Cells Form 0642 specifies that "A parental or guardian consent for autopsy and collection tissue is obtained for each donor". The consent form that is used does not inform the parent that an autopsy is to be performed.

6. BioWhittaker did not provide documentation that the procedures used in South America for storage of the Human Neonatal Kidney Cells are followed to ensure their integrity and safety. In particular, documentation of the separation of human neonatal kidney cells from potentially infectious material of human and animal cells was not provided.

7. BioWhittaker did not provide a chart showing a visual representation of the facilities used in the cell isolation process and the flow of material from the time of death of the neonate to the times of cell freezing.

8. BioWhittaker did not provide a description of the precautions taken to prevent adventitious contamination and cross contamination during the processing of the neonatal tissues and cells (kidney, liver, lung, central nervous system cells are harvested simultaneously) in the South America facilities.

9. There is no assurance that orphans with unknown mothers are not used as a source of Human Neonatal Kidney Cells. Human Neonatal Kidney Cells Specimen Form 0642 states in part: "...(in certain cases neonates are orphans and parents are unknown)..." However in a letter to FDA dated November 3, 1989. BioWhittaker stated that the cells will be utilized only if written parental consent is given.

10. Informed Consent for lot 2018 was signed 1 day after harvesting the tissue. Consent is required prior to the harvesting of these Human Neonatal Kidney Cells.

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

TESTING

11. BioWhittaker was unable to verify a statement made in a letter to the FDA dated November 3, 1989 in which BioWhittaker states that [redacted] performs the test on human neonatal kidney cells for the presence of CMV.

12. BioWhittaker has not submitted an Amendment to their Master File OB-MF-3157 since submitting their Annual Report in January 1996. Their Master File documents that the following test kits are used:

- Human Immunodeficiency Virus Type 1 (HIVAB HIV-1 EIA) ([redacted]
- Antibody to Human Immunodeficiency Virus Type 1 (HIVAG-1) ([redacted]
- Hepatitis C Virus Encoded Antigen (Recombinant c100-3, HC- 31, and HC-34) [redacted] HCV EIA 2.0

Package inserts provided during the inspection identify that different kits are used to test the cadaveric blood of the neonate.

- Human Immunodeficiency Virus (HIV-1/HIV-2): [redacted] HIV-1/ HIV-2 3RD Generation Plus EIA
- Antibody to Human Immunodeficiency Virus Type 1 HIVAG-1 Monoclonal [redacted]
- Hepatitis C Virus Encoded Antigen [redacted] HCV EIA 3.0

13. BioWhittaker failed to notify FDA of a change in the testing site for Retrovirus (Reverse Transcriptase) and Hepatitis B Antigen from their facility to [redacted] MD.

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

RETESTING

14. The firm did not follow their retest SOP #1300.1040, entitled: "Investigation of Quality Control Initial Test Failures", for failures due to bacteria contamination that were noted in lots 1722, 1842, 1855, 1860, 1865, and 1870. Form #1165 was not completed as required by the SOP.

15. Bacterial contamination occurred in lots 1722, 1842, 1855, 1860, 1865 and 1870. The firm failed to conduct an investigation into the cause of the contamination.

16. Lots 1842, 1855, 1865, and 1870 passed QC tests for sterility, but were contaminated with bacteria when they were tested in the cell production area for growth in serum containing media. No investigations was initiated to determine why QC's sterility tests failed to detect the contamination.

SHIPPING/STORAGE

17. BioWhittaker is receiving Human Neonatal Kidney Cells in the United States that are not being declared as an FDA regulated commodity. These Human Neonatal Kidney Cells will ultimately be used by [redacted] for the manufacturer of a pharmaceutical product.

18. According to the Master File, BioWhittaker is testing for HIV-1, HBsAg, HTLV-1 and HCV, but not for HIV-2 and Mycoplasma. The current shipping label for Human Neonatal Kidney Cells are labeled as non-reactive for HIV-2 and Mycoplasma. The label contains the statement that the cells are tested and found non-reactive for HIV-2 and Mycoplasma. The firm provided no confirmation that these test are currently being performed in South America.

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

19. There is no assurance that the [redacted] Series Liquid Nitrogen Biological Shipping containers that are used in the transport of the Human Neonatal Kidney Cells preserves the integrity of these cells. The [redacted] containers are used to ship Human Neonatal Kidney Cells from South America to BioWhittaker and also are used to ship the Human Neonatal Kidney Cells from BioWhittaker to [redacted] No temperature/seasonal studies have been performed on the [redacted] There is no documentation to show that the temperature of the cells are checked when they arrive.

20. BioWhittaker failed to provide documentation of the temperature readings of the Liquid Nitrogen tanks used for storage of their Human Neonatal Kidney Cells.

21. BioWhittaker does not segregate Human Neonatal Kidney Cells intended for production of pharmaceutical Urokinase from the following: untested Human Neonatal Kidney Cells from potentially infectious material of human and animal origins (human tumorigenic cell lines, African Green Monkey, Buffalo Green Monkey, Rhesus Monkey, Cynomolgus Monkey, Canine, and Rabbit sources).

22. BioWhittaker's shipping containers used to ship Human Neonatal Kidney Cells to [redacted] are not labeled as: "HUMAN SOURCE MATERIAL. TREAT AS POTENTIALLY INFECTIOUS..." according to their master file.

INVENTORY

23. An examination of the inventory records revealed that a lot of primary Human Neonatal Kidney Cells (lot 1870) identified as contaminated with bacteria remained unsegregated from non-contaminated lots. Lot 1870 was stored together with other lots of Human Neonatal Kidney Cells for 5 months after being found contaminated and before being destroyed.

24. There was no signature on the inventory record sheets for removal of contaminated lot 1870. Furthermore, the specific day in which the ampules of Human Neonatal Kidney Cells were removed from the freezer were not recorded in the inventory record (only the month and year are recorded).

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Lynette P. Salisbury Barry Cherney	Lynette P. Salisbury, CSO Dr. Barry Cherney, Biologist, CBER	8/3/98

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 900 Madison Avenue Baltimore, MD 21201 Phone: (410) 962-3396	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Noel L. Butterbaugh	PERIOD OF INSPECTION 7/14-16, 21-23/98 & 8/3/98	C. F. NUMBER 1114298
TITLE OF INDIVIDUAL President of BioWhittaker, Inc.	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer	
FIRM NAME BioWhittaker, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 8830 Biggs Ford Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Walkersville, Maryland 21793	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

AUDIT REPORTS

25. An audit report of the [redacted] performed on April 22, 1996 documented that the facility is used for safety testing (RT / HIV co-cultivation tests) of primary human neonatal kidney cells intended for research purposes only. However, such cells are used for the production of the drug Urokinase.

26. BioWhittaker has no written record that an audit of their Human Neonatal Kidney Cell supplier had been performed within the last 5 years. The last audit was performed in June 1993.

27. Audits performed at the supplier of Human Neonatal Kidney Cells are not sufficient to assess safety issues in that they do not include:

- evidence that the facilities, equipment, personnel, and procedures used in the harvesting of neonatal kidneys in the South America hospital have ever been audited;

- verification that the parents of the neonates signed the consent forms for the use of neonatal tissue;

- verification into the cause of the termination of pregnancy and the causes of the neonates death;

- verification of the clinical history (e.g. medical records) of the mother and neonate used to evaluate the potentially occurrence of infectious disease and evidence of genetic defects;

- verification that written procedures for the acceptance of fetuses, kidney removal, disaggregation, dispension, freezing, and storage of the Human Neonatal Kidney Cells are followed;

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Lynette P. Salisbury, CSO Dr. Barry Cherney, Biologist, CBER	8/3/98

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 900 Madison Avenue Baltimore, MD 21201 Phone: (410) 962-3396	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Noel L. Batenbaugh	PERIOD OF INSPECTION 7/14-16, 21-23/98 & 8/3/98	C. F. NUMBER 1114298
TITLE OF INDIVIDUAL President of BioWhittaker, Inc.	TYPE ESTABLISHMENT INSPECTED Medical Device Manufacturer	
FIRM NAME BioWhittaker, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 8830 Biggs Ford Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE (Zip Code) Walkersville, Maryland 21793	CITY AND STATE (Zip Code) Same	

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

- verification that appropriate equipment is used for the required testing of the Human Neonatal Kidney Cells and that maintenance and appropriate calibration has been performed (i.e., spectrophotometer, incubators, refrigerators, freezers, thermometers, centrifuge, and vacuum pumps).

28. BioWhittaker failed to verify that the deficiencies noted in the audit report of 1993 for the Human Neonatal Kidney Cells supplier were corrected. The deficiencies included liquid nitrogen daily check logs of the storage tanks and an oven which lacked a temperature recorder.

29. The firm's SOP Human Neonatal Kidney Cells 1.00 entitled: "Processing of Human Neonatal Kidney (HNK) Frozen Ampules" was not followed for the following reasons:

a. Kidney tissue should be washed with [redacted] Solution containing antibiotics. Batch record #'s 1958, 1977, and 2029 do not indicate that these tissues were washed according to the SOP.

b. Kidney tissue should be washed with [redacted] to [redacted] ml of [redacted] Solution. Batch record #'s 1948, 1975, and 2036 indicate that 180 ml was used instead of what was specified in the SOP.

c. Incubate the thioglycollate sterility media at [redacted] C for [redacted] days. Records show that the incubation temperature and times were not followed according to the SOP.

o Batch #1628 incubated for 16 days at 37°C
o Batch #1736 incubated for 17 days at 37°C
o Batch #1965 incubated for 16 days at 37°C

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Lynette P. Salisbury Barry Cherney	Lynette P. Salisbury, CSO Dr. Barry Cherney, Biologist, CBER	8/3/98

IA #57-B10 - Revised 8/11/98, Import Bulletin #57-B10, "Importation of Human Neonatal Kidney Cells From South America Represented As Noninfectious Biological Material For Medical Research And Use"

********** IMPORT BULLETIN**********

Baltimore district has learned through establishment inspection that human neonatal kidney cells (HNK cells) are being imported to the United States for use in the manufacture of a FDA approved drug. Available information indicates the HNK cells are represented during importation as "Noninfectious Biological Material For Medical Research and Use." The statement appears on records accompanying the shipments, but not on the product container labels. The product container label states "WARNING: Human Source Material. Treat as Potentially Infections."

The HNK cells are not declared through Customs as a FDA regulated commodity and are packaged in CryoPac metal cryogenic vessels containing liquid nitrogen.

Serious safety issues per Section 361 of the Public Health Service Act were raised during Baltimore's inspection which cause concern for the following reasons.

* Inadequate medical history exists for the mother.
* Virology testing procedures have not been validated.
* Inadequate testing and documentation exists to demonstrate adherence to the Drug Master File.
* Audits of the foreign firm are not adequate to ensure compliance with all Drug Master File requirements.

All districts, especially Florida district and the Miami Resident Post, should be on the alert for shipments of human neonatal kidney cells from South America in cryogenic vessels represented as "Noninfectious Biological Material For Medical Research and Use."

Should districts encounter shipments of HNK cells from South America, contact one or both of the contact persons listed below for additional information.

CBER Compliance: Jerome Davis, CSO, at (301) 827-6220,
FAX = (301) 443-3874.
Baltimore District: David Gallant, SCSO, at (410) 962-3590,
FAX = (410) 962-2219.

SHIPPER:

^

^

PRODUCT: Human Neonatal Kidney Cells

PRODUCT CODE: 88KIR (Cells, Animal, Human, Cultured)

PAC: 41B800

EXPIRATION DATE: 90 days after date of issue.

KEY WORDS: Cells, Neonatal, Kidney, Human, Tissue, Colombia.

[redacted]

FOI: Purging between ^ ^ is required.

PREPARED BY: Alwin Collins, O & P SDWG, DIOP, (301) 443-6553.

Date Loaded
into FIARS: August 11, 1998

DEPARTMENT OF HEALTH & HUMAN SERVICES

M0065N

Public Health Service

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

CBER-98-026

WARNING LETTER

SEP 18 1998

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Noel L. Buterbaugh
President and Chief Executive Officer
BioWhittaker, Inc.
8830 Biggs Ford Road
Walkersville, MD 21793

Dear Mr. Buterbaugh:

During an inspection of BioWhittaker, Inc., Walkersville, Maryland, on July 14 through August 3, 1998, FDA investigators documented violations of Sections 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and significant deviations from current good manufacturing practices for drug components. The deviations were presented to you on a 29-item list of inspectional observations (Form FDA 483) at the close of the inspection. Specific areas of concern include, but are not limited to, the following:

1. The serum of ———— donors is tested for antibody to the human immunodeficiency virus types 1&2, and the hepatitis C virus encoded antigen using test kits that are not FDA-approved. There are no assurances that the testing is performed correctly by adequately trained and experienced personnel.

2. There is no evidence that the ———— are adequately screened for risk factors for infectious diseases such as HIV and hepatitis.

3. Standard operating procedure number 1300.1040, "Investigation of Quality Control Initial Test Failures" is not followed in that, for at least — lots of ———— that initially failed sterility testing, there was no investigation into the cause of the contamination and form 1165, "Quality Control Initial Test Failure Inter-Department Investigation" was not completed.

4. The containers used to ship ———— from ———— to BioWhittaker have not been validated.

5. The storage temperature of ———— is not monitored or documented.

6. ——— intended for use in the production of ——— are not stored in a manner to prevent contamination, in that this material is stored in the same ——— tank as potentially infectious material of human and animal origin.

In addition, the Food and Drug Administration has determined that your firm's ——— ——— are misbranded within the meaning of Section 502(a) of the FD&C Act in that:

1. The warning labeling for ——— shipments states in part, "Each serum/plasma donor unit used in the preparation of this product has been tested by an FDA approved method and found non-reactive for the presence of HBsAg and antibody to HIV-1, HIV-2, and hepatitis C," when in fact, the test kits used for the antibody to HIV-1 (anti-HIV-1), HIV-2 (anti-HIV-2), and the hepatitis C virus (HCV) are not U.S.-licensed products.

2. The labeling for shipments of ——— states, "These cells are NON-HAZARDOUS - NON-INFECTIOUS, and NON-RESTRICTED," when in fact, this material is potentially infectious.

3. The labeling for shipments of ——— states, "...ampules containing ——— ——— for medical research purposes," and "Non infectious biological material for medical research," when in fact, this material is intended for use in the production of a drug product, ———

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deviations at your facility. It is your responsibility as management to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and all applicable regulations and standards. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your response dated August 13, 1998, to the Form FDA 483 issued at the close of the inspection. We have made an initial review of the contents of your response and we have a number of comments addressing the adequacy of your corrective actions which are, in part, detailed below. The items correspond to the observations listed on the Form FDA 483.

Observation 12

Your response is inadequate in that it does not explain the time frame or mechanism by which the technology for anti-HIV-1 and HCV testing will be changed back to correspond with the test kits listed in the current Drug Master File. You provide no assurances that this transition from use of unapproved viral marker test kits to U.S. licensed kits by the supplier in ——— will be implemented in a controlled manner and verified by BioWhittaker. Additionally, the current Drug Master File does not contain any information relative to testing ——— donors or ——— serum samples for anti-HIV-2.

Observation 19
In your response, you state that BioWhittaker has implemented the use of a form to record the temperature of the ———— shipping container upon receipt from your supplier. You intend to collect the recorded data over the next year to "validate this process." It is our view that merely recording the temperature of the shipping container upon receipt for one year does not constitute an appropriate validation plan. Your response is also inadequate in that it does not address the wide variation in ambient temperature possible during shipment or the extended duration of time between shipment and receipt of ————, which may be up to six days.

Observation 22
You state that shipping containers for ———— will be labeled with the same shipping label as described in your response to observation 18, however, you do not address the remainder of the labeling which routinely accompanies shipments of ———— from your supplier and was found by the agency to contain false and misleading statements.

We acknowledge receipt of your letter dated September 11, 1998, the contents of which you will present during the meeting with the FDA on September 22, 1998. Please submit in writing, within 15 working days of receipt of this letter, your responses to the violations identified in this letter. Failure to promptly correct these deficiencies may result in regulatory action, such as seizure or injunction, without further notice. In addition, failure to promptly correct these deficiencies may result in FDA denying entry into the U.S. of ———— manufactured for your firm. Such drug components could be subject to refusal of admission pursuant to Section 801(a)(3) of the FD&C Act in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practices within the meaning of Section 501(a)(2)(B) of the FD&C Act.

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, please contact Anita Richardson at (301) 827-6201.

Sincerely,

for Elaine Knowles Cole
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 300 S. Riverside Dr., Ste 550 S Chicago, IL 60565 312/353-5863	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Joseph C. White	PERIOD OF INSPECTION 10/26-11/20/98	F.E. NUMBER 1611365
TITLE OF INDIVIDUAL Vice President, Q.A./Reg. Affairs	TYPE ESTABLISHMENT INSPECTED Biologic Manufacturer	
FIRM NAME Abbott Laboratories, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
STREET ADDRESS 1401 Sheridan Rd.	STREET ADDRESS OF PREMISES INSPECTED SAME	
CITY AND STATE (Zip Code) North Chicago, IL 60064-4000	CITY AND STATE (Zip Code) SAME	

DURING AN INSPECTION OF YOUR FIRM I OBSERVED

1. Review of the 1997 study conducted to validate the viral inactivation/reduction process used on urokinase products revealed the following discrepancies:

a) Data does not address the reproducibility of model virus removal/inactivation by heat treatment or chromatography in that only a single independent study was performed.

b) Validation study was conducted on a scale down version of the chromatography steps [redacted] No evaluation was conducted to assure these steps represented the purification process used in urokinase production.

c) Validation study did not include an evaluation of chromatography resin performance, or documentation that the level of purification is representative of the production process

d) Validation study did not evaluate the distribution of virus load in the different chromatographic fractions.

e) [redacted] column used in the validation study, do not represent columns used under production conditions. Fresh slurry gel was used in the [redacted] column during the validation study. Slurry currently used in production is up to two years old, and has an undefined use cycle.

f) No evaluation was conducted to determine if using a similar chromatography step twice [redacted] the calculation of overall virus reduction leads to an overestimation of the overall virus reduction factor obtained from the manufacturing process.

g) Process steps with reduction values in the order of 1 log [redacted] were included in the summation of the total reduction in virus titer without any justification.

h) A single study was conducted to evaluate HIV inactivation by heat treatment. Temperature data was not recorded for the last 4 hrs, 12 minutes of the 10 hr, 30 minute cycle

2. Human Neonatal Kidney Cells used for the production of urokinase during 1997 and 1998 manufacturing campaigns (lot numbers 953, 954, 1055, 1057, 1238, 1289, 1300, 1528, 1550, and 1635) have not been tested for the presence of Hepatitis C Virus.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type) Jeanne M. Morris, CSO Barry W. Cheney, Biologist	DATE ISSUED 11/20/98

FORM FDA 483 (5/83) PREVIOUS EDITION MAY BE USED INSPECTIONAL OBSERVATIONS PAGE 1 OF 1 PAGES

[redacted] FDA INSPECTION OF ABBOTT [redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 300 S. Riverside Dr., Ste 550 S Chicago, IL 60565 312/353-5863	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Joseph C. White	PERIOD OF INSPECTION 10/26-11/20/98	CF. NUMBER 1411365
TITLE OF INDIVIDUAL Vice President, Q.A./Reg. Affairs	TYPE ESTABLISHMENT INSPECTED Biologic Manufacturer	
FIRM NAME Abbott Laboratories, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
STREET ADDRESS 1401 Sheridan Rd.	STREET ADDRESS OF PREMISES INSPECTED SAME	
CITY AND STATE (Zip Code) North Chicago, IL 60064-4000	CITY AND STATE (Zip Code) SAME	

DURING AN INSPECTION OF YOUR FIRM I OBSERVED

3. Supplier's Certificate of Analysis for Human Neonatal Kidney Cells (HNK) indicated cell lot numbers 1030 and 845 passed the tests for Hepatitis B surface Antigen (HBsAg) and mycoplasma. However, in similar tests performed by Abbott, HNK lot number 1030 was positive for HBsAg and HNK lot number 845 was positive for mycoplasma. No documentation can be located to assure the supplier was contacted to request an investigation be initiated to determine the cause of the non-conformance and to assure corrective actions will prevent future occurrence.

4. Supplier's Certificate of Analysis and the HNK Specimen Information Form (0642) report that the donors of HNK lot numbers 906, 979, 1096, 1473, and 1486 exhibited no evidence of abnormality or congenital defects. However, the HNK cells derived from these donors had abnormal karyologies (trisomy 8, 13, or 18) that are associated with severe congenital malformations. No documentation can be located to assure the supplier was contacted to request an investigation to be initiated to determine the cause of the non-conformance and to assure corrective actions will prevent future occurrence.

5. HNK cells received and accepted by Abbott prior to implementation of HIV and HTLV-I testing of neonate's blood (1991) remain in inventory. Cells from untested neonates and cells tested under current procedures are stored in the same liquid nitrogen tanks.

6. HNK lot numbers 901, 1047, and 1093 failed the in vivo adventitious viral assay (embryonated hen's eggs) Documentation of investigation, including attempts to identify the viral agent causing the failure, was not provided.

7. The supplier's Certificate of Analysis for Human Neonatal Kidney Cells, lots 933, 1550, and 2036 did not identify the cause for the termination of pregnancy or the cause of the neonate's death. Despite the lack of information used to assess donor suitability, Abbott's review of the supplier's certificate did not elicit a rejection of these lots for production of urokinase.

8. The [redacted] are used at this facility to detect the presence of cytomegalovirus (CMV). Review of the studies validating these tests, completed

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type) Jeanne M. Morris, CSO Barry W. Cherney, Biologist	DATE ISSUED 11/20/98

FORM FDA 483 (3/93) PREVIOUS EDITION MAY BE USED INSPECTIONAL OBSERVATIONS PAGE 2 OF 3 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 300 S. Riverside Dr., Ste 550 S Chicago, IL 60606 312/353-5863	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED To: Joseph C. White	PERIOD OF INSPECTION 10/26-11/20/98	C.R. NUMBER 1411365
TITLE OF INDIVIDUAL Vice President, Q.A./Reg. Affairs	TYPE ESTABLISHMENT INSPECTED Biologic Manufacturer	
FIRM NAME Abbott Laboratories, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
STREET ADDRESS 1401 Sheridan Rd.	STREET ADDRESS OF PREMISES INSPECTED SAME	
CITY AND STATE (Zip Code) North Chicago, IL 60064-4000	CITY AND STATE (Zip Code) SAME	

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

on 11/02/98, revealed that:

a) There was no assurance that naturally occurring strains of CMV would be detected by these methods.
b) Evaluation of the ability to detect CMV by electron microscopy was performed using [redacted]. The cells that are screened by this test method, human neonatal kidney cells, were not used in the validation study.

9. The number of use cycles for the [redacted] and the [redacted] column are undefined. The GC-50 resin is regenerated with various solutions including NaOH, while the [redacted] of continuous flushing with 2% NaCl. No validation studies have been conducted to assure that any virus (or other contaminant) potentially retained on the resin or column, would be adequately removed or destroyed prior to reuse, preventing cross contamination between lots.

10. HNK cell culture supernatant is harvested daily and placed into a chilled tank (2-8 C) where it is stored for up to one week prior to further processing. There are no tests performed to evaluate the level of bacteria, endotoxin, mycoplasma, or adventitious virus in the in-process bulk at the end of this hold period. In addition, harvest storage tanks have exceeded temperature specifications. For example, Process Deviation 41683 reports product in tank was exposed to elevated temperatures (up to 36 C) for up to 13 hours. In this instance, no additional testing was conducted to evaluate product integrity.

11. There are insufficient in-process controls to assess column performance to ensure consistent removal of contaminants, including adventitious viruses.

12. In the Process Validation Report (96-456-015R), Abbott has identified the [redacted] chromatography step as critical for removal of pyrogenic materials and High Molecular Weight-UK. Studies did not control for the concentration of endotoxin loaded onto the columns, and resultant data revealed endotoxin levels increased following chromatography on 2 of 3, validation assessments. Studies did not quantititate the log removal of high molecular weight UK.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Jeanne M. Morris	EMPLOYEE(S) NAME AND TITLE (Please Type) Jeanne M. Morris, CSO Barry W. Cherney, Biologist	DATE ISSUED 11/20/98

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED INSPECTIONAL OBSERVATIONS PAGE 3 OF 7 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 300 S. Riverside Dr., Ste 550 S Chicago, IL 60565 312/353-5863	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Joseph C. White	PERIOD OF INSPECTION 10/26-11/20/98	C.F. NUMBER 1411365
TITLE OF INDIVIDUAL Vice President, Q.A./Reg. Affairs	TYPE ESTABLISHMENT INSPECTED Biologic Manufacturer	
FIRM NAME Abbott Laboratories, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
STREET ADDRESS 1401 Sheridan Rd.	STREET ADDRESS OF PREMISES INSPECTED SAME	
CITY AND STATE (Zip Code) North Chicago, IL 60064-4000	CITY AND STATE (Zip Code) SAME	

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

13. In the Process Validation Report (96-456-015R), the[ ] chromatography and[ ] filtration step have not been identified as critical steps for product quality, despite the potential role in removing both process-related and product-related impurities, including adventitious viruses.

14. Process-related impurities and product-related impurities are not evaluated to assure consistency of the product.

15. Review of Abbokinase finished product sterilizing filter validation revealed:

a) No bacterial challenge studies have been conducted on Abbokinase, 250,000 IU/5 mL (product 6109).
b) Bacterial challenge studies conducted on Abbokinase Open–Cath, 5000 IU/mL (products 6111 and 6145) may not mimic production conditions for filtration flow rates or pressures, as these parameters are not defined in written procedures or work orders used by production personnel.
c) No studies have been conducted on Abbokinase, 250,000 IU/5 ml to evaluate filter extractables following the1997 conversion from disk filters to cartridge filters.

16. Each lot of Water For Injection, USP, (a component used in Abbokinase final product formulation and as univial upper chamber fill solution), is not tested for endotoxin levels. This water is collected from a drop just downstream from site 384, which revealed[ ] [ ]including[ ]; between

17. Following lyophilization, sterile Abbokinase Open-Cath (products 6111 and 6145) remains unstoppered, for up to four days, while being purged with filtered, compressed air. During this time, open product vials are stored in covered trays, in aseptic transfer carts, in class 10,000 areas. No routine environmental monitoring is done to assure open vials are maintained under class 100 conditions during this hold period.

18. Lines, supplying compressed air used to purge open vials of sterile Abbokinase Open-Cath (products 6111 and 6145), are only tested for microbial quality 4 - 12 times each year.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Jeanne M Morris	EMPLOYEE(S) NAME AND TITLE (Print or Type) Jeanne M. Morris, CSO Barry W. Cherney, Biologist	DATE ISSUED 11/20/98

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED INSPECTIONAL OBSERVATIONS PAGE 4 OF 7 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 300 S. Riverside Dr., Ste 550 S Chicago, IL 60565 312/353-5863	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Joseph C. White	PERIOD OF INSPECTION 10/26-11/20/98	C.F. NUMBER 1411365
TITLE OF INDIVIDUAL Vice President, Q.A./Reg. Affairs	TYPE ESTABLISHMENT INSPECTED Biologic Manufacturer	
FIRM NAME Abbott Laboratories, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
STREET ADDRESS 1401 Sheridan Rd.	STREET ADDRESS OF PREMISES INSPECTED SAME	
CITY AND STATE (Zip Code) North Chicago, IL 60064-4000	CITY AND STATE (Zip Code) SAME	

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

In-line filters are not integrity tested prior to, or after each lot is manufactured, but instead are evaluated twice annually.

19. Management reports compressed air filtration set-ups (two 0.2 microns filters in separate stainless steel housings, with a quick-connect (approx. 2 inches in length) fitting) are autoclaved as an intact unit, twice annually. No written procedures or work orders can be located to describe this filter set-up, the sterilization load configuration diagram, or the autoclave cycle used to sterilize the filtration train.

20. The four day hold period for sterile, unstoppered Abbokinase Open Cath was last assessed during a media fill study conducted between December 1996-January, 1997. Only one of the three media fills, lot 25-870-Z7, was continuously purged with compressed air, a condition required during Abbokinase Open-Cath production. Review of records related to this lot revealed the following discrepancies:

a) D85Y Worksheet (used to record sterility test results) and the Equipment Qualification Validation Report, both show [ ] vials were tested for sterility, with [ ] vials showing growth. However, review of manufacturing records for this lot revealed only [ ] vials had been delivered to the laboratory for sterility testing.

b) Media fill protocol required at least [ ] vials be assessed per run. As reported on the study documents, only [ ] units were assessed. Although summary report attributes this discrepancy to a "fill line problem" neither the manufacturing record nor other documents contained a reference to this event.

21. In the past year, [ ] media fills were conducted for Abbokinase univials products (6111 and 6145). Product accountability discrepancies were uncovered in [ ] lots as defined below:

Media Fill Lot	Unaccounted Vials
[ ]	[ ]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		James M. Morris, CSO Barry W. Chaney, Biologist	11/20/98

FORM FDA 483 (8/95) Circle Applicable Copy — PREVIOUS EDITION MAY BE USED — INSPECTIONAL OBSERVATIONS — PAGE 5 OF 7 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 300 S. Riverside Dr., Ste 550 S Chicago, IL 60565 312/353-5863	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Joseph C. White	PERIOD OF INSPECTION 10/26-11/20/98	C.F. NUMBER 1411365
TITLE OF INDIVIDUAL Vice President, Q.A./Reg. Affairs	TYPE ESTABLISHMENT INSPECTED Biologic Manufacturer	
FIRM NAME Abbott Laboratories, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
STREET ADDRESS 1401 Sheridan Rd.	STREET ADDRESS OF PREMISES INSPECTED SAME	
CITY AND STATE (Zip Code) North Chicago, IL 60064-4000	CITY AND STATE (Zip Code) SAME	

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

[redacted]

These discrepancies were not evaluated as media fill procedures allow up to [redacted]% of fill vials to be unaccounted for, prior to investigating the event.

22. Due to power outage which caused product sterility to be compromised, Abbokinase lots 168982Z7 and 168997Z7 were reconstituted following lyophilization, and returned to CAPD for bulk reprocessing, including repeated chromatography and heat treatment steps. The reprocessed bulk was then reformulated by HPD, and released as Abbokinase (product 6109), lot 30751Z7. No process validation was conducted for these reprocessing steps and released product was not placed into the firm's stability program.

23. Process Deviation revealed one cart of sterile, lyophilized Abbokinase Open-Cath, lot 34-777-Z7, was not purged with Compressed Air for more than 7 hours prior to center sealing. Because Loss On Drying results on 2 of 2 vials tested from this cart met specification, the lot was released into distribution. Although this lot was placed on stability, samples were taken at random after product labeling, and may not represent unpurged portion of the lot.

24. Under the current system for investigating Abbokinase medical complaints, manufacturing record reviews are only conducted when requested by the individual reporting the event. Examples of medical complaints, which did not include a manufacturing record review include the following:

PCA #	EVENT
69366	[redacted]
7393526	
7390052	
7394185	
7394117	

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type) Jeanne M. Morris, CSO Barry W. Chaney, Biologist	DATE ISSUED 11/20/98

FORM FDA 483 (8/85) PREVIOUS EDITION MAY BE USED — INSPECTIONAL OBSERVATIONS — PAGE 6 OF 7 PAGES

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 300 S. Riverside Dr., Ste 550 S Chicago, IL 60565 312/353-5863	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	PERIOD OF INSPECTION 10/26-11/20/98	C.F. NUMBER 1411365
TO: Joseph C. White	TYPE ESTABLISHMENT INSPECTED Biologic Manufacturer	
TITLE OF INDIVIDUAL Vice President, Q.A./Reg. Affairs	NAME OF FIRM, BRANCH OR UNIT INSPECTED SAME	
FIRM NAME Abbott Laboratories, Inc.	STREET ADDRESS OF PREMISES INSPECTED SAME	
STREET ADDRESS 1401 Sheridan Rd.	CITY AND STATE (Zip Code) SAME	
CITY AND STATE (Zip Code) North Chicago, IL 60064-4000		

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

25. In September, 1998, complaint 305F98, reported [ ] adverse reactions (cold sweats, chills, and trepidation) correlated to bulk urokinase lot 20405N2. CAPD's investigation reported "no unusual circumstances" were associated with lot manufacture. Our review of the associated records revealed this lot had been manufactured under a non-validated process; extended heat treatment for time and temperature. Further review revealed CAPD's investigation was limited to final product filtration/filling, and did not extend to other manufacturing operations.

A Developmental Report was conducted to characterize potential modifications to the final bulk caused by this process deviation. This report does not justify the conclusion that overheating did not modify the characteristics of the final bulk product. For example:

a)
b) [ ]

26. When a manufacturing record review is conducted in response to a finished product complaint, PPD forwards this request to HPD. No procedures exist within HPD to define the investigation review operation, including a description of which records require review, timeframes for conducting reviews, or documentation requirements.

27. In 1998, [ ] Process Deviations were filed for Abbokinase Open-Cath (product 6145) reporting the human readable field for the Julian date for the case expiration date was incorrect. The Process Deviations reported the error was caused by a calculation error, which did not recognize the year 2000 as a leap year.

Although this problem was first uncovered in May 1998, no written investigation was conducted until 11/5/98 to identify the root cause of the error or to identify other affected labels. This investigation revealed the cause of the error was not the software, but instead, a human error made in 1995 when the master label format was created.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type) Jeanne M. Morris, CSO Barry W. Cheney, Biologist	DATE ISSUED 11/20/98

FORM FDA 483 (6/88) PREVIOUS EDITION MAY BE USED INSPECTIONAL OBSERVATIONS PAGE 7 OF 7 PAGES

U.S. Food and Drug Administration

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

January 25, 1999

IMPORTANT DRUG WARNING

Dear Healthcare Provider:

The purpose of this letter is to inform you of important safety information regarding the use of Abbokinase (Urokinase). This information is intended to help physicians and patients understand the potential risks of transmitting infectious agents associated with the use of this product. **The FDA is recommending that Abbokinase be reserved for only those situations where a physician has considered the alternatives and has determined that the use of Abbokinase is critical to the care of a specific patient in a specific situation.**

During recent inspections of Abbott Laboratories and its supplier of the human neonatal kidney cells used in the manufacture of Abbokinase, the United States Food and Drug Administration (FDA) identified numerous significant deviations from the Current Good Manufacturing Practice regulations designed to help assure product safety.

Abbokinase is produced from primary cultures of kidney cells harvested post-mortem from human neonates. Products manufactured from human source materials have the potential to transmit infectious agents. While some procedures to help control such risks in products of human source are in place, recent manufacturing inspections revealed deficiencies in some of the procedures used by Abbott and its supplier of the human neonatal kidney cells that could increase the risk of transmitting infectious agents. In considering this risk, the prescriber should be aware of the following information regarding currently available lots of Abbokinase:

- The kidney cells used in the manufacture of this product were harvested post-mortem from human neonates from a population at high risk for a variety of infectious diseases, including tropical diseases. The screening of potential donors did not include the questioning of the mothers to determine infectious disease status or specific risk factors for infectious diseases. Although some efforts were made by Abbott's supplier to screen and test the mothers, neonate donors, and kidney cells, Abbott's testing of the materials it received indicates that these measures were not consistently or reliably performed.

- Neither the mothers nor the neonate donors were tested for hepatitis C virus (HCV) infection. Abbott has recently instituted a test for HCV in the kidney cells used in the manufacture of Abbokinase and negative test results have been obtained for currently available lots. However, Abbott has not validated this test.

- Prior to use in the manufacture of Abbokinase, the human kidney cells were harvested, stored and handled in a manner which may have permitted contamination with infectious agents.

[redacted]

DR. K. ZOON (FDA CBER)
WARNING LETTER

- A viral inactivation procedure that substantially inactivates HIV and HCV in other biological products was used in the production of the currently available lots of Abbokinase. This process has variable effects on other infectious agents and has not been fully validated for viral inactivation of Abbokinase.

The FDA is not aware of any cases of infectious diseases that can be attributed to the use of Abbokinase. However, the likelihood that cases of infectious diseases caused by Abbokinase, if any, would have been recognized as such and reported to FDA is probably very low. Therefore, the actual risk to patients of developing an infectious disease as a result of using Abbokinase is unknown. For each setting in which the use of Abbokinase is being contemplated, we encourage you to consider the appropriateness of other treatment options. FDA approved indications for Abbokinase are: pulmonary embolism, coronary artery thrombosis, and i.v. catheter clearance. It should also be noted that the FDA has not approved the use of Abbokinase for clearance of peripheral venous and arterial obstructions or for clearance of arterio-venous cannulae.

Other thrombolytic products on the U.S. market with well-described experience in multiple indications include Streptase® (Streptokinase), Kabikinase® (Streptokinase), Activase® (Alteplase), Eminase® (Anistreplase), and Retavase® (Reteplase). We encourage all physicians to consider the appropriateness of other treatment options. The following is a list of FDA-approved indications for each of the other thrombolytic products currently available in the U.S.:

Streptase® (Streptokinase) [Hoechst Marion Roussel]-distributed by Astra USA
Acute evolving transmural myocardial infarction
Pulmonary embolism
Deep vein thrombosis
Arterial thrombosis or embolism
Occlusion of arteriovenous cannulae

Kabikinase® (Streptokinase) [Pharmacia & Upjohn AB]
Acute evolving transmural myocardial infarction
Pulmonary embolism
Deep vein thrombosis
Arterial thrombosis or embolism

Activase® (Alteplase) [Genentech, Inc.]
Acute myocardial infarction
Acute ischemic stroke
Pulmonary embolism

Eminase® (Anistreplase) [Wulfing Pharma GmbH]-distributed by Roberts Pharmaceutical Corporation
Acute myocardial infarction

Retavase® (Reteplase) [Centocor, Inc.]
Acute myocardial infarction

Abbott has committed to updating the labeling for Abbokinase to include the information regarding the potential risk for transmission of infectious diseases and to expeditiously correcting the deviations from Current Good Manufacturing Practice.

It is important that adverse experiences involving suspect infections following the administration of Abbokinase be included among those adverse events reported to Abbott Laboratories, Pharmaceutical Products Division, North Chicago, IL 60064, at 1-800-633-9110, or to the Agency via the MedWatch program by phone at 1-800-FDA-1088,

by fax at 1-800-FDA-0178, via the MedWatch website at www.fda.gov/medwatch, or by mail (using postage-paid form) at MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787. Health professionals and consumers should use the Form 3500 for adverse event/product problem reporting.

FDA will provide updated information on this product, as appropriate, via the Internet at http://www.fda.gov/cber. Information also will be available from the CBER voice information system at 1-800-835-4709, the CBER FAX information system at 1-888-CBER-FAX, and to subscribers of CBER's automated mailing system, CBERINFO. Prescribers are encouraged to consult these resources.

-- Signature --

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

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Last Updated: ***1/25/99***

This information is intended for U.S. residents only.

ABBOKINASE®

UROKINASE FOR INJECTION

ABBOKINASE (urokinase for injection) should be used in hospitals where the recommended diagnostic and monitoring techniques are available. Thrombolytic therapy should be considered in all situations where the benefits to be achieved outweigh the risk of potentially serious hemorrhage. When internal bleeding does occur, it may be more difficult to manage than that which occurs with conventional anticoagulant therapy.

Urokinase treatment should be instituted as soon as possible after onset of pulmonary embolism, preferably no later than seven days after onset. Any delay in instituting lytic therapy to evaluate the effect of heparin decreases the potential for optimal efficacy.[1]

When urokinase is used for treatment of coronary artery thrombosis associated with evolving transmural myocardial infarction, therapy should be instituted within six hours of symptom onset.

DESCRIPTION

Urokinase is an enzyme (protein) produced by the kidney, and found in the urine. There are two forms of urokinase differing in molecular weight but having similar clinical effects. ABBOKINASE (urokinase for injection) is a thrombolytic agent obtained from human kidney cells by tissue culture techniques and is primarily the low molecular weight form. It is supplied as a sterile lyophilized white powder containing mannitol (25 mg/vial), Albumin (Human) (250 mg/vial), and sodium chloride (50 mg/vial).

Thin translucent filaments may occasionally occur in reconstituted ABBOKINASE vials, but do not indicate any decrease in potency of this product. No clinical problems have been associated with these filaments. See "Dosage and Administration" section.

Following reconstitution with 5 mL of Sterile Water for Injection, USP, it is a clear, slightly straw-colored solution; each mL contains 50,000 IU of urokinase activity, 0.5% mannitol, 5% Albumin (Human), and 1% sodium chloride. The pH is adjusted with sodium hydroxide and/or hydrochloric acid prior to lyophilization.

ABBOKINASE is for intravenous and intracoronary infusion only.

CLINICAL PHARMACOLOGY

Urokinase acts on the endogenous fibrinolytic system. It converts plasminogen to the enzyme plasmin. Plasmin degrades fibrin clots as well as fibrinogen and other plasma proteins.

Intravenous infusion of urokinase in doses recommended for lysis of pulmonary embolism is followed by increased fibrinolytic activity. This effect disappears within a few hours after discontinuation, but a decrease in plasma levels of fibrinogen and plasminogen and an increase in the amount of circulating fibrin (ogen) degradation products may persist for 12-24 hours.[2,3] There is a lack of correlation between embolus resolution and changes in coagulation and fibrinolytic assay results.

Information is incomplete about the pharmacokinetic properties in man. Urokinase administered by intravenous infusion is cleared rapidly by the liver. The serum half-life in man is 20 minutes or less. Patients with impaired liver function (e.g., cirrhosis) would be expected to show a prolongation in half-life. Small fractions of an administered dose are excreted in bile and urine.

[redacted]

NEW ABBOKINASE LABEL

INDICATIONS AND USAGE

Pulmonary Embolism

ABBOKINASE (urokinase for injection) is indicated in adults:

- For the lysis of acute massive pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments.
- For the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, such as pulmonary angiography via an upper extremity vein, or non-invasive procedures such as lung scanning.

Angiographic and hemodynamic measurements demonstrate a more rapid improvement with lytic therapy than with heparin therapy.[4-8]

Coronary Artery Thrombosis

ABBOKINASE has been reported to lyse acute thrombi obstructing coronary arteries, associated with evolving transmural myocardial infarction.[9] The majority of patients who received ABBOKINASE by intracoronary infusion within six hours following onset of symptoms showed recanalization of the involved vessel.

IT HAS NOT BEEN ESTABLISHED THAT INTRACORONARY ADMINISTRATION OF ABBOKINASE DURING EVOLVING TRANSMURAL MYOCARDIAL INFARCTION RESULTS IN SALVAGE OF MYOCARDIAL TISSUE, NOR THAT IT REDUCES MORTALITY. THE PATIENTS WHO MIGHT BENEFIT FROM THIS THERAPY CANNOT BE DEFINED.

CONTRAINDICATIONS

Because thrombolytic therapy increases the risk of bleeding, urokinase is contraindicated in the following situations: (See WARNINGS.)

- Active internal bleeding
- History of cerebrovascular accident
- Recent (within two months) intracranial or intraspinal surgery
- Recent trauma including cardiopulmonary resuscitation
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis
- Severe uncontrolled arterial hypertension

WARNINGS

Bleeding

The aim of urokinase is the production of sufficient amounts of plasmin for lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle puncture, will also lyse, and bleeding from such sites may occur.

Intramuscular injections and nonessential handling of the patient must be avoided during treatment with urokinase. Venipunctures should be performed carefully and as infrequently as possible.

Should an arterial puncture be necessary (except for intracoronary administration), upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

In the following conditions, the risks of therapy may be increased and should be weighed against the anticipated benefits:

- Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of non-compressible vessels
- Recent (within 10 days) serious gastrointestinal bleeding
- High likelihood of a left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Subacute bacterial endocarditis
- Hemostatic defects including those secondary to severe hepatic or renal disease
- Pregnancy
- Cerebrovascular disease
- Diabetic hemorrhagic retinopathy
- Any other condition in which bleeding might constitute a significant hazard or be particularly difficult to manage because of its location

Should serious spontaneous bleeding (not controllable by local pressure) occur, the infusion of urokinase should be terminated immediately, and treatment instituted as described under ADVERSE REACTIONS.

Product Source

ABBOKINASE is produced from cultures of primary human neonatal kidney cells. Products manufactured from human source materials have the potential to transmit infectious agents. Procedures to control such risks can reduce but cannot completely eliminate the risk of transmitting infectious agents. The procedures used in the manufacture of currently available ABBOKINASE raise concerns regarding the risk of transmission of infectious agents. In considering this risk, the prescriber should be aware of the following information regarding currently available lots of ABBOKINASE:

The kidney cells used in the manufacture of this product were obtained from populations at high risk for a variety of infectious diseases, including tropical diseases. Although efforts were made to screen and test the mothers and neonate donors, the screening and testing measures were inadequate and were not consistently or reliably performed. For example, the screening of potential donors did not include the questioning of the mothers to determine infectious disease status or specific risk factors for infectious diseases, and donors were not tested for hepatitis C virus (HCV) infection. While Abbott has recently instituted a test for HCV in kidney cells used in the manufacture of currently available lots of ABBOKINASE, this test has not been validated. A viral inactivation procedure that has been shown to substantially inactivate HIV and HCV in other biological products was used in the production of the currently available product. However, this process has variable effects on other infectious agents and has not been fully validated for viral inactivation of ABBOKINASE.

Use of Anticoagulants

Concurrent use of anticoagulants with intravenous administration of ABBOKINASE is not recommended. However, concurrent use of heparin may be required during intracoronary administration of ABBOKINASE. A clinical study[9] with concurrent use of heparin and ABBOKINASE during intracoronary administration has demonstrated no tendency toward increased bleeding that would not be attributable to the procedure or ABBOKINASE alone. Nevertheless, careful monitoring for excessive bleeding is advised.

Arrhythmias

Rapid lysis of coronary thrombi has been reported occasionally to cause atrial or ventricular dysrhythmias as a result of reperfusion requiring immediate treatment. Careful monitoring for arrhythmias should be maintained during and immediately following intracoronary administration of ABBOKINASE.

▲ PRECAUTIONS

Laboratory Tests

Before commencing thrombolytic therapy, obtain a hematocrit, platelet count, and a thrombin time (TT), activated partial thromboplastin time (APTT), or prothrombin time (PT). If heparin has been given, it should be discontinued unless it is to be used in conjunction with ABBOKINASE for intracoronary administration. TT or APTT should be less than twice the normal control value before thrombolytic therapy is started.

During the infusion, coagulation tests and/or measures of fibrinolytic activity may be performed if desired. Results do not, however, reliably predict either efficacy or a risk of bleeding. The clinical response should be observed frequently, and vital signs, i.e., pulse, temperature, respiratory rate and blood pressure, should be checked at least every four hours. The blood pressure should not be taken in the lower extremities to avoid dislodgment of possible deep vein thrombi.

Following the intravenous infusion, *before (re)instituting heparin*, the TT or APTT should be less than twice the upper limits of normal. Following intracoronary infusion of ABBOKINASE, blood coagulation parameters should be determined and heparin therapy continued as appropriate.

Drug Interactions

The interaction of urokinase with other drugs has not been studied. Drugs that alter platelet function should not be used. Common examples are: aspirin, indomethacin and phenylbutazone.

Although a bolus dose of heparin is recommended prior to intracoronary use of urokinase, oral anticoagulants or heparin should not be given concurrently with large doses of urokinase such as those used for pulmonary embolism. Concomitant use of intravenous urokinase and oral anticoagulants or heparin may increase the risk of hemorrhage. (See "WARNINGS" section.)

Carcinogenicity

Adequate data are not available on the long-term potential for carcinogenicity in animals or humans.

Pregnancy

Pregnancy category B. Reproduction studies have been performed in mice and rats at doses up to 1,000 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to urokinase. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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UNIVERSITY MEDICAL FACULTY GROUP

DEPARTMENT OF MEDICINE
VASCULAR MEDICINE UNIT

February 5, 1999

Sidney M. Wolfe, M.D.
Director, Public Citizen's Health Research Group
1600 20th St., NW
Washington, DC 20009-1001

Dear Dr. Wolfe,

In response to your letter of February 4, regarding claims that urokinase (UK) has unique benefits for the treatment of peripheral vascular disease, I would have the following comments.

While statements that UK is the best thrombolytic for peripheral arterial occlusion (PAO) can be found in the literature, they are based primarily on personal experience, retrospective analyses or historical controls with other agents such as streptokinase (SK) or tissue plasminogen activator (tPA). Since different trials necessarily have significant distinctions in patient attributes, treatment regimens, endpoint determination and statistical analysis, definitive conclusions are not tenable and are susceptible to biased interpretation. The conclusion for treatment of PAO has generally been that both UK and tPA have better thrombolytic and safety profiles than SK, but the data proving this conclusion are not available and the point is not proven. As to a comparison of UK with tPA therapy in PAO, both were equally safe and effective (Annals Surgery 220: 251-268, 1994), but SK was not even included, thereby precluding any statement beyond that pertaining to UK and tPA.

For the treatment of deep vein thrombosis (DVT), UK is applied quite broadly by interventional radiologists as part of a "registry" sponsored by Abbott Laboratories, using catheter administration of agent into the thrombus itself. The results have been promising, but this is an experimental approach and we do not have any comparative trials of UK with other thrombolytics. In addition, most of these patients could be managed by systemic (intravenous) administration, an approach which would obviate any need for catheter delivery of the agent, and for which all of the agents would be usable.

My overall conclusion is that any plasminogen activator is equivalent to another until proven otherwise by direct comparison in a properly-performed randomized and blinded trial. Evidence available to date suggest that there is little to choose between the agents relative to their efficacy profiles. Aspects such as FDA approval, safety, side effects and cost could influence the ultimate choice of one agent over another, but not to the extent that only one would be expected to have therapeutic benefit.

I hope these brief comments are of help to you.

Victor Marder, M.D.
Professor of Medicine

vm

601 Elmwood Avenue, Box 610
Rochester, New York 14642
(716) 275-3761 Fax: (716) 473-4314

THROMBOLYTIC THERAPY

Chapter

Victor J. Marder, M.D.

Vascular Medicine Unit, Department of Medicine

University of Rochester School of Medicine & Dentistry

Rochester, NY 14642

For: Hoffman, et al. Hematology: Basic Principles and Practice, 3rd Ed.

TABLE 9 COMMENTARY ON FDA APPROVAL* AND COMMON USAGE OF PLASMINOGEN ACTIVATORS

AGENT	CLINICAL INDICATION	FDA-APPROVED REGIMEN	COMMON USAGE
Urokinase (Abbokinase®)	PE	12 hour infusion	2 hour infusion suffices
	Acute MI	Intracoronary only	Infrequent, for reocclusion or with PTCA
	IV catheter	5,000 U in 1 ml	Popular therapy
	PAO, DVT	Not approved	Widespread usage "off-label", catheter delivery
Streptokinase (Streptase®)	Acute MI	IV or IC	IV usage only
	PE DVT PAO	Duration 24 hrs for PE, 72 hrs for DVT, 24-72 hrs for PAO.	Therapy tailored for each patient
	AV Cannulae	Local installation	
Reteplase (Retavase®)	Acute MI	Two bolus injections, 30 minutes apart	Just approved
Alteplase (Activase®)	Acute MI	3 hrs or 90 min	"Accelerated" dosage used
	Acute ischemic stroke	90 mg/1 hr, within 3 hrs of symptoms	Limited usage
	PE	100 mg/2 hrs	UK over 2 hrs has equal efficacy
	PAO, catheter	Not approved	Used off-label
Anistreplase (Eminase®)	Acute MI	30 U over 2-5 min	Infrequently used

*Based upon Physician's Desk Reference, 1998

02/03/99 13:00 UR VASCULAR MEDICINE → 12025887796 NO.855 D37

TABLE 11. Comparison of outcome using different plasminogen activators

Thrombotic Disorder	Comparison of Agent
DVT	No direct comparison, but equivalent results in separate trials.
PE	SK (12 hrs) equal to UK (12 hrs or 24 hrs), UK (2 hrs) equal to t-PA (2 hrs), no comparison of SK with t-PA in equivalent regimens.
PAO	t-PA equal to UK, historically better results for UK and t-PA than SK, but no direct comparisons.
MI	Comparable results with SK, t-PA and APSAC in two megatrials, marginal survival advantage (0.9%) of t-PA over SK in a third, reteplase equivalent to t-PA and SK. Intracranial hemorrhage less common with SK than t-PA, reteplase or APSAC.
CVA	Only t-PA approved, but no comparative trials and other agents had longer delays (>3 hrs) before treatment.

Public Citizen

NEWS RELEASE

Hold for release:
11 a.m. Wednesday, Feb. 10, 1999

Contact: Dr. Sidney Wolfe (202) 588-1000
Brian Dooley (202) 588-7703
Booth Gunter (202) 588-7741

Potentially Infectious Colombian Kidney Tissue Used in Clot-Busting Drug Abbokinase

Suspect Tissue From Deceased Newborn Babies and Aborted Fetuses Imported in Violation of U.S. Law, Used for Abbott Drugs

WASHINGTON, D.C. -- Potentially infectious kidney tissue harvested from deceased newborn babies and aborted fetuses is being used to make the clot-busting drug Abbokinase, said Dr. Sidney Wolfe, Director of Public Citizen's Health Research Group, in a letter today calling for an immediate recall of the drug sent to Food and Drug Administration (FDA) Commissioner Dr. Jane Henney.

According to FDA inspection reports and other information on the import of the tissue obtained by Dr. Wolfe, Abbokinase has been derived from kidneys taken from deceased newborn babies or aborted fetuses in a hospital in Cali, Colombia, without evidence of adequate informed consent from the parents, and without adequate screening or testing of babies or their mothers for infections.

Then, in violation of U.S. law, it is imported into the United States by BioWhittaker without being declared through customs as an FDA-regulated commodity or identified as "Treat as Potentially Infectious." It is then processed by BioWhittaker and sent to Abbott Laboratories, in Abbottpark, Illinois.

Tens of thousands of Americans used Abbokinase last year, representing $250 million in sales for Abbott.

"This kidney tissue has been obtained from Colombia under extremely suspicious circumstances and has been processed in an extraordinarily dangerous way, exposing patients to potentially contaminated Abbokinase," said Dr. Wolfe. "It is difficult to come up with a more dangerous scenario for an FDA-regulated biologic."

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