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QUALITY CONTROL OF PLASMA VS. HEAT TREATMENT

Earlier this year Cutter Laboratories intensified its plasma donor screening program in response to increasing medical concern over AIDS. This intensification keeps the emphasis on providing quality product squarely where it belongs. By eliminating potential unhealthy and hepatitis B positive donors, Cutter has traditionally reduced the risk of transmission of serious disease agents through blood products.

With the initiation on March 1, 1983 of additional screening procedures to reduce the possibility that AIDS may potentially be transmitted through certain blood products (see appendix I), Cutter has reinforced its existing program of donor screening to assure that the raw material for its quality plasma products continues to be of high quality. This approach is in keeping with the philosophy of Good Manufacturing Practices which holds that quality safeguards to control the quality of starting material are preferred to procedures to remove and reduce risk at a later point in manufacturing.

There is, for example, no known method acceptable for manufacture of coagulation factor products intended for human use which will inactivate the hepatitis B virus. Even the Hyland Hemophil T package insert (appendix III) states this in several places (see boxes and underlined sentences in appendix III).

In the area of research and development and in manufacturing, Cutter is working intensively to develop and refine a process which will exclude from Factor VIII concentrates not only the hepatitis B virus but any other disease transmitting agents which may be present in blood plasma. These efforts, as well as the efforts of other manufacturers, are hampered by the fact that it is not known whether or not AIDS is caused

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by a transmissible agent and whether or not that agent is present in blood. As a result, any actions taken to refine the manufacturing process to exclude such transmissible agents -- such as heat-treatment or chemical inactivation -- cannot yet be proven to be effective. In fact, it has been shown by chimpanzee studies that heat-treatment by itself is not sufficient to inactivate the hepatitis B virus in Factor VIII concentrates. This is confirmed in appendix II which is part of a brochure on heat-treated AHF produced by Hyland. (A similar product, manufactured in Germany, has never been tested this thoroughly to determine the degree of risk of hepatitis transmission).

As a result of the lack of positive evidence of complete inactivation of viruses, an assumption of increased protection from viral transmission from heat-treated Factor VIII concentrate is not warranted at this time.

In the meantime, it is our feeling that it would be of questionable value for hemophilia patients to be persuaded to change to products which raise the cost of an already expensive therapy in return for no guarantee of increased protection. It would also be inadvisable for hemophiliacs to suspend or reduce treatment and thus increase the probability of bleeding episodes which may result in disability and death.

As long as the AIDS agent is not known and as long as viral inactivation procedures cannot be shown to be effective, it is more feasible to prevent the introduction of a possible AIDS agent in the starting material than to attempt to eliminate it at a later stage of the process.

In summary, then, the following points are of interest:

- Cutter carefully screens plasma donors to eliminate donations from unhealthy individuals and "high risk" AIDS and hepatitis groups. (see appendix I)

- No known method compatible with production of coagulation factor plasma products for human use is effective in inactivating the hepatitis B virus. (see appendix II)

- Cutter is working diligently to discover a means of viral inactivation which can be applied to plasma products. Until such a method can be

devised, controls to assure the high quality of the raw material -- plasma -- are more effective in preventing disease transmission than any current process modification.

- Remember above all that it is not known whether AIDS can be transmitted by blood and certain blood products. This is speculative, controversial, and even contradicted by some data. Cutter, nevertheless, in order to avoid any possible risk, however remote, to its customers, has deliberately chosen to act on the assumption that AIDS may possibly be transmitted by certain blood products.

Attached are copies of the guidelines which were followed to establish additional screening procedures to eliminate "high risk" donors (appendix I). Also attached are statements from the Travenol Hemophil T brochure (appendix II) and package insert (appendix III) showing that Hemopil T -- although heat-treated -- still can transmit hepatitis.

Remember if hepatitis cannot be eliminated by heat-treatment, there is no assurance that any other viruses are inactivated by this process.

Merrill Boyce, Ph.D.
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Letter sent to Cutter Distributors overseas. D. Aston

Acquired Immune Deficiency Syndrome

The increased medical concern over the Acquired Immune Deficiency Syndrome (AIDS) has spread to the hemophiliac population during the last year. Little is known about it and because a variety of groups have attempted to address the issue, AIDS has become the center of irrational response in many countries. This is of particular concern to us because of unsubstantiated speculations that this syndrome may be transmitted by certain blood products, specifically cryoprecipitate and AHF concentrates.

What is known -- or rather unknown -- about AIDS is important.

A. The mechanism of the disease itself is unknown. Theories range from a viral agent or agents to immune system overload. Many theories abound -- some are technical and quite complex medically; others are wildly speculative. (See point 1 and 2, below.)

B. While it has not been explicitly postulated that AHF concentrates are responsible for the appearance of this AIDS-like syndrome, nevertheless there exists an implied assumption that they may be implicated in the transmission of the syndrome seen in hemophiliacs. What little evidence exists, however, in fact tends to suggest that AHF concentrates have no direct role in this syndrome. (See points 3-6, below and Q1 in the Q and A summary.)

C. The AIDS-like syndrome as seen in hemophiliacs may be a very different syndrome from that seen in cases from other high risk groups. There is even some question as to whether the syndrome in hemophiliacs can be defined as AIDS. (See point 2, below.)

D. In the United States, plasma procurement has always been the subject of very stringent governmental controls. Cutter's plasma products thus come from a raw material source that is carefully screened and controlled to reduce the risk that disease agents will be transmitted through certain plasma products.

More recent measures further provide a reduction of the possibility that AIDS -- if in fact it can

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be transmitted by blood and certain blood products -- will be transmitted by plasma products.

Any actions taken to refine the manufacturing process to exclude such transmissible agents -- such as heat-treatment or chemical inactivation -- cannot yet be proven to be effective. In fact, it has been shown by chimpanzee studies that heat-treatment by itself is not sufficient to inactivate the hepatitis B virus in Factor VIII concentrates. As a result, we cannot assume that a possible AIDS-related transmissible agent in blood would be inactivated by any known method acceptable for manufacture of products intended for human use. Until such a method can be devised, controls to provide the high quality of the raw material -- plasma -- offers more hope in preventing disease transmission than any current process modification. (See points 8-10.)

It is also important for you to know the following about the relationship between AIDS, hemophilia, and AHF concentrates:

1. An AIDS victim does not die of AIDS. AIDS is simply a medical term which indicates a generally suppressed or malfunctioning immune system. Mortality usually comes when pathogens routinely encountered in daily life and repelled by the body's immune system enter the defenseless "host" and multiply without interference from the immune system.

2. As a result, unusual diseases and infections occur and common infections are seen in a more virulent form. Although a type of cancer (Kaposi's sarcoma) has been seen in many AIDS victims, it has never been seen in hemophiliacs.

3. Last year out of a population of approximately 20,000 hemophiliacs in the U.S., only 12 have been diagnosed as having an apparent AIDS-type syndrome; nine of them have died. No cases of this syndrome have been reported in hemophiliacs in the U.S. this year

4. All of the hemophiliacs who were diagnosed as having an AIDS-like syndrome used AHF concentrates. Some used other blood products as well; one was an I.V. drug user.

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5. Koate AHF concentrate was not used by any of the 12 hemophiliacs who were reported as having an AIDS-like syndrome.

6. In only rare instances had the 12 cases in question been exposed to common lots of AHF concentrates. A lot of AHF concentrate may contain up to 7,000 vials and may be used by as many as 100 hemophiliacs. In a single year, about 800 lots of AHF concentrate are produced in the U.S. and an average hemophiliac, using 30,000 to 50,000 IU/year, will get material from 5 to 10 lots.

7. The Centers for Disease Control in Atlanta report that in 1982 the largest single cause of death in hemophiliacs is still bleeding episodes.

8. Intensified donor screening procedures were instituted throughout the U.S. on March 1, 1983. At Cutter, however, some of the AIDS-related screening procedures -- such as routine checks for weight loss and generalized lymphadenopathy -- which are now required by the FDA, have been in use for many years. Thus, Cutter already had a screening program in place prior to March 1, 1983.

   Additionally, Cutter's "donor screening" procedures to eliminate high-risk groups of unhealthy and HBsAG positive donors have always complied with the regulations of the U.S. FDA which are the most rigorous in the world.

9. There are no Cutter centers in New York, San Francisco, Los Angeles or Miami, where the vast majority of AIDS cases to date have been reported.

10. Heat-treatment for complete viral inactivation in Factor VIII concentrates has not been shown to be effective. Heat-treated product recently released by a U.S company caused hepatitis in test animals. A heat-treated Factor VIII concentrate of European origin is said to be free of the risk of hepatitis transmission but this has not been documented nor has the product been tested with the necessary rigor to substantiate this claim.

Q and A Summary

Q1. Does Koate AHF concentrate transmit AIDS?

A1. This has not been shown. Koate? AHF concentrate has not been implicated in any of the 12 AIDS-like cases seen in hemophiliacs. It is not proven that AIDS is transmitted by AHF concentrates.

If AHF concentrates transmit AIDS, it is impossible to explain why all hemophiliacs who used a common lot did not contract this AIDS-like-syndrome rather than the 12 reported cases.

Q2. Can Koate? AHF concentrate be safely used?

A2. The U.S. FDA requires the most rigorous screening procedures in the world to control the quality of plasma used in the manufacture of Cutter's products. These screening procedures have been intensified in order to eliminate donors at high risk for AIDS.

Cutter has declared the location of its plasma collection centers and none of them are located in New York, San Francisco, Los Angeles or Miami where the vast majority of AIDS cases have been reported.

Q3. Does heat-treated AHF provide any advantage over Koate? AHF concentrate?

A3. This cannot be proven. As a result of the lack of positive evidence of complete inactivation of viruses, an assumption of increased protection from viral transmission from heat-treated Factor VIII concentrate is not warranted at this time.

In the meantime, it is our feeling that it would be of questionable value for hemophilia patients to be persuaded to change to products which raise the cost of an already expensive therapy in return for no guarantee of increased protection. It would also be inadvisable to suspend or reduce treatment and thus increase the probability of bleeding episodes which result in disability and death.

As long as the AIDS agent is not known and as long as viral inactivation procedures cannot be shown to be effective, it is more desirable to prevent the introduction of a possible AIDS agent in the starting material than to attempt to eliminate it with unproven procedures at a later stage in the process.

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Q4. Will Cutter introduce a heat-treated AHF concentrate?

A4. The Cutter goal is to produce a virus-free AHF concentrate which is safe and effective. Since it appears that heat-treatment at present is not completely effective for viral inactivation in AHF concentrates, Cutter will pursue heat-treatment as an interim step with the aim that heat-treatment under proper conditions will result in viral inactivation.

Final Statement

Your interests and those of the patient are of paramount concern to us. Be assured that every avenue for research and exploration into these new and challenging questions is being addressed. As new developments occur we will inform you fully; we will keep you in touch with progress.

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