Cutter

MILES

TO: Those Listed

FROM: S.J. Ojala, H. Mozen, B. Louie, C. Moore

DATE: 10/12/83

SUBJECT: Marker Viruses and the Potential Infectivity of Plasma Derivatives - Held at the National Institutes of Health, OB, Oct. 6, 1983

COPIES TO:

H. F. Schaeffler
J. Hjorth
M. Mozen/D. Schroeder/R. Guzman
B. Louie/K. Lembach/G. Mitra/P. Ng
M. Sternberg/M. Boyce
K. Fischer/J. Hink/B. Barden
B. Cole/E. Potere
C. Turner/S. Cullen/D. Hoffman
J. Cherry/J. Huxsoll
B. Hodersbach
P. Short/L. Ambrus/R. Victor
M. Ashworth/E. Greene/P. DeHart
J. Ryan/C. Patrick/J. Peterson/D. Terry
R. Schwartz/M. Budinger
R. Rousell/S. MacKenzie
T. Monroe/E. Weichert (CLAYTON)
G. Nakamura

Marker Virus Meeting:

The meeting opened with a number of technical presentations mostly from the staff of the OB. Dr. Dennis Donohue gave the opening remarks in which he indicated that the main purpose of marker viruses was to establish whether a decrease in such marker viruses could lead to a claim that hepatitis is decreased. For new products, he wanted to address: 1) How to assess infectivity with regards to hepatitis B virus? 2) Can major changes in a process be done without a chimpanzee test? 3) Can we tell clinicians that products are decreased in hepatitis B infectivity based on marker virus work?.

Dave Aaronson made a statement regarding the problem and pointed out that HBV and NANB are the only presently known viruses in plasma products. He indicated that there are other viruses (implied candidate AIDS agents) which may contaminate plasma products, namely HTLV and Serum parvo-like virus (SPLV). The risk from hepatitis B today is very low, whereas the NANB risk approaches 100% in plasma products. Aaronson listed methods to reduce virus load in plasma products:

1. By fractionation with PEG
2. By affinity chromatography (Stanley Charm)
3. Chemical inactivation methods
4. Use of lipid solvents
5. Use of physical methods such as heat

Dr. Hiatt, a former member of the Division of Biologics Standards (DBS) staff, gave a rather theoretical presentation on virus inactivation referring back to work done some 30 years ago.

CUD212 11970 19660

MDL-986
CONFIDENTIAL
PER PRETRIAL ORDER NO. 2

831012SJOC-1

OCT 13

105 3786

MIL 074017

Following the closed sessions, the panel deliberated on what they had heard. Some of the points made included the following: Dr. Bove stated that he had heard nothing that in his opinion would allow licensing a product without chimpanzee studies i.e., marker viruses had no meaningful correlation with results obtained in chimpanzees with hepatitis viruses. Then Bove stated that inactivation of marker viruses can be useful as a guide in selecting procedures which would be ultimatley confirmed in chimp studies.

Reference was made to the so-called "hidden agenda" (referring to AIDS) with the recognition that many users of plasma products are concerned with this issue. Obviously, nothing in the regulatory responsibilities and labeling can deal with the AIDS issue. Bove further said that markers are a process developing tool not a licensure or labeling tool. Donohue stated that a temporary position paper will be issued in the use of marker viruses. This must wait on input from Dr. Robert Gerety.

Meeting with Drs. Purcell and Feinstone:

Following the opening meeting, we had a discussion with Drs. Bob Purcell and Steve Feinstone in their laboratory regarding the use of chloroform and inactivation of hepatitis. These gentlemen are the inventors on a patent application which Cutter has licensed from NTIS non-exclusively from the the government. With respect to chloroform, these investigators believed their system more efficient that the Ether-Tween 80 lipid extraction method. Chloroform is classified as a carcinogen and it would be necessary to insure total removal.

Factor VIII preparations extracted dry and in solution retained most of the VIII:C activity.

We discussed how they might interact with us in pursuing their chloroform procedure. Purcell indicated that they can aid us in planning our chimp studies and give us counsel and advice but, as employees of the government, they cannot receive compensation. They indicated that they could make available to us the H strain of NANB plasma for studies that we might wish to carry out. They could visit us and present a seminar if the invitation and expenses were paid for by a non-profit organization e.g., community blood bank or university. Our general impression was that Purcell and Feinstone would be excellent collaborators with whom we could work. They are probably also involved with other manufacturers e.g., Armour, Kabi?

We had an interesting hallway conversation with Alfred Prince, who is head of the virology lab at the New York Blood Center. Dr. Prince also heads a chimpanzee facility in Liberia, where studies with hepatitis have been carried out. We spoke to Dr. Prince about the availability of chimps for studies we might wish to engage in and he indicated that he could accommodate us. We will need to follow this up in greater detail. He further indicated that he did not believe his process employing Tween 80 and ether infringed on the Shanbrom patent, but this issue will have

831012 S'J OC 03

Dr. Finlayson described a number of chemical inactivation procedures. He pointed out that Dr. Lo Grippo had screened some 623 chemicals with a battery of viruses in serum and ADC plasma and from that summarized 5 effective inactivators:

1. Ethylene oxide
2. Butylene oxide
3. Sulphur mustard
4. Nitrogen mustard
5. B-Propiolactone (BPL)

He focused on BPL and from this work emerged the products presently manufactured in Germany which are cold sterilized with BPL. BPL acts as an acylating or alkylating agent depending on the chemical site on which it reacts. He referred to a paper by Stephan, who was able to show by immunoelectrophoresis that albumin treated with BPL had a different migration.

Dr. S. Feinstone of the NIAID who works with Purcell gave a very interesting presentation on inactivation of NANB and HBV using lipid solvents but particularly focusing on chloroform. In his laboratory, they have a source of NANB referred to as H-plasma from a donor named Hutchinson which contains 10^6 CID/ml. Then he described his experiments on the use of chloroform inactivation of hepatitis B and NANB virus. These experiments were very interesting to us because the results were verified in chimpanzees. He also described Alfred Prince's work (New York Blood Center) on the use of 1% Tween 80 and 20% Ether for inactivation of hepatitis B viruses and NANB. Again, the Hutchinson strain of NANB was used. It was mentioned that Dan Bradley at CDC has also carried out experiments with chloroform which demonstrated its effectiveness.

Ed Tabor reviewed the requirements for carrying out chimpanzee studies of hepatitis inactivation in plasma products.

Following these presentations, all of the manufacturers which included Alpha, Armour, Behringwerke, Immuno, NYBC, Hyland, and Cutter gave closed session presentations to the Blood Products Advisory Committee on in-house work with inactivation of marker viruses. M. Mozen made the Cutter presentation. Aaronson asked whether we have tested porcine parvo virus in albumin solution at 60° for 10 hours. We have not done this but intend to do so. Nothing substantive came out of the Cutter closed session presentation.