Infected Blood Inquiry

Presentation by Counsel to the Inquiry

Pharmaceutical Companies: Response to Risk

INTRODUCTION

1. This is a presentation by Counsel to the Inquiry on the response of pharmaceutical companies involved in the fractionation of blood products to the risk of infection from those products, and in particular the emerging risk of AIDS in the early and mid-1980s. Its focus is on four companies within the United States – Alpha Therapeutic Corporation ("Alpha"), Armour Pharmaceutical Company ("Armour"), Cutter Laboratories Inc. / Miles Laboratories Inc. ("Cutter" or "Miles/Cutter"), Hyland Division of Travenol Laboratories Inc. ("Hyland" or "Hyland/Travenol"). In order to examine the way in which those companies responded to the AIDS epidemic among people with haemophilia, it is also necessary to consider to some extent the decisions, acts and omissions of various other bodies, in particular the US regulatory authorities, the blood-banking industry within the country, and the principal representative organisation for haemophilia patients and their families, the National Hemophilia Foundation ("NHF"). Reference is also made to contemporaneous events taking place within the United Kingdom. Where possible, the actions of the Austrian firm Immuno AG ("Immuno") are also included, given that this was the fifth fractionation company that imported factor concentrates into the UK during the 1970s and 1980s.

2. This presentation should be read alongside those made orally in September and October 2021 on other aspects of the actions of these pharmaceutical companies. As with those earlier presentations, this should not be seen as a comprehensive history but an overview of some of the more significant events. Efforts have been made to avoid repetition with the previous presentations. As a result, little is said here about the licensing of the products in the UK, the way in which the risks of the products were presented to the doctors and patients using them, the donor pools from which the product were drawn (other than in respect of changes to those pools made as a consequence of AIDS), or the interaction between the companies and UK clinicians and regulators.

3. The presentation is intended as a neutral, factual narrative. The approach taken is broadly chronological, tracing events through 1982, 1983 and the first half of 1984. During this period, the main debates and actions concerned the approach to be taken to donor screening, surrogate testing, and the recall of products containing plasma from donors known or suspected to have AIDS. After mid-1984, the presentation

departs from a strict chronological narrative to consider the issues of heat treatment of factor concentrates, and then the introduction and effect of a screening test for HTLV-III.

Sources

4. This presentation draws on a wide range of documents that have been disclosed to and by the Inquiry. Although voluminous, the documents are by no means comprehensive. As is to be expected at a distance of 40-50 years, archives are incomplete and difficult to navigate. Corporate acquisitions and mergers over the years mean that in some instances it is difficult to identify which company holds, or held, which documents. The Chair has no powers to compel the production of documents held outside of the United Kingdom and so has relied on the co-operation of the relevant companies and individuals whom the Inquiry has contacted.

5. Analysing the documents may be compared to a journey through a dense forest. A huge amount of information can be studied from the main paths, but it is not always possible to identify what lies behind it. There is a risk that pursuing minor paths and granular detail will lead to author and reader becoming lost in an unenlightening thicket. In terms of presenting the results, Counsel to the Inquiry take the view that it is more useful to provide an overview of the forest, identifying the most significant features and providing case studies, rather than providing a botanist's list of all available specimens. Inevitably, this involves a degree of judgement and of selection of material. This has been undertaken from an independent perspective, with the purpose of providing the Chair, Core Participants, those infected and affected and the public with a greater understanding of what have been assessed to be the main events. Core Participants have access to the documents referred to in this presentation, and to many others that have been disclosed by the Inquiry. They will make their own submissions on matters that they consider to be important, and on the conclusions that they invite the Chair to make from them. Ultimately, it will be for the Chair to decide on his findings, taking into consideration all of the evidence and submissions that he has heard. A document does not obtain any enhanced evidential status by being included in this presentation.

6. The documents on which Counsel to the Inquiry rely are identified throughout the presentation, but three are worthy of note as principal secondary sources that help to provide a route map of the relevant events. These are:

- Lauren B, Leveton, Harold C. Sox Jr., Michael A. Stoto, eds., "HIV and the Blood Supply: An Analysis of Crisis Decision Making", commissioned from the Institute of Medicine ("IOM") by the Department of Health and Human Services, National Academy Press, 1995 **[JREE0000019]**, ("the IOM Report")
    - The report was commissioned by the United States Department of Health and Human Services, in response to concerns raised by members of Congress. The Department requested that the IOM establish a committee to study the transmission of HIV through the blood supply. The Preface to the report stated that it resulted from a year-long study, which involved fact finding interviews with 76 individuals and the review of over 700 documents [ep.5-7].
    - The editors were, respectively: a psychologist who served as Study Director; a physician with a background in immunology and a research interest in medical decision making; and the Director of the IOM's Division of Health Promotion and Disease Prevention, whose Ph.D was in statistics and demography. The IOM committee charged with producing the report was chaired by Dr Sox, and contained a further 13 members with a range of expertise and experience. [ep.329-336]

- Report of the Commission of Inquiry on the Blood System in Canada – the Krever Report, 1999 **[KREV0000001]** ("Krever Report")
    - The report of the Canadian inquiry into infected blood. See in particular Part IV, *"International Responses to the Risk of HIV in the Blood Supply"*

- Dr B.L. Evatt, *"The tragic history of AIDS in the hemophilia population, 1982-1984"*, Journal of Thrombosis and Haemostasis, **4**: 2295-2301, 2006 **[CVHB0000042]** (*"Tragic History"*)
    - This article, by one of the lead protagonists in the events, was published in 2006 as an *"historical sketch"*.

7. All three of these documents contain the subjective analyses, conclusions and opinions of their respective authors. At points, this presentation summarises or quotes those views. This is done neutrally, in order to describe what those authors thought of certain matters. It is important to note that some of their observations have

been challenged by other authors and it will be for the Chair to make such use of this material as he considers helpful.[1]

8. The citations to documents in this presentation use the Inquiry's referencing system. References to "[ep.]" are to the electronic page numbers of those documents, which are used in preference to the internal page numbers.

Relevant organisations

9. A helpful summary of the US regulatory and blood supply system is contained in the IOM Report **[JREE0000019, ep.39-69]**. This is not repeated here, but it may be helpful to set out very briefly the main roles of the principal bodies involved.

10. The Federal Government Department with responsibility for blood supply and its regulation was the **Department for Health and Human Services**, overseen by its Secretary and various Assistant Secretaries. One of the agencies of the Department was the **Public Health Service**, which was responsible for public health management.

11. The **Food and Drug Administration ("FDA")** was the body charged with regulating and reviewing the blood supply system. The FDA comprised various divisions, of which the most significant for this presentation was the **Bureau of Biologics**. In 1982, this was merged into the **Center for Drugs and Biologics**, although its old name continued to be used by many.

12. The FDA consulted formally and informally with organisations and individuals with an interest in its work. One formal body is of particular relevance, the **Blood Products Advisory Committee** (sometimes referred to as "BPAC"). This was a standing committee that contained various individuals drawn from relevant medical, commercial and charitable establishments. The blood banking industry was particularly strongly represented. The Committee would hold regular meetings, some of which would be public meetings. It would invite representatives of different groups, including the fractionation companies, to attend.

13. The **Centers for Disease Control and Prevention ("CDC")**, based in Atlanta, was an agency of the Public Health Service. Its principal function was to protect the health

[1] See, for example, the summary of the critique of the IOM Report contained in the Krever Report **[KREV0000001, ep.786-787]**.

of the nation by providing leadership and direction in the prevention and control of diseases, and in the response to public health emergencies.

14. The **National Institute of Health** was the Federal Government's principal biomedical research agency. Among its institutes were the **National Institute for Allergy and Infectious Diseases**, and the **National Heart, Lung and Blood Institute**.

15. There were two trade bodies for fractionation interests in this period, the **Plasma Manufacturers Association** (often referred to as the "PMA"), which represented those pharmaceutical companies affiliated to it, and the **American Blood Resources Association**, a wider body that incorporated plasma collection companies as well.

16. A number of organisations involved with whole blood collection are also of relevance. These include the **American Red Cross**, the **American Association of Blood Banks** and the **Council of Community Blood Centers**.

1982

The risk identified: 1980 to mid-July 1982

17. In his *Tragic History*, Dr Evatt states that AIDS first became apparent in the USA in the last quarter of 1980 **[CVHB0000042, ep.3]**. In July 1981, the CDC established a task force on symptoms that came to be associated with AIDS, and in particular Kaposi's sarcoma, under Dr James Curran **[KREV0000001, ep.749]**. In March 1982, the first inter-agency meeting relating to the issue was convened. It was organised by the CDC and involved both the FDA and the National Institute of Health. Dr Evatt and Dr Curran attended, as did various other clinicians and officials, including Dr Anthony Fauci and Dr Robert Gallo [**KREV0000001**, **ep.749; JREE0000006, ep.427**].

18. According to Dr Evatt, the course of investigation began to change in 1982, as the CDC learned of patients with haemophilia who had developed *pneumocystis carinii* pneumonia ("PCP"). He identified June and July 1982 as being *"pivotal months,"* during which the CDC was informed of a second, and then a third, haemophilia patient who had developed an immune disorder. He said that this led him and his colleagues to become *"reasonably convinced that hemophilic patients were another risk group for AIDS"* **[CVHB000042, ep.3-4]**.[2]

19. Dr Evatt raised the issue with senior figures within the CDC, and the CDC then did the same with other bodies and agencies **[CVHB0000042, ep.3-4]**. On 9 July 1982, Harry M. Meyer, Director of the FDA's National Center for Drugs and Biologics, wrote a circular to all manufacturers of plasma fractionation products, informing them that three cases of PCP in people with haemophilia had been reported to the CDC. He stated that, *"Although the cause of this outbreak is unknown, the information suggests that a transmissible agent might be involved and concern about transmission through blood and blood products has been raised."* **[CGRA0000288]**

20. On 14 July 1982, the NHF issued a patient alert concerning the three cases and the possibility of an infectious agent transmitted through blood or blood products. The document stated that it was *"important to note that at this time the risk of contracting*

[2] The CDC had, during the same period, developed its first definition of the symptoms that would later be classified as AIDS **[KREV0000001, ep.750]**

this immuno-suppressive agent is minimal and CDC is not recommending any change in blood product use" (emphasis in the original). The NHF also referred to the establishment of a *"'blue ribbon' panel of experts"* for the purpose of evaluating the problem. **[JREE0000019, ep.279; KREV0000001, ep.750]**

21. Two days later, on 16 July 1982, the CDC published a report of the three cases in its Morbidity and Mortality Weekly Reports ("MMWR") **[PRSE0000523; CVHB0000042, ep.4]**.

22. The evidence suggests that US pharmaceutical companies were, as of mid-July 1982, given notice of PCP infections in patients with haemophilia, and of the possibility of transmission of an infectious agent though blood and blood products. An internal Hyland/Travenol memorandum, written by Dr Henry S. Kingdon on 5 January 1983, recorded the following about the company's state of knowledge at that time **[CGRA0000668]**:

> "We have been closely monitoring the AIDS issue at Hyland since the original description of the syndrome in male homosexuals in the December 10, 1981 issue of *The New England Journal of Medicine*, and more intensively since the first three hemophilia cases were reported in the *Morbidity and Mortality Weekly* report from the CDC on July 16, 1982."

23. Dr Kingdon subsequently contributed to the production of a draft witness statement in 1990.[3] He gave consistent evidence on this point, and stated that the July 1982 MMWR reports: *"Crystallised the concern that haemophiliacs may develop AIDS and raised a question whether the disease may be blood borne. There was however still much controversy about the disease and its causes and modes of transmission."* He noted that the first patients had been treated with a mixture of products including red cells, platelets, whole blood and concentrates, and it was not clear which (if any) were responsible for passing on infection. **[CBLA0000011_005, ep.26, §75]**.

24. The news that there may be concerns about the safety of US Factor VIII products also reached UK health officials in July 1982, although the exposition of the cause of the concern was, at that time, far from clear. **[DHSC0002219_009; DHSC0002219_012]**

[3] The witness statement was prepared for the UK HIV litigation. It remained in draft form as the litigation was settled. The covering note and marginalia clearly shows that Dr Kingdon had reviewed the statement that had been drafted in his name, and had made amendments where he considered them necessary. **[BPLL0016042_021; CBLA0000069_074]**

The meeting of 27 July 1982

25. An open meeting was held on 27 July 1982, from 8.30am to 4.30pm, to discuss the significance of the occurrence of opportunistic infections with PCP in the three patients with haemophilia. Invited participants included representatives of the CDC, FDA, National Institute of Health and other interested parties such as the NHF, various bodies involved in the collection of blood and the manufacture of blood products, and organisations representing the National Gay Task Force. Among the officials present were Dr Evatt and Dr Meyer. Dr Michael Rodell of Hyland was invited to attend on behalf of the Plasma Manufacturer's Associations.[4]

26. According to the Summary Report made of the meeting, it discussed the epidemiology of AIDS and agreed that the pathological process concerned would be referred to by that name **[JREE0000019, ep.280-282]**. The main risk groups were identified as being homosexual men, intravenous drug users, and Haitians, and it was concluded that AIDS had the characteristics which suggested an infectious aetiology. The three cases of PCP in haemophilia patients were described as being *"disturbing"*, not least as it was noted that there was *"no known intrinsic immune disorder in hemophilia patients that would permit or promote such opportunistic infections."* In the conclusions section of the summary, it was stated that these cases raised *"the question of whether the underlying immunodeficiency seen in these patients has the same etiology as among other groups with PCP."* The meeting called for a high priority to be given to obtaining information that would answer that question.

27. The meeting made a number of recommendations, including the establishment of a surveillance system, the need to conduct laboratory studies to obtain further data on the immunological competence of patients with haemophilia, and the need for ongoing broad input into these issues, including from representatives of the groups affected. Concerns were raised over funding of relevant groups. The meeting also concluded that there was an *"urgent need to determine practical technique to decrease or eliminate the infectious risks from Factor VIII."*

[4] See **BAYP0004205, ep.4-8** for the list of invitees.

28. The summary of the meeting also included an overview of the number of people with haemophilia within the USA, and the change in their treatment over the past ten years through the use of cryoprecipitate and factor concentrates. The benefits of home treatment were recorded, both in terms of lifestyle and the decrease in hospitalisation. It was stated that haemorrhage *"remains the major cause of death in hemophilia patients."* The risk of hepatitis B and non-A non-B hepatitis was noted, but it was recorded that, *"Because of the freedom and reduction of suffering permitted hemophilia patients by Factor VIII concentrate, the product's benefits are perceived by patients to vastly outweigh currently known risks."*

29. The meeting also heard that Factor VIII was considered to be heat labile. Details were given of donor pool sizes (which were said to be prepared from 1,000 to 5,000 donors) and the large amount of factor concentrate used by patients (40,000 to over 65,000 factor units per year). It was recorded that most plasma was pooled from paid donors in plasmapheresis centers, and that *"donors come from many parts of society."*

30. A number of themes and tensions can be discerned from the summary of this meeting, which ran through the debates that followed in the months and years to come.

    a. The tension between (i) the potential gravity of the problem and resulting calls for action, and (ii) the scientific and medical uncertainties involved and resulting calls for further information and research.
    b. The association between the suspected risk of AIDS and the known risk of hepatitis.
    c. The reliance on plasma from paid donors from *"many parts of society"*.
    d. The emphasis placed on the beneficial effects of the use of factor concentrates, and consequent concerns about risk to the supply of these products.
    e. The approach to the way in which the conclusions and recommendations of the meeting were expressed. Instead of identifying the opinions of individuals, and differences between those opinions, the note is drafted to record the view of the meeting as a whole. Inevitably, this gives rise to a broader and less specific set of observations.

31. In his *Tragic History*, written more than twenty years later, Dr Evatt gave the following account of the meeting, which stands in contrast to the collegiate tone of the summary **[CVHB0000042, ep.4-5]**:

> "It was a long day. Detailed histories of the hemophilia cases were systematically presented, followed by data from the other risk groups, and comparison of hypothetical risks posed by various etiologic theories to each risk group. Only the high risk for blood-borne infection could explain a common risk to all form groups [drug users, Haitians, gay men, and people with haemophilia]. But, rather than expressing alarm at a possible blood-borne infection and suggesting ways to reduce a blood-borne risk, the audience expressed an almost universal reluctance to act. The scientific community had yet to see *'published evidence that the syndrome was indeed an infectious disease'*, let alone blood borne and sexually transmitted. Homosexuals were major blood donors in the large cities on the east and west coasts. It was thought that singling out homosexuals for exclusion would unnecessarily stigmatize them without evidence that they were indeed transmitting the disease. The blood industry, threatened by losing a large donor pool, strongly supported the position of the gay groups on this issue; *'three hemophilia patients with the syndrome did not mean that they should spend millions of dollars'* changing recruitment and screening practices. The hemophilia groups expressed concerns that the data showing immune suppression in hemophilic patients could have reflected the effects of prolonged use of blood products and did not necessarily mean they had the new syndrome. They also feared the stigma of having a disease associated with homosexual patients and were concerned that reducing the use of clotting factor concentrates would bring back old issues of deformities and early death, the fate of hemophilic patients before concentrate treatment. The FDA, which had regulatory authority over the blood industry, had not yet accepted the collection of disorders related to immune deficiency as a single disease, and was also sceptical that hemophilic patients represented another risk group. Thus, no consensus was reached concerning blood donors."

32. Dr Evatt did consider, however, that two important steps were accomplished. First the disease was officially named AIDS, and its recognition allowed for an expansion of investigations. Second, the CDC was encouraged to continue its studies of patients with haemophilia. **[CVHB0000042, ep.4-5]**

33. Dr Rodell provided an account of the meeting in a letter dated 3 August 1982, which was sent to the managing director of the Plasma Manufacturers Association, Paul Kaufman, and was copied to representatives of Alpha (Dr Penny Carr), Armour (Dr Robert Johnson) and Cutter (Dr Lee Hershberger). The letter indicates that the results of the CDC investigations into case histories of AIDS patients were given by Dr Curran and Dr Evatt of the CDC, who explained that interviews had indicated that the three haemophilia patients were not intravenous drug users or homosexuals. The

overview of haemophilia and its treatment was provided by Dr Louis Aledort, a haemophilia physician with links to the NHF. Dr Rodell wrote that he provided information to the meeting in response to questions, including about the existence of six to eight plasma collection centres in prisons that produced about 2% of the total plasma collected in the country. He also said that plasma collection centres were located throughout the country, including in inner city and university locations. According to Dr Rodell, Dr Sandler of the American Red Cross, *"commented that CDC had not yet proven that AIDS is transmissible by blood or blood products and that no donor population should be implicated at this time."* Scepticism on this point was also expressed by the representative of the American Association of Blood Banks, but other participants, notably including those from New York, were more persuaded by the CDC position. **[CGRA0000287]**

34. According to Dr Rodell, he spoke privately to Dr Denis Donohue, then the Director of the Division of Blood and Blood Products at the FDA. Dr Donohue said that his Division could *"find itself in the position of having to make a politically expedient decision to disapprove the operation of plasmapheresis centers specifically intended to collect anti-HBs plasma from homosexuals"* **[CGRA0000287]**. There is no evidence that this issue was raised in the meeting itself. In a witness statement in 2002, Donald Francis, a CDC employee who attended the meeting, criticised representatives of pharmaceutical companies who were at the meeting for failing to disclose the practice of using plasma from such centres in the production of Factor VIII concentrates **[CGRA0000404, §12]**.

The exclusion of plasma from HBIG donors

35. Dr Donohue did approach fractionators in August 1982 in an effort to persuade them voluntarily to exclude plasma obtained from donors – typically gay men – who had been recruited because they were likely to have high levels of antibodies to hepatitis B in their plasma. These approaches were discussed during Counsel to the Inquiry's presentations on the pharmaceutical companies in September and October 2021, and that evidence is not repeated in detail. In general, companies expressed a willingness voluntarily to suspend the use of such plasma in factor concentrates (although not necessarily from other products):

a. Cutter agreed to such a suspension, although it was noted (internally) that *"we will not be fractionating any of this material into factors VIII and IX for sale anyway."* **[CGRA0000330]**
b. Alpha also agreed to a voluntary suspension until further notice. **[CGRA0000277]**
c. Contemporaneous documents suggest that Hyland did not fractionate such plasma in their own products, although they may have sold it to Alpha **[CGRA0000330; BAUM0000008; CGRA0000246]**. In one document, a Cutter representative recorded that Dr Rodell of Hyland *"expressed great surprise that we would even consider fractionating this material in to factors VIII and IX (anything other than HIBG)*[5] *because of the history of hepatitis problem"* **[CGRA0000330]**
d. Armour's position is not clear from the documents obtained by the Inquiry.

36. There is some evidence that at least some from within the pharmaceutical companies understood Dr Donohue's request to be based on *"political"* rather than scientific considerations. That was implied in Dr Rodell's note of his initial conversation with Dr Donohue on this topic **[CGRA0000287]**. Dr Hershberger of Cutter also referred to *"political reasons"* behind the decision **[CGRA0000330;** see also **CGRA0000652** and **BAUM0000008]**. He recorded that Dr Donohue *"feels that the hold will not be necessary for more than two or three months unless more donors develop AIDS"* **[CGRA0000330]**.

37. The terms of the contemporary correspondence suggest that the commitments given regarding plasma from this category of donors were prospective. They describe what would happen in the future, with no comment made on what would be done with existing stocks of plasma that had been, or were being, processed into blood products. Counsel to the Inquiry have seen no evidence that efforts were made to withdraw or withhold factor concentrates that had been produced from such plasma.

38. However, by 12 August 1982 the FDA Bureau of Biologics had requested that Cutter quarantine four units of plasma from a donor hospitalised for AIDS. Dr Hershberger commented **[CGRA0000652]**:

> "We were extremely fortunate that we were able to quarantine [these units] before they were pooled. Had they been pooled the BoB [Bureau of Biologics]

[5] "HBIG" refers to hepatitis B immuno-globulin, a product that could be used to protect the recipient from hepatitis B and other infections.

might have found it politically expedient to make hard line decisions regarding the fate of the products made from the pool. This kind of risk will continue for some time until there is solid data to prove that AIDS is not transmitted by blood products. Meanwhile we should try to help the BoB develop a rational policy for dealing with AIDS that will withstand political panic."

Meeting on heat treatment, 9 September 1982

39. The issue of heat treatment of factor concentrates is discussed later in this presentation. It is relevant to mention at this stage, however, that a meeting between fractionators and the FDA took place on 9 September 1982 to discuss *"certain technical problems with regard to heat inactivation of viruses, particularly non-A, non-B hepatitis in plasma derivatives."* It is notable that the summary of the meeting contains no reference to the relevance of heat treatment to the inactivation of the infectious agent for AIDS. While it is possible that this was discussed in the margins of the meeting, it does not seem to have been a central topic. **[SBTS0000313_101]**

Meeting of the Blood Products Advisory Committee, 23 and 24 September 1982

40. The Blood Policy Advisory Committee met on 23 and 24 September 1982. According to a short summary provided to a later Congressional investigation, the meeting discussed *"non-specific methods of detecting infectious agents in donated blood"*. This would appear to be a reference to surrogate testing. The minutes of the meeting recorded a discussion of the issue of AIDS, at the end of which the committee concluded that *"there are insufficient data to suggest that any immediate action [be taken] with licensed blood products."* Representatives of a number of pharmaceutical firms attended, including Armour, Hyland, Cutter and Hyland/Travenol. **[KREV0000001, ep.751; JREE0000006, ep.419]**

Further investigations by the CDC, autumn 1982

41. During autumn 1982, the CDC continued to investigate and identify potential cases of AIDS. It set out its criteria for the syndrome in an editorial in the MMWR on 24 September 1982, which referred to the *"spectrum of AIDS manifestation, which range from absence of symptoms to specific disease"* **[OXUH0002848]**. Dr Evatt recalled that the CDC identified four additional cases, and one probable case, of AIDS in people with haemophilia, including in two children. It also investigated AIDS transmission through whole blood transfusions, culminating in the identification of an

"unequivocal transfusion case" in a 20 month-old infant in San Francisco **[CVHB0000042, ep.5]**. Dr Evatt, in his *Tragic History*, stated that some blood banks *"severely hampered investigations"* by refusing to share patient details on the ground of confidentiality. He also stated that **[CVHB0000042, ep.5]**:

> "As the cases accumulated, the author routinely provided briefings to the blood industry, FDA panels and NIH [National Institute of Health] conferences of blood banking experts, who seemed only to request more patients and proof, without yielding on recommendations for changes in blood policy."

42. It is important to note that Dr Evatt's frustration was aimed not just, and indeed not principally, at the pharmaceutical companies at this point (although it is reasonable to infer that they were part of the *"blood industry*" to which he referred). It appears that the blood banks were a greater source of difficulty for him at that time. He also referred in his *Tragic History* to *"widely divergent"* views among members of the NHF's Medical and Scientific Advisory Committee ("MASAC"), the foremost body for issuing guidelines for clinical care for people with haemophilia in the United States. In Dr Evatt's view **[CVHB0000042, ep.5]**:

> "The situation was, and continued to be, emotionally stressful. As a result, the MASAC's recommendations were compromises, attempting to accommodate the opinion spectrum."

43. In October 1982, the NHF resolved that no plasma should be sourced from gay men, intravenous drugs users, or people from Haiti **[KREV0000001, ep.751]**. The response of the pharmaceutical companies to this proposal is considered further below.

44. From a UK perspective, it is relevant to note that it was at around this time that Dr Craske produced his initial report on AIDS, having been asked to do so by UK Haemophilia Centre Directors **[CBLA0001653_003]**. In the covering letter to the report **[HCDO0000557]**, Dr Craske stated that he had spoken to the *"project leader of the team looking into the epidemiology of the disease"* at the CDC, probably a reference to either Dr Evatt or Dr Curran. Dr Craske said that he had been told that five people with haemophilia had been identified with the disease, two of whom had died. The cases revealed no association with homosexual practices, drug addiction or treatment with immunosuppressive drugs. The cases were in areas of the USA where the syndrome had not previously been described. Dr Craske recorded that:

> "The hypothesis at present being used to explain the acquisition of these cases … is that one or two patients in the incubation period of the disease donated plasma which has since been used to prepare factor VIII or IX concentrates. All the haemophiliacs who have had the disease have had severe coagulation defects requiring regular treatment with factor VIII. The likelihood is, therefore, that other cases will be identified amongst severe haemophiliacs, though probably at a low prevalence."

Meeting of the Blood Policy Advisory Committee, 3 and 4 December 1982

45. The Blood Policy Advisory Committee met again on 3 and 4 December 1982 **[CGRA0000674]**. Among a large number of items discussed were the following:

    a. Methods for decreasing the infectivity of Factor VIII and Factor IX concentrates in respect of hepatitis B. It was noted that this was also of interest because of the occurrence of AIDS in some haemophilia patients. [ep.8, §22-25]
    b. The risk groups for hepatitis B in donors, including intravenous drugs users and gay men. [ep.8, §22]
    c. A study showing lower T4/T8 cell ratios in patients using factor concentrates when compared to those using cryoprecipitate. It was noted that *"similar changes have been found in patients with AIDS"*. [ep.9, §26]

46. Dr Evatt reported on the CDC investigation into AIDS [ep.9, §27]. He stated that the epidemic was growing at an almost exponential rate, doubling every six months, and expressed a concern that transfusion cases *"may follow the same increasing pattern seen with haemophilia patients."* He said that eight people with haemophilia had been reported with AIDS, only three of whom were still alive. Five transfusion cases had been reported, including a child who had received a transfusion at birth. One patient developed AIDS seven months after transfusion.

47. Dr Evatt commented that [ep.10, §27]:

> "The incubation period, as determined from about 35 cases where person-to-person transmission had been documented, is about 4 to 7 months with a prodrome before diagnosis of about the same period. The epidemiological pattern seems to be similar to that of hepatitis B."

48. The committee discussed steps intended to reduce the risks of using factor concentrates, including relying on cryoprecipitate, viral inactivation techniques,

excluding high risk donors, and surrogate testing. The meeting concluded that *"there was a sense of urgency because of the continuing spread of AIDS and because of its long incubation time"* [ep.10, §29]. However [ep.10, §30]:

> "The committee did not recommend any immediate changes in the biological regulations or regulatory activities at this time. Several investigations are being intensely pursued by the blood bank community, CDC, NIH, FDA, and the manufacturers which may lead to steps to reduce the risk to recipients of blood products."

49. It was noted that further meetings were planned on viral inactivation and tests to prevent transfusion transmitted hepatitis. [ep.10, §29]

Discussion of further measures of donor exclusion, December 1982

50. On 9 December 1982, the NHF informed its members that four new cases among people with haemophilia had been identified, and stated that *"while there is insufficient data to directly link the spread of AIDS to concentrates, there is an increased concern that AIDS may be transmitted through blood products."* It advised that *"patients and parents should be aware of the potential risks."* **[KREV0000001, ep.777]**

51. Dr Rodell of Hyland sent a letter to the NHF on the same day, responding to its recommendations to exclude high risk donors **[CGRA0000655]**. In It, Dr Rodell said:

    a. Hyland had consistently sought to exclude intravenous drug users from donating, through checking forearms for needle marks and scar tissue.
    b. The company had, *"within the past several months"*, made a commitment to withhold plasma obtained through targeted recruitment of gay donors from use in factor concentrate production. As was discussed in previous hearings, the wording of this response may indicate that Hyland did not process this material itself, but supplied it to another company (Alpha) **[Transcript, 28.09.82, p.71-79]**.
    c. Hyland had not, at the time of writing, sought to determine the sexuality of their donors, and Dr Rodell raised the difficulties that would be involved in seeking to identify donors, or to question them directly on that matter. He indicated that the company would rely instead on education and self-exclusion.

d. Donors would, however, be asked directly about whether they had been residents in, or visitors to, Haiti.
e. Dr Rodell also raised the issue of the limited knowledge that pharmaceutical companies had in respect of donors whose plasma was recovered from whole blood donations.

52. On the following day, 10 December 1982, an informal meeting took place between representatives of the FDA and those of pharmaceutical companies. This had been convened at Dr Donohue's request, with the intention of exploring possible actions to minimise the risk of AIDS. A memorandum prepared by Dr Steven Ojala of Cutter recorded that *"Although the transmission of AIDS via blood products (and specifically AHF) has not been conclusively demonstrated, there is some evidence that a possibility does exist"* **[CGRA0000425]**. That statement is notably less definitive than the view expressed (retrospectively) by Dr Evatt, who – like his CDC colleagues – was not present at the meeting.

53. According to Dr Ojala's memorandum **[CGRA0000425]**, a number of issues were discussed.

a. Dr Donohue asked if donors from high risk areas such as New York, San Francisco and Hollywood could be excluded. Dr Rodell of Hyland responded with the suggestion that an education programme would be more meaningful. His company, he said, intended to ask specifically whether donors were high risk (i.e. were they homosexuals or drug users), as *"the public health risks overrode any concern with discrimination"* (a position that seems to be at odds with his letter to the NHF the previous day). Others expressed doubts over whether an education programme would be *"completely successful"*, but it would be a first step. It was recommended that the education programme be coordinated between manufacturers, and that it be prepared by an experienced professional firm.
b. Dr Donohue asked if the manufacturers were willing to exclude plasma collected from prisons, which was stated to constitute about 2% of collected plasma. Dr Ojala recorded that *"The other manufacturers [i.e. those other than Cutter] had no problem with this suggestion."* It was pointed out (it is not stated by whom) that there had been no cases of AIDS reported from prisons, but Dr Donohue responded that this was because of the aetiology and

incubation period. Dr Ojala expressed a view that *"they [i.e. the FDA] will remain relatively non-negotiable on this point."*

c. Dr Donohue also raised the issue of recovered plasma (i.e. plasma collected from whole blood donations made to blood banks), and the lack of control the pharmaceutical companies had over this source. He specifically mentioned the Irwin Memorial Blood Bank, which was located in San Francisco, an area considered to be "high risk" in terms of donors who may have AIDS.

54. Dr Ojala recorded his impression that **[CGRA0000425]**:

> "while the agency is concerned about the question of AIDS, they are not going to overreact to the situation. Concerns have been expressed about the safety of 'paid' donors versus voluntary sources and there are those who are championing the return to single donor cryo. I think the Bureau will take a more studied and scientific approach until sufficient information is available."

55. The same day, 10 December, the CDC published its report of the transfusion related AIDS case in a 20 month old infant in San Francisco in the MMWR **[PRSE0003276]**. The incubation period was identified to be 18 months. The same report identified that the three people with haemophilia whose cases had been reported in July had all died. Dr Evatt commented in his *Tragic History* that **[CVHB0000042, ep.5]**:

> "We [he and his colleagues at the CDC] were now convinced that in spite of the absence of an identified agent, the pattern of the epidemiological evidence was sufficient to implicate a blood-borne disease. This evidence could no longer be ignored; in our opinion urgent changes in blood policy were needed to reduce the risk."

Alpha's introduction of donor screening measures: 15-16 December 1982

56. On 15 December 1982, the Executive Committee of Alpha met for what was described as an *"AIDS meeting"*. The Committee decided on a number of steps.

57. On donor screening, it was decided to add donor history questions pertaining to homosexuality and Haitians. A donor information bulletin would be developed, explaining the reasons for the additional questions. The donor questions would be required in centres that contracted with Alpha to provide blood, and Alpha would *"recommend they be included for all volunteer donors"*. Counsel to the Inquiry understand this to mean that Alpha would include such questions in its own centres, would insist on them being included in any plasmapheresis centres with which they contracted, and would encourage agencies who supplied them with recovered

plasma from voluntary whole blood donations to put the questions. As will be seen, the latter proposal led to a breakdown in relations between Alpha and some blood banks.

58. The Executive Committee also recommended the suspension of deliveries from the Irwin Memorial Blood Bank in San Francisco, the facility raised by Dr Donohue at the meeting five days earlier. Reference was also made to the *"recent"* closure of Alpha's San Francisco plasmapheresis centre. An evaluation was to be made of other contract centres. The meeting also discussed a *"bulletin"* that was to be sent to the Alpha sales force, advising them on AIDS.

59. Several of the proposed actions were put into effect the following day, 16 December 1982. A circular was sent to centre directors enclosing a background memorandum on AIDS for centre personnel, a donor information document, and a memorandum that was intended to be given to deferred donors (i.e. those who excluded themselves or were excluded from the process as a result of the additional measures) **[CGRA0000627]**. The background memorandum contained the following information [ep.2].

    a. Several haemophiliacs who had received blood products had *"contracted life-threatening infections of the same type as seen in AIDS patients. Some believe that there is transmission of AIDS by blood products."*
    b. It was noted that no causative agent had yet been identified for AIDS. No test was available and there was no known treatment. The CDC had suggested that the mode of transmission of AIDS might be similar to that of hepatitis B.
    c. The problem *"has significant implications for the entire blood and plasma industry"*. None of the data available addressed whether *"the AIDS problem was more or less prevalent in paid donors than in non-paid donors."*

60. The donor information letter informed the reader about concerns in the medical community about the *"serious disease"* known as AIDS, and the increasing number of cases that the CDC was identifying [ep.3]. Although little was known of the disease, it had been fatal and there was no known treatment. The disease was thought to occur *"more frequently in certain groups of people which include male homosexuals, Haitians, and drug abusers."* A direct appeal was made to the donor [ep.3]:

"In past years, you have helped us help others through your plasma donations. We are now faced with a situation in which only you can help us ensure a safe product to those whose lives depend on it. Because of our shared goal of producing a continuing safe supply of plasma products for use worldwide, Alpha had committed its resources to reducing the possibility that this disease might be transmitted through our products. We are now asking for your commitment also.

Until the cause of this disease is determined, we are asking that people who are part of any of the following groups do not donate:

- Haitians
- Drug abusers
- Male homosexuals."

61. The donor letter also mentioned that those in the three named groups may be eligible for a special plasma program. This was a process adopted by Alpha where such plasma was segregated from that fractionated for factor concentrates, but which could be used in other products.

62. It is clear from the contemporary documents that Alpha did not rely simply on the donor reading the sheet and deciding on what steps to take. An instruction was provided to centres directing that Medical Reception would add the following questions to its existing screening questions **[JREE0000019, ep.286]**:

> "Have you ever been to Haiti?
> Have you ever used illicit drugs intravenously?
> Have you ever had sexual contact with a man (For male donors only?)
> If any of the above questions are answered "yes", the donor must be rejected."

63. The document that was provided to an excluded donor explained that the exclusion did not necessarily mean that the person had AIDS. It urged those who had questions about their health to contact their personal doctors or local health facilities. The donors were asked to refrain from donating until further information became available. **[CGRA0000627, ep.4]**

64. A similar letter was also sent to plasmapheresis centres that contracted with Alpha, identifying the same three groups to be excluded from donations [ep.5-6]. The letter directed that plasma obtained after 26 December 1982 from donors who had not been screened according to the new process should not be sent to Alpha.[6] The letter concluded that [ep.6]:

[6] The letter said these measures did not apply to donors of "special Hepatitis plasma", which Counsel to the Inquiry understands refers to plasma used to produce HBIG.

> "While we recognise the potential for the rejection of long term donors, we strongly believe that the loss of these donors is more than offset by the protection of our patients."

65. Alpha's measures were introduced unilaterally, and were the first of their kind. They went beyond the collective steps put forward on behalf of fractionators as a whole at the 10 December meeting with Dr Donohue. As will be seen, they also went significantly beyond the measures that many voluntary and commercial blood banks were willing to take in the months that followed. Notably they included a direct question on the donor's sexuality. Alpha would later report that 308 homosexual donors had been excluded from donating in the first three weeks of implementation, and that an even larger number had voluntarily excluded themselves **[CGRA0000321, ep.1]**. By the summer of 1983, 800 potential donors had *"voluntarily disqualified themselves from the pool"* **[CGRA0000665_001, ep.1]**.

66. The company explained the measures in its newsletter of Winter 1982, quoting the Medical Director, Clyde McAuley, as saying that **[HCDO0000276_025]**: *"So long as there is any question about the involvement of blood products, Alpha is taking all possible steps to reduce the potential risk for the hemophiliac receiving our factor VIII and IX concentrates."*

67. The steps were prospective. Returning to the minutes of the Alpha Executive Committee meeting of 15 December 1982, those attending also considered a number of issues that raised the question of whether retrospective action should be taken. **[CGRA0000599, ep.2]**

68. The meeting considered what was to be done with products that had been produced using the three units of plasma that had been obtained from what was described as *"the AIDS donor."* It is not clear from the minutes how many lots were affected, but reference was made to one in particular – A1-3661, comprising 2,841 vials – which had been shipped in April and August 1982. The situation was to be reported to the FDA, and the company would "*wait for the [Bureau of Biologics] opinion on what should be done."* Counsel to the Inquiry have not identified material to establish what steps, if any, were taken in respect of this material.

69. The meeting also considered the use of cryoprecipitate as an alternative to factor concentrates [ep.2]. The following calculation was set out.

a. The *"average hemophiliac"* uses 70,000 AHF units per year.
b. The US haemophilia population was estimated to be 10,000.
c. The annual usage was therefore around 700 million units (70,000 x 10,000)
d. Assuming a maximum recovery of 100 units AHF per unit of whole blood or single unit of plasmapheresis, 7 million donations would be required to meet US demand.
e. Within a year, a patient requiring 70,000 units would be exposed to 700 donations per year (70,000/100).
f. In the same period, a patient using 20% of the current average level of 70,000 units would be exposed to 140 donations per year (14,000/100).

70. The meeting concluded that *"The use of cryo may do nothing to solve the incidence of AIDS related to AHF transfusion,"* and that *"Risk would be approaching that of pooled AHF"*. The minutes did not record what that risk was defined to be, or why it was considered to be approaching that of factor concentrates.

71. The costs of switching to cryoprecipitate were estimated to be [ep.2-3]:

a. An additional $1 per unit due to increased labour, thus adding a cost of $7 million in the USA if the figure of 7 million donations were to be achieved.
b. An estimated $20 million to $30 million in equipment and shipping costs for 7 million units, with additional costs for shipping at -20°C.

NHF guidance on use of factor concentrates

72. On 21 December 1982, the NHF made recommendations on the treatment of people with haemophilia in light of the risk of AIDS. This was summarised by the Krever Report in the following terms **[KREV0000001, ep.777]**:

> "[The organisation] said that there was no conclusive evidence that the use of cryoprecipitate or fresh frozen plasma would reduce the risk of AIDS, but it recommended that patients who had not yet used concentrates should not begin to do so unless there was an overriding medical indication for so doing. This group included children under the age of four, newly diagnosed haemophilia patients, and those with mild haemophilia. All other patients were advised to continue using concentrates. In January 1983 these recommendations were modified slightly. Physicians were also advised to use DDAVP, or desmopressin, a drug that increases the release of factor VIII in the body, for patients with mild or moderate hemophilia A … and to weigh the

advantages and disadvantages of postponing elective surgery for all patients."

Summary of the position reached by the end of 1982

73. By the end of 1982, pharmaceutical companies and other relevant bodies were aware of the potential risk of the transmission of AIDS through blood products, though there was no consensus about the aetiology of the disease, or the nature and extent of the risk. That lack of consensus was evident between government agencies, as well as between those agencies and the organisations involved in blood banking and fractionation. In broad terms, the CDC (or at least a number of significant figures within the CDC) seems to have been considerably more concerned about the risk of AIDS than were other participants within the debate.

74. Some steps had been taken in respect of the source of the plasma used in fractionation. Companies had agreed voluntarily to forego future manufacture of blood products from plasma obtained from donors specifically recruited because they were gay. Hyland (and by inference other companies) had expressed an intention to educate donors about the three known high risk groups for AIDS, and to rely on self-exclusion. Other measures, such as avoiding plasma from prisons and geographical areas thought to be "hot spots" for AIDS, were under consideration. One company, Alpha, had gone considerably further, unilaterally introducing direct questioning of donors about whether they were gay, intravenous drug users, or had links with Haiti. Heat treatment for factor products was in development and had been the source of some discussion, but the focus of such programmes at that time remained on inactivating hepatitis viruses.

75. As events in January 1983 would show, there was a gulf between the steps that the blood industry generally was at that stage willing to take, and those that some within the CDC considered that they should be taking with immediate effect.

1983

The meeting of the Workgroup[7] to Identify Opportunities for Prevention of AIDS, 4 January 1983

76. The meeting held on 4 January 1983 in Atlanta is perhaps the most prominent, and controversial, event in the history of AIDS and infected blood in the United States. Various different records of it exist including: the formal summary report **[JREE0000019, ep.287-90]**; a note made by Dr John Hink of Cutter **[CGRA0000300]**; an account in *Medical News*, 4 February 1983 **[BAYP0000028_024]**; and Dr Evatt's recollection in his *Tragic History* **[CVHB0000042, ep.5-6]**. Numerous other accounts exist in the secondary sources.

77. The meeting was convened by the Assistant Secretary for Health, Dr Edward Brand Jr, at the urging of the CDC **[CVHB0000042, ep.5-6]**. It was a public meeting, chaired by Dr Jeffrey Koplan. Although Dr Koplan was a senior figure within the CDC, he was chosen as chair as he was considered to be a neutral figure in the developing debate around AIDS **[JREE0000019, ep.130]**. A helpful overview of the meeting is contained in the Krever Report, seemingly drawn from the formal summary **[KREV0000001, ep.752]**.

> "A meeting of the advisory group was held on 4 January 1983. More than 200 persons were present at that meeting,[8] including employees of the CDC, the Food and Drug Administration, and the National Institutes of Health, representatives of the blood and plasma centres, the plasma sector, the four large U.S. blood product manufacturers, the gay community, and the National Hemophilia Foundation, as well as some treating physicians.
>
> At the meeting, Dr Evatt presented evidence suggesting that AIDS could be transmitted by blood. He discussed the cases of AIDS seen in hemophiliacs, described the case of an infant in California who had received a transfusion at birth, and said that five unconfirmed cases of transfusion-associated AIDS were under investigation.
>
> Several measures were suggested to reduce the risk of transmission. Dr Donald Francis, the assistant director for medical science in the CDC's division of virology, advocated direct questioning of blood donors about behaviour that would have placed them at risk of contracting AIDS. He also recommended that donations be tested for the presence of antibody to the

[7] The body is sometimes referred to as an "Advisory Committee." It was an ad hoc group, who were invited to attend what was a public meeting.
[8] The list of invitees is at **JREE0000006, ep.428**, though many others attended what was an open meeting.

> hepatitis B core antigen, in the belief that persons who had been exposed to hepatitis B would also be at greater than normal risk of contracting AIDS. Representatives of the gay community objected to his first proposal because it would be discriminatory, and representatives of the blood banks and plasma industry objected to the second, primarily because it would be too expensive. Dr Oscar Ratnoff, a physician at Case Western Reserve University who treated hemophiliacs, recommended that hemophiliacs use cryoprecipitate instead of factor concentrates. Ultimately, the meeting endorsed none of these measures. Although the participants reached a general consensus that *"it would be desirable to exclude high-risk donors to reduce the risk of AIDS transmission,"* there was no agreement about a method of accomplishing that goal. There was also no consensus on the question of whether AIDS was caused by a transmissible agent, on the risk of AIDS from blood donations, or on the desirability of introducing new methods of donor screening or testing to reduce the risk of transmission. Instead, the CDC, the Food and Drug Administration, and the National Institutes of Health were each asked to submit a set of recommendations after the meeting for the prevention of AIDS in patients with hemophilia and for other recipients of blood and blood products, so that a uniform set of recommendations might be developed."

78. It is respectfully suggested that an examination of the wider documentation of the meeting allows for a more nuanced picture of the debate on surrogate testing. The CDC's case was presented by Dr Francis. He and his colleagues had conducted studies that they said showed that 90% of known definite AIDS cases were positive for the antibody to hepatitis B core antigen (anti-HBc). This compared to a 5% figure in the general population of <u>voluntary</u> donors. These figures would later be contested. His position won some support, with some indicating a willingness to run programmes at their blood collection facilities. The objections to the test were both that it would be expensive and that it would lead to the destruction of plasma without direct evidence that the plasma was infected with AIDS (i.e. that the test was not sufficiently specific). Some concerns were also raised about the availability of materials for the test, and the need for additional training procedures. The Cutter note of the meeting recorded one (unknown) participant estimating the cost of introducing anti-HBc testing on all donations as *"at least $100,000,000 per year"*. Another, Dr Robert Gerety, did not think that the test was *"a good marker"*, and noted that the test was not licensed and would not be that year. Dr Gerety was the Director of the Hepatitis Branch of the FDA's Division of Blood and Blood Products. Dr Hink, the author of the Cutter note, summarised the debate in the following terms: *"Question of cost and implementation bothered many but not CDC, several objected on scientific grounds."* **[CGRA0000300, ep.3; JREE0000019, ep.288-289; JREE0000006, ep.428]**

79. Dr Evatt's account in his *Tragic History* provides a personal reflection of the meeting **[CVHB0000042, ep.6]**:

> "Naively we [Dr Evatt and colleagues within the CDC] reasoned that the meeting would be routine and produce a *pro* forma stamp for action, that is, review the data, accept the evidence as significantly supporting the case for a blood-borne infection and produce recommendations that high-risk groups be excluded from the donor pool and/or adopt a surrogate test, for example hepatitis B core testing, or immune complex tests to exclude possible infected donors…
>
> Unfortunately, 4 January 1983, became possibly the most discouraging and frustrating day of the epidemic for the CDC staff. Rather than a rational discussion of the data, the meeting quickly became a forum to advance individual agendas and 'turf protection'. In the presence of (and perhaps in reaction to) news reporters and TV cameras, each group voiced essentially the same skeptical reasoning they had at the earlier meeting in July 1982. On this occasion some were less polite, sometimes attacking CDC data as inadequate and over stated. The particularly vocal blood bank organizations still strongly adhered to the philosophy that transfusions were a life saving procedure; some adverse reactions were acceptable to save a life. A 'rare disorder' that affected only eight hemophilia patients and one transfused patient should not force a change in blood policy. Calls were to *'Show us the agent ... subject it to Koch's postulates'*.[9] The attendees regarded the data as only anecdotal evidence, without merit. Two views emerged. To us, the attendees' reactions seemed to be those of a group approaching an idealized science problem in the abstract world; to the audience, their position was that of a group acting as careful scientists in accordance with their training.
>
> All attendees underestimated the already high disease incidence in the population because AIDS was obscured by a long, still undetermined incubation time. Dismissed as inadequate were our data on the high frequency of immune disorders affecting the hemophilia population that were identical to those found in homosexual patients with lymphadenopathy associated syndrome. Above all, the blood bank organizations remained unconvinced that the CDC had shown the condition to be a blood-borne disease and some FDA officials remained unconvinced that AIDS was actually a distinct disease. Dr Koplan proposed a set of consensus recommendations at the end of the day and all were soundly defeated.
>
> The blood banking organizations were clearly displeased with what, in truth, was the CDC's intrusion into areas considered FDA's responsibility. The attitude was reflected in a memo from a senior ARC[10] official that stated, *'It has long been noted that CDC increasingly needs a major epidemic to justify its existence … In short, we can not depend on the CDC to provide scientific, objective, unbias[ed] leadership.'*[11]"

---

[9] Koch's postulates are a series of criteria that are used to test the causative link between a suspected infective agent and a disease. They include a criterion to identify and isolate the organism said to cause the disease, something that could not be done with AIDS as of January 1983, as the infective agent (HIV) had not been identified.

[10] American Red Cross.

[11] The relevant minute is quoted at greater length in the IOM report **[JREE0000019, ep.129]**. The ARC official also referred to Federal funding cuts, a perceived *"marketing"* approach by the CDC, and a suspicion that *"AIDS probably played some positive role in CDC's successful battle … to fund a new $15,000,000 virology lab."*

80. In an interview for an ITV television programme,[12] Dr Francis of the CDC confirmed accounts that have been given of him slamming his fist on the table during the meeting, asking in effect how many AIDS cases, or how many deaths, would be needed before those attending took action. **[ITVN0000052, to 08.07 to 09.14]**[13]

81. The Cutter memorandum, prepared by Dr Hink, contains some further insights into the meeting **[CGRA0000300, ep.1]**.

> "Most of the morning was devoted to presentations of information and data by individual experts … There is little question that these individuals knew their subject but as the day wore on, it was evident that experts in other fields paid little attention to these overviews. For instance it became obvious that few people understood, or cared about the differences between blood and plasma collection regulations or procedures and just how all this related to manufacture of AHF. Consequently while one individual would be proposing some action with regard to AHF donors processed by plasmapheresis, he would refer to blood donors and an argument with a blood banker would arise. (This is just an obvious example. There appeared to be a considerable communication difficulty between experts within restricted but diverse fields and between expert and the non-scientific types on a number of other issues.)
>
> I believe, but am not certain, that the objective of this CDC sponsored Workshop was to arrive at a meaningful recommendation for action(s) which would reduce the rapidly increasing number of AIDS disease cases being identified in the US. In particular it appeared that they directed attention to the 8 or 10 hemophiliacs with confirmed or suspected AIDS assumed to have been caused by infusion of blood products and what should be done quickly to prevent a further increase in these numbers.
>
> However, difficulties in communication and political power struggles made progress towards these objectives difficult. The anti-discrimination position of the gays, self-serving comments of blood bankers and lack of data to provide legitimacy to many proposals resulted in an overall stalemate. I felt a great deal of empathy for the meeting chairperson who I felt did a good job under the circumstances."

82. Dr Hink recorded that there were two *"ever recurring proposals for actions"*, namely education and self-exclusion for high risk donors, and the introduction of anti-HBc testing. He noted that gay rights bodies were *"greatly opposed"* to the exclusion of male homosexual donors. **[CGRA0000300, ep.1-2]**

---

[12] *"The Cook Report: Profits Before Patients"*

[13] The first speaker in the clip is Dr William O'Connor, who was described as an advisor to the US government on AIDS from 1986.

83. The possibility of a reversion to cryoprecipitate was also raised. Dr Ratnoff said that he did not believe that the infectious agent would be eliminated from *"mega donation pools"* in the next year or thereafter, and hence he preferred to use cryoprecipitate until a genetically engineered (recombinant) product was available. Dr Donohue of the FDA raised (unspecified) *"logistical problems"* to which this would give rise. The memorandum also records the two instances on which prison plasma was raised, neither of which appear to have led to recommendations on this point. The prominence of this issue in the note suggests that it was a matter of particular concern or sensitivity for Cutter. [ep.2-3]

84. Dr Hink concluded his memorandum by making his own recommendations for Cutter. They were [ep.3-4]:

    a. Institute a *"high risk donor"* education and voluntary exclusion programme at all Cutter plasma collection facilities.
    b. Continue to exclude plasma collected from centres dealing with predominantly gay donors (i.e. those recruited for hepatitis B antibodies).
    c. *"Take no extraordinary action (other than [point a.] above) at our two prison centres which supply about 3,000 litres/mo. (there are no data to support the emotional arguments that prison plasma collected from adequately screened prisoners is 'bad'. To exclude such plasma from manufacture of our coagulation product would only be a sop or gratuity to the Gay Rights and would presage further pressure to exclude plasma collected from the Mexican border and the paid donor.)"*
    d. Continue to attend meetings of this type and accumulate information, and investigate potential new assay procedures.

85. One further point to note from the meeting is a suggestion that some attendees may have considered that the CDC itself had not reached a settled view on how to proceed. Dr Gerald Sandler of the American Red Cross told IOM investigators that *"not one of Donald Francis' superiors had supported a recommendation to implement hepatitis core testing. As a result few in attendance accepted Francis' suggestions, as they did not have the support of CDC Director William Foege."* It was also noted that the FDA's attitude to surrogate testing was that more research was needed. **[JREE0000019, ep.130-131]**

Meetings convened by the NHF, 6 and 14 January 1983

86. On 6 January 1983, a meeting took place between the NHF and representatives of plasma fractionators. The NHF requested an end to plasma collection in AIDS *"hot spots"*. Alpha indicated that they had already taken such steps. Armour, Cutter and Hyland did so shortly thereafter. **[KREV0000001, ep.756]**

87. A week later, on 13 January 1983, a joint statement was published by the major blood banking organisations, the American Red Cross, the American Association of Blood Banks and the Council of Community Blood Centres. This stated that the possibility of blood-borne transmission of AIDS was *"unproven"* and the evidence *"inconclusive"*. The organisations accepted that there were sufficient grounds of concern to warrant some steps being taken, given the increasing number of cases in people with haemophilia and the *"long incubation period"*. The recommended steps included further questions intended to elicit relevant features of medical history (including night sweats, unexpected weight loss, lymphadenopathy and Kaposi's sarcoma). The organisations, however, considered that *"Direct or indirect questions about a donor's sexual preference are inappropriate."* The organisations noted ongoing studies of various surrogate tests, but did not advise routine implementation at that time. **[JREE0000019, ep.291-292]**

88. The statement appears to have been intended to pre-empt a *"strategy meeting"* that took place the following day, 14 January 1983, at the behest of the NHF. The meeting involved representatives of the fractionators (including Dr Eibl from Immuno), the voluntary and commercial blood banking industry, the CDC (including Dr Evatt), the FDA (including Dr Donohue), a number of clinicians, and members of the NHF **[CGRA0000327, ep.4-6]**.

89. In the morning, before the full meeting was convened, *"the major industry representatives collected … to determine a consensus strategy to the actual NHF meeting"*. Those attending included representatives of all of the major fractionation firms, as well as a representative of a trade body, the American Blood Resources Association. It appears that this was a meeting just of fractionators and plasma collectors, and not of whole blood banks. A record of the meeting was made by Dr Ojala of Cutter **[CGRA0000321]**.

90. Dr Ojala recorded that the *"primary concern"* was the possibility of a recommendation for anti-HBc testing of plasma. Dr Rodell (Hyland) pointed to studies suggesting that this would exclude approximately 10% of donors, and all high titre donors who were useful for providing immune serum globulin (which helped to provoke immunity to hepatitis B in a recipient). The meeting agreed that *"We would support testing in concept, but defer until a more specific test was available."* It was noted that Dr Donohue of the FDA was *"not particularly enthusiastic"*. [ep.1]

91. The meeting also *"agreed that the CDC was getting increasingly involved in areas beyond their areas of expertise and whenever possible we would try to deflect activity to the NIH/FDA."* [ep.1]

92. In terms of other actions to limit the risk of AIDS [ep.1-2]:

    a. Alpha informed the meeting of its donor screening programme, of the 308 people who had identified themselves as homosexuals and the *"even larger number"* who had voluntarily excluded themselves.
    b. Hyland stated that it would have its own programme in place by 1 February, while Armour were working on theirs.
    c. Small pool fractionation was discussed, but *"everyone agreed [this] was of questionable benefit"*. One hypothetical example was given: a ten donor pool would (with *"very effective"* manufacturing) result in eight to twelve vials, but eight of these would be required for quality control procedures,[14] leaving between zero and four for sale: *"The economics of this procedure are relatively discouraging."*
        i. A note of this meeting made on behalf of the Plasma Manufacturer's Association recorded that **[BAYP0004375]**: *"Any attempt to reduce batch sizes of AHF was considered ineffective because Hemophiliacs receive product representing hundreds of thousands of donors during the year regardless of batch size. Also so little is known regarding the effect of dilution that a batch size reduction could conceivably have a detrimental effect. Finally batch size reduction could have serious negative repercussion on product availability and, most especially, on cost.*

[14] Manufactures would require four vials for testing for potency, purity and sterility, two for retention, and the FDA would require two for testing.

d. It was agreed that whatever requirements were placed on fractionators in terms of plasma collection should also be applied to blood banks, as the conceptual risks involved applied to both.
e. Some information was shared about progress on heat treatment processes.

93. Dr Ojala noted that *"Both Alpha and Hyland are taking the AIDS problem very seriously."* [ep.2]

94. Two accounts exist of the full meeting: the NHF record **[CGRA0000327]** and Dr Ojala's note **[CGRA0000321]**. The meeting began with a review of the evidence of the aetiology of AIDS, including by reference to an article in the *New England Journal of Medicine*, which had found that 40-60% of patients using factor concentrates had a reverse T-cell ratio, a higher proportion than those using cryoprecipitate (though it was noted that *"no data was conclusive"*).

95. The NHF then explained the recommendations that the organisation's Medical and Scientific Advisory Committee had developed to prevent AIDS in patients **[CGRA0000327, ep.1]**. These were in three parts, directed respectively at physicians, fractionators, and regional and community blood centres. The recommendations directed at fractionators were **[JREE0000019, ep.293-294]**:

a. Identification, by direct questioning, of those in high risk groups (gay donors, intravenous drug users, and recent Haitian residents).
b. *"Evaluation and implementation (if verified) of surrogate laboratory tests that would identify individuals at high risk of AIDS transmission."*
c. An end to the fractionation of plasma from high risk geographical areas.
d. Continuation of viral inactivation efforts (e.g. heat treatment).
e. An evaluation of the feasibility of small pool production. *"While this will certainly be more costly, it may be the only way to break out of the present dilemma without going to an all-cryoprecipitate effort."*
f. An end to purchases of recovered plasma from centres not complying with the recommendations on donor screening.
g. An acceleration of efforts towards the production of recombinant factor products.

96. The NHF minutes provide an overview of the discussion at the meeting **[CGRA0000327, ep.1-3]**. On donor screening, Alpha again explained its programme

(and its results). In general, the fractionators expressed support for these steps and for the exclusion of geographical areas, while the blood banking organisations expressed scepticism. Dr Ojala recorded in his memorandum that: *"It is unusual for us to come away wearing the white hats while the 'volunteer' sector wear the black"* **[CGRA0000321, ep.2]**. On surrogate testing, the fractionators indicated a willingness to accept an exclusion rate of around 10% of donations and the higher costs associated with the testing if *"an appropriate test"* could be identified. It was agreed that more work was required on this matter **[CGRA0000327, ep.2]**.

97. On donor pool size, it was noted that as many as 22,500 donors might contribute to one lot, while a single infusion of cryoprecipitate may involve 25 to 60 donors. The problems with small pool production, as set out in the morning meeting, were raised **[CGRA0000327, ep.3]**. According to Dr Ojala's memorandum, Dr Eibl of Immuno pointed out that small pools were common practice in Europe, but other attendees replied by saying that a substantial amount of American product was exported to Europe **[CGRA0000321, ep.4]**.[15]

98. None of the industry foresaw an early breakthrough on recombinant products **[CGRA0000327, ep.3]**.

99. Summing up the meeting, the chair referred to the *"complicated issues involved"* and said that *"no regulations would develop from the meeting"*. He thanked the parties for entering into *"open and frank"* dialogue. **[CGRA0000327, ep.3]**

The *New England Journal of* Medicine, 13 January 1983

100. On 13 January 1983, the *New England Journal of Medicine* published two articles and an editorial concerning the respective risks of factor concentrates and cryoprecipitate in respect of AIDS. The editorial, written by Dr Jane F. Desforges, urged consideration of the increased use of cryoprecipitate **[PRSE0002410]**:

> "The present program [of treatment by concentrate] has been extremely successful and would be given up by physicians and patients only with great reluctance. Yet it is time to consider doing so, even though we may not have enough evidence to demand such a radical change. The fact that haemophiliacs are at risk for AIDS is becoming clear. If the use of

[15] It is also relevant to note that the memorandum contains no reference to what Dr Eibl classified as a "small pool". Immuno's pool sizes were stated to be up to 1,000 donors **[SHPL0000071_181, ep.12]**.

cryoprecipitate will minimize this risk, the current home-infusion program needs to be revised … Preventing the complications of the present treatment may have to take precedence over preventing the complications of haemophilia itself."

101. The editorial did not address issues concerning the logistics of a reversion to cryoprecipitate.

Screening measures introduced by fractionators, January and February 1983

102. On 28 January 1983, the American Blood Resources Association, the fractionators and plasma collectors' trade body, made a public statement containing its recommendations. The statement accepted that the cases of AIDS in people with haemophilia *"suggest that AIDS may be of infectious aetiology."* The organisation urged that *"steps be taken as soon as possible to screen plasma donors to minimize the possibility of transmitting AIDS."* The group recommended focussing on the education of donors and plasma centre staff, and screening measures (including further questions on medical history and seeking confirmation from donors that they were not in high risk groups). On surrogate testing, the group recommended that no large scale testing be implemented at that time, but noted that assessment of the issue was *"under study"*. The recommendations were intended to apply to all plasma collected by plasmapheresis and also that supplied by voluntary blood organisations. **[JREE0000019, ep.297]**.

103. As anticipated at earlier meetings, Hyland introduced revised donor screening procedures in late January and early February 1983. These included providing an information leaflet to donors before asking them if they were in a high risk category, and introducing examination of lymph nodes. By that time, the company had also closed plasmapheresis centres in San Francisco, Miami, Houston, New Orleans and New Jersey, and had elected not to contract with or open centres in those locations, New York City or Hollywood. In his draft witness statement from 1990, Dr Kingdon stated that he was *"convinced by the available evidence … that we were dealing with a virus that had an epidemiology similar to hepatitis and that we should take measures to reduce the risks of transmitting AIDS through blood products."* **[CBLA0000011_005, ep.28, §§80-83]**

104. Cutter introduced additional physical examination of donors, and additional screening questions in February 1983. These included questions intended to elicit a

history of night sweats, unexplained dramatic weight loss and recurrent fever, and an examination that included checking lymph glands and a full body examination for lesions. Donors were required to sign the company's AIDS Information Notice to state that they were not a member of any of the three high risk groups (male homosexuals, intravenous drug users, or recent residents of, or visitors to, Haiti). **[KREV0000001, ep.757; BAYP0005807_003; BAYP0000028_076]**

105. Armour introduced what it described as a *"more aggressive programme"* of donor screening in the same month. This included **[BART0000863, ep.4]**:

> "Direct communication with each donor in the form of written and oral information and questions, designed to defer from the donor population individuals at risk for contracting AIDS. Each donor is presented a fact sheet describing the high risk groups thus far identified with AIDS, the seriousness of the syndrome, and the possible link to the treatment of haemophilia. Furthermore, all donors are questioned by trained processors as to their being members of high risk groups and as to the presence of any signs (night sweats, diarrhoea, chills etc.) that might be indicative of AIDS. Donors are required to affirm in writing that they are not members of any of the several high risk groups involved, without having to reveal any facet of their personal and private lives. Periodic physical examinations performed by plasma centre attending physicians also include evaluations for possible signs and symptoms of AIDS."

106. The company explained its procedures in a later letter to UK doctors, which was sent in May 1983. The letter also contained background information about AIDS and the role of the CDC. The company expressed reservations about the practicality of anti-HBc or other surrogate testing due to its lack of specificity. It considered that *"until the causative agent responsible for transmission of AIDS is identified and isolated, it is highly unlikely that a suitable laboratory tool will be available for implementation of any general testing programme."* **[BART0000863, ep.3]**

107. At that time the company had no plasmapheresis centres in areas recognised as having a high incidence of AIDS; nor did they source plasma from such areas. **[BART0000863, ep.3-4]**

108. While the steps taken by the pharmaceutical companies stood in contrast to the general approach of the blood banking organisations, some individual centres were more receptive to change. February saw implementation of donor screening programmes at the Irwin Memorial Blood Bank and at the Greater New York Blood Program. The latter pioneered a process by which donors could, confidentially,

indicate that their plasma should not be used for fractionation and transfusion, a system that became known as *"confidential unit exclusion"*. This produced a 1.4% deferral rate. **[KREV0000001, ep.755-756]**. Both of these centres were in areas of high incidence of AIDS, and hence faced significant questions about their futures in the absence of effective measures to identify and exclude high risk donors.

109. From a British perspective, it is worth noting that January 1983 saw discussion of AIDS, led by Dr Craske, at the Haemophilia Centre Directors Working Party on Hepatitis **[HCDO0000558]**, and at the meeting at Heathrow airport that had been organised by Immuno **[PRSE0002647]**.

Blood Products Advisory Committee meeting, 7-8 February 1983

110. A further meeting of the Blood Policy Advisory Committee took place on 7 and 8 February 1983 **[CGRA0000347_008; JREE0000006, ep.421; CGRA0000347_007]**. The open section of the meeting was attended by representatives of the fractionators, but it appears that they may have left before the longer closed session. Dr Duncan Thomas of the (UK) National Institute for Biological Standards and Control attended both parts of the meeting on a "consultant" basis. The open meeting saw a discussion of viral inactivation of hepatitis through heat treatment, in light of imminent licensing of heat treated products (on which, see below). In closed session, a lengthy – and often sceptical – discussion took place of the cases of AIDS identified by the CDC. Dr Donohue reported on the NHF strategy meeting, and welcomed the proposals for further donor screening. He also stated that since that meeting the fractionators had *"agreed that there would be no fractionation into Factor VIII from plasma which is collected in prisons"* **[CGRA0000347_008, ep.83]**. Counsel to the Inquiry are not sure that this was a correct summation of the position, at least in respect of Hyland, which appears to have continued to use prison plasma in this period (see below).[16]

111. Dr Donohue also stated (in closed) that *"Everyone has agreed that there is not a screening test which is appropriate to attempt to define immune deficiency as it applies to donors. There just is not one that fits."* He discussed anti-HBc testing, and

[16] Fractionators had been present at the open part of the BPAC meeting, but this discussion took placed in closed session, meaning that they may not have been excluded from the meeting by that time.

emphasised the potentially high exclusion rate of donors who would be eliminated even though they were not at risk of carrying AIDS [ep.85-88].

112. A lengthy discussion (in closed) followed on donor screening and surrogate testing. The CDC and the American Blood Resources Association were both criticised for what were perceived to be their over-reaction to events, including by Dr Joseph Bove, the chair of the meeting and the director of the Yale-New Haven Hospital blood bank [ep.102, 106]. Professor Dorothea Zucker-Franklin of New York University Medical School stated that she *"did not think there is a shred of evidence that this [AIDS] is transmitted by blood as of today"* [ep.103]. Dr Bove also told the meeting that he had heard that Alpha were at risk of being sued both by a patient who had contracted AIDS through the use of one of their blood products, and by *"gay rights groups"* who had consulted the American Civil Liberties Union, presumably over allegedly discriminatory donor screening [ep.106-107].

113. The scepticism expressed by many at the meeting is, however, balanced by the following exchange, which is instructive of Dr Bove's thinking at this time [ep.111-112]:

> "Dr Bove: Well, one of the most vigorous, one of the most outspoken, one of the shoe-pounding-on-the-table people for the blood collecting community to do something, to be aggressive and get your heads out of the sand, is the Commissioner of Health of New York City. And I want to say that he must be absolutely correct. The real problem that bothers me more than anything bothered me in my professional life is that everybody who talks about this may be correct. And in the next 12 months there may be an amazing epidemic which will clearly implicate blood transfusion and show that the blood collecting community behaved irresponsibly.
> Dr [David] Aronson: But, Joe, we have that worry every day.
> Dr Bove: I haven't had it quite like this. I don't think there had been any situation that was quite this dramatic. I don't think we have ever had a situation where we are talking about an illness with anywhere from 40 to 100 per cent mortality –
> Dr Aronson: And that could show up every day –
> Dr Bove: Yes, it could but the question is, has it? I mean it is not whether it could or not; it is whether it has and whether we ought to be much more aggressive.
> One can predict that surrogate – I hate the word – surrogate testing would cost about 150 million dollars a year and is there any reason that we should delay instituting that?
> Dr [Louis] Sullivan: But what percentage of possible bad units would be ruled out?
> Dr Bove: Who knows? We don't have any data at all.
> Dr Donohue: That is right.
> Dr Aronson: We don't know that any is caused.
> Dr Bove: We don't know that there are any bad units."

Alpha AIDS Task Force meeting, 18 February 1983: when to recall suspect products?

114. Alpha's recently formed AIDS Task Force met on 18 February 1983. Among the issues discussed was a trial of anti-HBc testing, and it was noted that Dr McAuley and Dr Carr both had objections to the project. **[CGRA0000278, ep.2]**

115. The meeting also discussed the news that Alpha had received 11 plasma donations from a donor in Dallas who "*possibly*" had "*some AIDS symptoms*" but had not been diagnosed with AIDS. The plasma was in four lots of AHF (i.e. concentrate) that had initially been put on hold. A discussion with the patient's physician had suggested that the donor had "*symptoms of lymphadenopathy but little else to connect him with AIDS*", though he was being followed up. Alpha decided to release the concentrate, but not to use any plasma from the donor which had not yet been pooled. It was agreed that Dr Carr would "*discuss with the Bureau [of Biologics] – What if we do find a donor who comes down with AIDS and we do have plasma in product in the field*". **[CGRA0000278]**

116. This issue, of when to recall blood products produced from plasma from donors who were known or suspected to have developed AIDS, became one of the main areas of debate in the coming months.

The Recommendations of the Public Health Service and the FDA, March 1983

117. The only agreed outcome of the 4 January 1983 meeting was a request that the CDC, the FDA, and the National Institutes of Health be asked to submit sets of recommendations about future steps. According to Dr Evatt's *Tragic History*, the CDC drafted a set of recommendations to be considered by the Assistant Secretary of Health and the other public health services agencies. He acknowledged that this was, in effect, bypassing the FDA's regulatory authority and was a *"clear breach of protocol"*. The CDC draft recommendations included both the exclusion of high risk donors and surrogate testing. According to Dr Evatt **[CVHB0000042, ep.6]**:

> "This draft was promptly rejected by the other agencies, but after appropriate amendments, the FDA, CDC and NIH agreed on a set of guidelines that was published by the PHS on 4 March 1983, although it was clearly short of what we, as individuals at the CDC wanted. By this time 12 patients with hemophilia and six possible transfusions cases had been identified. The

publication of these guidelines marked the beginning of a slow change in public policy on transfusion-associated AIDS."

118. The PHS recommendations focussed on donor education and screening, did not include surrogate testing, and were not binding. However, their principles were endorsed three days later by the major blood banking organisations. **[JREE0000019, ep.74; KREV0000001, ep.756-757]**

119. More significant, at least from a British perspective, were the recommendations made by the FDA on 23 and 24 March 1983, which replaced the PHS recommendations **[DHSC0001203, DHSC0001204]**. These non-binding guidelines have been considered extensively during the course of the Inquiry, and so for present purposes the summary of them contained in the Krever Report is adopted **[KREV0000001, ep.757]**.

> "Blood banks were told to introduce educational programs to inform groups at increased risk of contracting AIDS to self-exclude, and to revise donor medical histories to include specific questions designed to detect possible symptoms of AIDS or exposure to persons with AIDS. There would be standard questions about a history of night sweats, unexplained fevers, unexpected weight loss, or signs of lymphadenopathy or Kaposi's sarcoma. Plasma centres were told not only to give donors information about AIDS and to question patients about symptoms of AIDS but to examine donors physically for lymphadenopathy and weight loss. Standards imposed on plasma centres were considerably more stringent than those imposed on the voluntary sector because officials thought that voluntary donors posed less risk than paid donors.[17] Finally, manufacturers were informed that plasma collected from donors suspected of being in a high-risk group might only be used in the production of derivatives not known to transmit infectious diseases. Although these guidelines lacked the force of regulations, they were promptly implemented by the blood and plasma industry."

120. As has been seen, the four US fractionation companies had all implemented their own donor screening procedures before the FDA recommendations, which were broadly equivalent. It was the blood banks, rather than the pharmaceutical companies, who had proved more reluctant to respond to pressure from the CDC and NHF on this issue.

121. The FDA notably did not recommend the implementation of surrogate testing, nor the recall of products that had been distributed to customers and were later found to have been produced from donors who were known or suspected to have AIDS. By

[17] Those standards included identifying through labelling each unit of plasma that it was intended should be fractionated into a factor concentrate.

this time, more than 1,100 cases of AIDS had been reported in the USA, with more than 400 deaths **[KREV0000001, ep.757]**.

122. As the Inquiry has heard, it was shortly after the FDA recommendations were published that Dr Joseph Smith of the Committee on the Safety of Medicines wrote to Dr Keith Fowler of the DHSS proposing that a meeting of the Sub-Committee on Biologics be convened to discuss AIDS and blood products **[CBLA0000043_034]**.

The licensing of the first heat treated product: March 1983

123. March 1983 also saw the first FDA licence granted for a heat treated product, Hyland's Hemofil T **[CBLA0000011_005, ep18, §51]**. The development of this and other heat treated products is considered below.

The recall of products: May 1983

124. In May 1983, Hyland withdrew a lot of factor concentrates, having discovered that they had been manufactured from a donor who was later diagnosed with AIDS. This was the first such withdrawal although, as we have seen, it was not the first occasion on which a fractionator had become aware that its product had or may have been contributed to by a donor who had developed AIDS. **[JREE0000019, 74, 90; KREV0000001, ep.778]**[18]

125. Hyland's UK sister company, Travenol Laboratories Ltd, wrote to the DHSS on 9 May 1983 providing details. It stated that Hyland had become aware that **[PRSE0004496]**:

> "[O]ne of its plasma donors, though not finally diagnosed, has been identified as a possible victim of AIDS. The donor in question is a member of the high risk groups, although on several occasions prior to donating, he denied being a member of such group. While healthy at the time of donation, he subsequently developed some of the clinical findings associated with AIDS, including an inverted T4/T8 ratio and generalised lymphadenopathy. His final diagnosis is still in question.
> This donor's plasma was included in pools that were fractionated into several therapeutic products for the haemophiliac, including Anti Haemophiliac Factor VIII, Factor IX complex, and Anti Inhibitor Coagulant Complex. No therapeutic

[18] Both the Krever Report and the IOM Report date the recall to 11 May 1983, two days after the letter that was sent by Travenol Laboratories Ltd to the DHSS, as described in the following paragraph. Counsel to the Inquiry are unable to explain this discrepancy.

products fractionated from plasma pools that contained this donor's plasma have been shipped to any customers in Europe.
In the United States, Hyland has recalled the only coagulation product fractionated from plasma containing that donor's plasma that had been distributed to customers.[19] The recall involves one lot of Anti Inhibitors Coagulation Complex and is being taken at Hyland Therapeutics initiative, and not at the request of the National Centre of Drugs and Biologics. As a precaution, all lots of Factor VIII and Factor IX Complex that were manufactured from this donor's plasma have been placed in quarantine pending future resolution of this donor's medical condition. None of these quarantined products have been distributed to customers in either the United States or Europe."

126. The author of the letter stressed the other measures that Hyland had taken in response to the risk of AIDS, and stated that the company intended to convert both its European and American facilities to manufacture only heat treated Factor VIII product *"as expeditiously as possible"*.

127. A copy of the same letter was sent to Professor Bloom on the same date **[DHSC0001291]**.

128. In a medical bulletin dated 11 May 1983, published in the wake of the recall, the NHF urged its members to continue using factor concentrates. It noted that the incidence of AIDS in people with haemophilia was very low, at 12 patients in a population of 20,000, and that *"the life and health of hemophiliacs depends upon blood products."* **[JREE0000019, ep.309]**

DHSS correspondence with US fractionators: May and June 1983

129. May 1983 saw considerable activity within the DHSS on matter relating to AIDS and blood products. Internal memoranda, in particular between Dr Walford and Dr Fowler, raised concerns about US companies *"dumping"* products manufactured from pre-March plasma on the UK market **[DHSC0001394; DHSC0002229_006]**. Dr Walford also produced an update on AIDS that was circulated within the DHSS, and prepared a number of papers that were considered at a meeting held on 3 June 1983 **[DHSC0002227_060; DHSC0002229_019; DHSC0002229_019; DHSC0003824_163; DHSC0003824_164; DHSC0003824_165; DHSC0002229_020; DHSC0003824_166; DHSC0002229_020; DHSC0003824_168; DHSC0001228]**

[19] The NHF Medical Bulleting, discussed below, identified this product as Autoplex, the product intended for patients with Factor VIII inhibitors. **[JREE0000019, ep.309]**

130. During the same month, Dr Fowler wrote to US fractionators posing questions about the precautions they were taking over donors, whether they had received reports about AIDS in any users of their products, and whether they had received reports about any of their donors developing AIDS or AIDS-like symptoms. The Inquiry has identified letters sent to and received from Miles/Cutter **[BAYP0000002_182; BAYP0000002_183]** and Armour **[ARMO0000118; ARMO0000119]**. It is a reasonable inference that such letters were also sent to Hyland and Alpha, although if they were the Inquiry has not identified the relevant correspondence to date.[20]

131. In his response to Dr Fowler, J.N. ("Newt") Ashworth, the Vice President of Scientific Affairs at Cutter, stressed the uncertainties surrounding AIDS (*"this enigmatic syndrome"*) and the sensationalist coverage of it. Dr Ashworth stated that the facts about AIDS were *"very limited"* and it therefore *"can only be an assumption that AIDS can be transmitted by certain blood products."* It was, he said, *"also … unclear whether the syndrome contracted by hemophiliacs really is the same as the AIDS syndrome contracted by other high risk groups."* Citing comment by Professor Bloom to the Haemophilia Society in support of his position, he argued that **[BAYP0000002_183]**:

> "As medicine and the plasma suppliers (commercial and NHS) struggle to find the correct actions to take to exclude the elusive AIDS donor, it is imperative that the supply of products (in particular Factor VIII) not be reduced to levels where patients cannot be treated."

132. In the absence of a test for the infective agent causing AIDS, Dr Ashworth said that:

> "What we (and presumably other countries, including the UK) are doing is to attempt an unproven and probably inadequate screening or donors by certain gross definitions of high risk groups and general physical examinations. Only time will tell if these checks on donors are accurate."

133. In response to Dr Fowler's direct questions, he answered that:

[20] It is unknown whether an equivalent letter was sent to Immuno. Although it was an Austrian firm, by this point in time its dominant factor VIII product in the UK was Kryobulin produced from American plasma.

a. By common agreement and with the regulatory pressure of the US Department of Health and Human Services, all donors were screened in line with present medical-scientific knowledge.
b. AIDS cases were hard to follow up, but Cutter's investigations indicated that none had received Koate.
c. *"So far* [the letter was dated 6 June 1983]*, we have not had to make a decision concerning disposition of a lot of Koate from a donor who had become an AIDS victim. It is our plan that if this circumstance should occur, the decision concerning the lot would depend on many factors including, most importantly, receipt of advice from government health authorities based on the latest knowledge concerning AIDS."*

134. Armour's response was sent by W.J. Tarbit of Armour Pharmaceutical Company Limited, on 8 June 1983. He stated that **[ARMO0000119]**:

> "We are not aware of any reports of AIDS or AIDS-like illness arising anywhere in the world from the use of Factorate specifically; however we have requested confirmation of this from our US affiliates. We are aware of a letter in *Lancet* of May 28th, 1983, from Beddall et al which describes an apparent increased susceptibility of haemophiliac children, receiving Factorate, to opportunistic infection following exposure to pulmonary tuberculosis but are not aware of any evidence suggesting that this may be due to transmission of AIDS-like illness. We are undertaking a more detailed study of this situation with the centre concerned. We have no reports of donors subsequently developing AIDS or similar illness in any of our Plasma Centres, However in view of the constantly changing situation we have again re-directed this question to the USA for information on the most recent situation."

135. This letter implied that further information would be provided by Mr Tarbit when it was received from his associates in the USA. If such information was sent, Counsel to the Inquiry have not yet identified it.

136. On the same day, K.W. Fitch, Chairman and Managing Director of Armour Pharmaceutical Company Limited, wrote to Professor Bloom. The professor had sought reassurance that Armour would not *"preferentially export"* to the UK products produced from plasma collected before the FDA recommendations were published **[DHSC0001288]**. In response, Mr Fitch wrote that Armour had implemented protocols a month before the FDA recommendations that were in compliance with those recommendations. He said that **[BPLL0001351_125]**:

"For your further advice and assurance, you should know that we supplied plasma prior to February 24, on a business-as-usual basis, but that most of this stock was supplied to customers in the USA, since 70% of our Plasma business is in the USA. At no time have we preferentially exported Plasma stocks ex the USA pre-February 24 or March 24."

137. A little later, on 14 June 1983, Dr Walford prepared a questionnaire for fractionators requesting information on the following matters **[DHSC0002229_041]**:

a. The products supplied to the UK, and their quantities.
b. The source of the plasma supply, and whether it was possible to trace the source and date of plasma collection for each batch.
c. Whether plasma from each centres was fractionated separately, or whether it was pooled with plasma from other centres.
d. Whether plasma was sourced from *"major 'epidemic' areas"* in the United States, for example New York, San Francisco, Los Angeles and Miami.
e. Whether the companies were conforming with the FDA's March recommendations.
f. Whether the company had instituted similar precautions prior to those recommendations.
g. *"If USA plasma is used, are you able to confirm that all future supplies of coagulation factor concentrate to be sold in the UK will be manufactured from plasma collected in accordance with the FDA directive of 23 March 1983 (or in accordance with the special precautions, if any, instituted by your company at an earlier date)? If the answer to [this question] is No, from what date can you meet this requirement."*

138. The Inquiry has identified the direct responses of the UK subsidiaries of Miles/Cutter **[BAYP0000002_185]** and Armour **[ARMO0000266]**. The DHSS also received responses from Alpha, Hyland and Immuno, which were compiled in a table **[DHSC0002229_055]**. A covering minute provided the epitome of the answers:

"Annual imports of FVIII by the above firms total 42 – 50 m [million] units.
With the exception of Immuno the firms state that they do not have or have ceased to collect in 'Epidemic' areas. All state that their collection centres are FDA licensed.
The plasma in each case is pooled prior to processing. In the case of Immuno products, European plasma and USA plasma are pooled separately.
The origin of all plasma is identifiable.
Each has given the assurance that future sales will comply with FDA guidelines. However Miles Labs [replying in respect of Cutter products] state

that FVIII manufactured from plasma collected since March '83 will not be available until August, and Immuno in September '83."

139. The table recorded that Miles/Cutter had *"screened for AIDS for some years"*. This appears to be a summation of the response that: *"For many years some AIDS related screening procedures – such as routine checks for weight loss and generalised lymphadenopathy had been used"* **[BAYP0000002_185, ep.3]**. Counsel to the Inquiry understand this to be a reference to screening checks on the donors' general health that were in place before the risk of AIDS was identified.

140. The answers contributed to a debate within the United Kingdom about whether a ban should be placed on products manufactured from *"pre-March"* plasma, a matter that was discussed at the meeting of the Committee on the Safety of Medicines Biologics Sub-committee on 13 July 1983 **[ARCH0001710]**. As has been explored elsewhere in the Inquiry, DHSS officials turned to the debate taking place in the USA, in the anticipation that the British position would mirror that taken by the American authorities **[DHSC0002229_062; DHSC0002353_020]**. The focus across the Atlantic, however, was moving from issues concerning donor screening to the question of what, if anything, should be done to recall products produced from the plasma of donors who were known or suspected to have AIDS. That debate posed existential questions of the US fractionators.

The recall debate: June and July 1983

141. On 9 June 1983, a meeting took place between representatives of the Plasma Manufacturers Association and the FDA. The fractionation companies represented were Hyland (Richard Strigley), Cutter (Dr Ojala), Alpha (Dr Carr), and Armour (Dr Rodell, who by that time had moved to the company from Hyland, and Bill Wethersby). FDA attendees included Dr John Petricciani, the Director of the Office of Biologics,[21] and Dr Donohue. The CDC was not represented at the meeting. **[CGRA0000231; CGRA0000267; CGRA0000598]**

142. The meeting was requested by the FDA with the intention of developing a policy to respond to situations where a donor whose plasma had contributed to a fractionation pool was later found to have AIDS. The Hyland note of the meeting recorded the following **[CGRA0000267, ep.1]**:

[21] The FDA's March 1983 recommendations were sent in Dr Petricciani's name.

> "The O.B. [the FDA's Office of Biologics] feels that there is a need to develop a policy to handle that eventuality and that the policy should be developed in a public forum involving the CDC, National Hemophilia Foundation and other interested parties. For their part, however, the policy must be one which does not interrupt the supply of coagulation products to hemophiliacs or cause a panic condition in the mind of users. Given the degree to which a relatively small number of donations can effect a large number of product lots and the uncertain – but long – gestation period for the disease, developing a policy which is acceptable to the major interest groups is seen as a real challenge."

143. The note stated that *"after considerable discussions two alternative points of view began to emerge."* These were [ep.2]:

a. A donor found to have AIDS would be excluded, but there would be no requirement to recall product if the manufacturer had followed screening guidelines and the donor record showed no sign of prior illness. *"Left unanswered are questions related to the status of processed, but undistributed product. One corollary to this plan which was discussed was the feasibility and legality of discontinuing the distribution of product under the company's control but not recalling product which had already been sold. While this appeared to be workable from the point of view of the Compliance people, it has obvious shortcomings."*
b. The imposition of a time period prior to diagnosis during which time the donor's plasma would be considered to be at risk. *"The difficulty pointed out with this plan was that unless a very short (perhaps indefensibly short) time period was chosen, the amount of product affected could be very large."*

144. No consensus view emerged, and the FDA undertook to arrange an open meeting in July to discuss AIDS and blood products, including the issue of recall. [ep.2]

145. The pharmaceutical companies also took the opportunity to criticise the *"double standards"* that resulted from the FDA's March recommendations being stricter on commercial plasmapheresis centres than on whole blood banks. Dr Petricciani argued that the companies could require any blood bank that they contracted with to meet their higher standards. Dr Carr said that *"Alpha had done just that, and had lost several vendors of recovered plasma as a result"* [ep.2]. This would appear to be further evidence that the fractionators continued to be more rigorous in

their donor screening than the blood banks, while continuing to use recovered plasma.

146. The note of the meeting made by Dr Ojala of Cutter provides further evidence of the FDA's position on this issue. He recorded Dr Donohue as saying, in respect of a series of forthcoming meetings in Europe, that **[CGRA0000231, ep.2]**:

> "his mission was to defend our current procedures. He asked assistance from the manufacturers to convince those overseas that we are doing an acceptable job of screening out any AIDS donors."

147. Dr Ojala's note also records a private conversation that he had with Dr Donohue and Dr Petricciani about Cutter's *"Orlando donor"* [ep.2]: *"They agreed based on the evidence that they saw no need for any recall action. The donor was only drawn once and Donohue commented that his symptoms were common to active homosexuals, but not indicative of AIDS."*

148. A further perspective on the meeting is provided in an internal memorandum produced for Alpha by Dr Carr **[CGRA0000598]**:

> "Dr Petricciani stated quietly but firmly that he considered it essential that the manufacturers, in presenting their [hypothetical future] proposal, discuss the feasibility of doing what we suggest, and the potential availability of product. The message is loud and clear. He stated frequently that this is a social, economic, public relations and emotional issue, not a scientific one. Please note, we must be prepared by the middle of July with a rational example of what could happen in terms of a long-term donor whose plasma has been used in the manufacture of AHF and PTC, and what the economic consequences would be to us in terms of cost and, secondly, in terms of availability of our blood products manufactured. One issue discussed over and over again was the potential for this wiping out a manufacturer totally economically. Therefore, when you're talking about the availability of product, you must also address the potential loss of products from AHF manufacture."

149. By the time of the June meeting, there were 1,508 identified cases of AIDS identified by the CDC, and 575 deaths. 15 people with haemophilia had been identified as having AIDS. **[CGRA0000231, ep.1]**

150. The open meeting on this topic took place on 19 July 1983.[22] The forum was the Blood Products Advisory Committee, which met at the National Institute of Health. Dr Petricciani introduced the topic and the difficulties involved, including the

[22] See **[JREE0000006, ep.424-426]** for the invited attendees. The meeting was chaired by Acting Chairman William V. Miller.

need to make decisions in the absence of a solid data base. Dr Evatt provided an overview of the epidemiology of AIDS, and stated that 17 cases in people with haemophilia had been identified by the CDC. There was further discussion of the criteria for AIDS and the research on its aetiology. **[BAYP0004674, ep.1-2]**

151. Dr Rodell then spoke on behalf of the Plasma Manufacturers Association, representing Alpha, Armour, Miles/Cutter and Hyland [ep.2-3].

> "Dr Rodell outlined the donor education and screening program initiated by each of the companies in early 198s to reduce the number of donors from the high risk groups. Approximately four to four and a half million litres of source plasms are fractionated on an annual basis which result in 800 million AHF units. Primary plasma pool sizes range from 1,000 to 10,000 litres with the result that a given pool could produce between 0.5 million to 5 million AHF units and treat an estimated 12 to 125 patients per year (or 500 to 5,000 individual treatments). Because the industry estimates that the average frequent plasma donor makes between 40 and 60 donations a year, a single donor could easily be represented in as many as 50 plasma pools in one year. Were this donor subsequently found to have AIDS and a decision made to recall all units collected in a time period of one year prior to that, 25 to 250 million AHF activity units could be affected, all in various stages of pooling production and distribution. Given the PHA estimate of 800 million AHF activity units produced annually by the fractionation industry, the potential for serious disruption of AHF supply described by Dr Rodell seems quite real."

152. Dr Ojala then presented the PMA's recommendation against an automatic recall of blood products [ep.3].

> "Automatic recall could lead to serious product shortages. PMA recommends that manufacturers continue current screening and policies of discarding plasma from suspected donors. Dr Ojala stated that recall decisions should be made following each company's policy in close consultation with the FDA and should be considered on a case-by-case basis in light of current knowledge of AIDS. One lot of final product has been voluntarily discarded by plasma derivative manufacturers.

153. Dr Ojala told the meeting that *"the economic realities associated with a policy of mandatory recall would cause the industry to make a critical evaluation of whether it could continue providing these products."* **[BAUM0000014]**

154. The NHF position statement, presented by Dr Aledort, was that concentrate should be recalled if it included plasma from an individual later diagnosed with AIDS or from *"an individual that in the best medical judgment of the manufacturer has characteristics strongly suggestive of AIDS."* However, Dr Aledort noted that, *"the NHF did not have access to the PMA data when the statement was formulated, and*

that there was a great concern about the continued supply of AHF." **[BAYP0004674, ep.3]**

155. A record of the meeting made by Dr J.B. Derrick of the Canadian Red Cross recorded that **[CBLA0000056_215, ep.8, §16]**:

> "Dr Aledort made this statement with some degree of embarrassment and actually disclaimed any personal responsibility for it. He stated that he personally feels that the recall position for AIDS contamination should be similar to current practice with reference to hepatitis B contamination (i.e. a similar position to that stated by Steve Ojala earlier). In an exchange on the floor it became apparent that *'the current state of knowledge simply does not lend itself to such an uncompromising policy'*."

156. According to Dr Derrick, a panel discussion covered the following points (among others) [ep.8-9, §17].

a. It was stated (without attribution) that the fractionators had demonstrated that they had *"a full appreciation of the need to respond to the present situation in a responsible manner."*
b. The *"attack rate"* of AIDS in people with haemophilia *"is no more and is probably less, then that of a year ago."* The source of this comment, and the data underlying it, are not set out in the note.
c. *"The present state of knowledge is simply not adequate enough for blanket decisions involving large scale recall or the initiation of an hiatus on Factor VIII concentrate production for an adjustment period (suggested 6 months) to allow for accumulation of plasma collected under more stringent conditions."*
d. *"While individual physician committee members might find it a difficult decision to treat their patients with material with which an 'AIDS donation' had been implicated, there was nothing to be gained by recall in the face of the present state of knowledge."*
e. In the circumstances *"drying up"* the supply of factor concentrates posed a greater risk to haemophilia patients than continuing therapy.

157. The formal summary of the Advisory's Committee's consideration of this issue is as follows **[BAYP0004674, ep.3-4**, emphasis added**]**.

> "It was very clear that confronted with this complex problem the Committee felt that a balance must be struck between theoretical risk of the product to recipients against the need for an uninterrupted supply of a life-sustaining therapy. As several members of the panel stressed, it would be undesirable to

distribute and use a lot of products which incorporated plasma from a donor with a definite diagnosis of AIDS. However, signs and symptoms suggestive of AIDS (e.g. persistent lymphadenopathy, night sweats etc.) would not be persuasive enough to dictate a recall of product. Enough concern was expressed about the question of supply that they Committee was unwilling to advise the agency to take an unalterable regulatory position calling for an automatic recall which would likely jeopardize product availability. Adding to the uncertainty with regard to the decision of whether to quarantine or recall a product lot, several Committee members and other participants expressed the opinion that the risk of AIDS from transfusion of plasma derivatives or use of AHF concentrates has not been definitively established. They cited the fact that nearly all the hemophiliacs with AIDS had used material from different lots, and that many other hemophiliacs receiving those same lots had not developed AIDS. They stressed the need for studies to follow up recipients of blood products derived from AIDS patients. **The consensus of the Committee was that the action to be taken for each incident of inclusion of plasma from a donor who might have AIDS into a product pool should be decided on a case-by-case basis.**"

158. Dr Derrick's note summarised the closing remarks of the Acting Chairman, Dr William Miller, in the following way **[CBLA0000056_215, ep.9, §19]**:

> "while it was abhorrent to the Committee to consider condoning the use of products for which there was a known risk of AIDS development in the recipient, there was an agreement on the part of the Committee that mandatory recall is not presently warranted in view of the lack of data and information on the extent of risk, and the potential for serious disruption of the supply of coagulation products."

159. Two days later, Dr Donohue wrote a memorandum to Dr Petricciani giving his interpretation of the Advisory Committee's review. His understanding was that as the risk of AIDS being transmitted via a specific lot was *"very, very small"*, the recall of such a lot when there were suggestions that a donor may have AIDS should be considered a *"discrete incident"*. It should, therefore, be considered on a case-by-case basis, by reference to the *"degree of specificity of the diagnosis, the time of onset of symptoms in relation to the time of donation, the potential effect upon immediate supply of factor VIII and the long term production of this "essential plasma derivative"* **[JREE0000019, ep.313**.

160. In Britain, Dr Fowler recorded his understanding of the meeting in a minute dated 28 July 1983 **[DHSC0002231_063]**.

> "Although the subject [AIDS and blood products] got a very thorough airing nothing new came to light. The possibility of banning all products made before the implementation of the March '83 regulations was discussed but rejected on a majority vote. The hiatus in supplies which such action would cause was the deciding factor. There is likely to be a congressional hearing on the same

subject next Tuesday [01.08.1983] and this is likely to be much more media orientated. I have been promised a report and will let you have it as soon as possible."

161. The source of this information may have been Dr Duncan Thomas, given that his name was included in the list of those attending the meeting on behalf of the FDA **[JREE0000006, ep.424]**. Counsel to the Inquiry understand that Dr Thomas may have been on secondment in the United States at that time. Dr Derrick's note of the meeting suggests that there was a discussion of a *"hiatus"* to allow for stocks of plasma to build up following the adoption of more stringent donor screening requirements, but that this and other measures of product recall were rejected by the majority of those at the meeting.

162. The Congressional hearing referred to by Dr Fowler took place on 1 and 2 August 1983, before a Subcommittee of the House of Representatives' Committee on Government Operations. It concerned the Federal Government's response to the AIDS epidemic as a whole. Among the evidence it adduced was the following, taken from a written statement by Dr Edward Brandt, Assistant Secretary for Health and the Department of Health and Human Services **[JREE0000006, ep.306, ep.325]**.

> "Based on the best available evidence, we believe AIDS is transmitted sexually, particularly among homosexual partners; less frequently, through transfusion of blood or blood products; or by the misuse of needles.
>
> At present the risk of acquiring AIDS through blood transfusion appears to be extremely small. Although as many as 10 million Americans received transfusions during the 3 years of the AIDS epidemic, CDC is investigating approximately two dozen AIDS cases in which transfusions may be a risk factor. We believe that the PHS recommendations issued in March 1983, which suggested that members of groups at increased risk not donate blood, will decrease the current risk."
>
> "Although we do not yet know the cause of AIDS, the evidence is strong that we are dealing with an infectious agent with a long incubation period … The most plausible agents are viruses."
>
> "At its July 19 meeting, FDA's Blood Products Advisory Committee discussed the safety of plasma derivatives. This is of concern because hemophiliac patients require treatment with a product, antihemophiliac factor (AHF), derived from plasma which is pooled from thousands of donors. However, I would emphasize that the risk of transmitting AIDS to an individual haemophiliac from a special lot of AHF is very small, if it exists at all. The Committee recommended that no regulatory requirements regarding the recall or destruction of lots of AHF, which may contain plasma from an AIDS donor, be developed but that any cases that are identified be examined individually. In reaching such a conclusion, a number of variables must be considered such as: the degree of specificity of the diagnosis, the time of onset of symptoms in relation to the time of donation, the potential effect upon

> the immediate supply of AHF and the long-term production of this essential plasma derivative. Let me emphasize that the health of the individual haemophiliac patient will be a continuing concern for the PHS.
>
> Additionally, through these collaborative efforts, progress in developing new procedures for increasing the safety of clotting factor concentrates have been accelerated. One such product is currently available and others are at a late stage of development."

163. Counsel to the Inquiry understand the final paragraph to refer to heat treated products. The Congressional hearing led to no change in approach in respect of product recall. It appears that Dr Fowler informed his DHSS colleagues of this in a minute dated 5 August 1983, which the Inquiry has not yet identified **[DHSC0002351_018]**.

Events in autumn 1983

164. By the end of August 1983, on Dr Evatt's assessment, 26 patients with haemophilia and 26 transfusion recipients had been diagnosed with AIDS in the USA **[CVHB0000042, ep.7; JREE0000019, ep.77]**.

165. The following month, Dr Luc Montagnier attended at conference in New York where he presented his team's findings that suggested that the virus he had isolated, LAV, was responsible for AIDS **[KREV0000001, ep.773]**. He would go on to co-operate with the CDC, providing samples of the LAV in February 1984, which were then used to develop an assay that would be used in testing viral inactivation in heat treated products **[CVHB0000042, ep.7]**.

166. During the autumn of 1983, fractionators recalled further blood products. Hyland and the American Red Cross did so in September **[KREV0000001, ep.778]**, Cutter in November 1983 **[KREV0000001, ep.778; BAYP0004916]**. An internal Armour memorandum responding to the Cutter withdrawal stated the following **[ARMO0000302]**:

> "We regret the unfortunate circumstances of the Cutter incident. However, the possibility of something like that happening to any plasma manufacturer cannot be excluded. It should be to our advantage to remind our customers in any appropriate form that Armour processes plasma from our wholly owned and fully controlle[d] plasmapheresis centres. Plasma Alliance has a worldwide reputation for excellent quality and highest standards. Although it is obvious that it is actually not known how to avoid transmission of AIDS, it should be emphasized that we have recently introduced Factorate HT [a heat treated product] to improve the safety of our product."

167. On 22 October 1983, the NHF issued a recommendation in effect restating the position it had initially held at the July 1983 meeting, namely automatic recall of products manufactured from plasma donated by a person later identified as having AIDS or characteristics strongly suggestive of AIDS **[KREV0000001, ep.766]**. This did not, however, lead to any change in regulatory policy, which continued on a case-by-case basis.

168. In the same month, Hyland took a policy decision to cease using plasma from prisons in the manufacture of coagulation factors. This is evidenced by a document recording a conversation between a representative of Hyland and Dr Donohue **[CGRA0000291]**:

> "'We had previously made the decision to discontinue the purchase of plasma from licensed centres in prisons. To that end we have chosen not to renew any pre-existing contracts with such centers after this year. Following my conversation with you yesterday, we have decided that we will promptly discontinue the use of such plasma for the manufacture of coagulation factors. We have pools in process this week which contain plasma drawn in prison centers. As of the end of this week, we will not make any coagulation factors from any of the prison plasma which remains in our possession or which we are contractually bound to purchase through the remained for the year; no further plasma pools used for coagulation factors will contain prison plasma. Any intermediate fractions manufactured from plasma pooled this week, or in previous weeks, would be processed to final product."

169. It is clear from this statement that Hyland/Travenol had previously manufactured coagulation factors from plasma obtained from prisoners. The statement does not define which concentrates were produced in this way, but there is no suggestion that prison plasma was intentionally excluded from any particular products, or that it was not used in products supplied to the UK or other markets.[23]

FDA evaluation of surrogate testing, 15 December 1983

170. On 15 December 1983, a joint meeting convened by the National Heart, Lung and Blood Institute and the Office of Biologics took place to consider work that had been done on surrogate testing, and in particular anti-HBc antigen testing. The Krever Report summarised the meeting in the following terms:

[23] According to the IOM Report, 16 cases of AIDS had been identified in prison inmates by 7 January 1983 **[JREE0000019, ep.76 and ep.83]**.

> "Four studies had been done on anti-core testing, two on Beta-2-microglobulins, and single studies had been made of cytomegalovirus, EBV, immune complexes, Neopterin, T-cell ratio measurement, Thymosinal, and Alpha interferon. Most of the discussion focused on the usefulness of anti-core testing. Dr Johanna Pindyck, for example, summarized the results of anti-core testing done at the Greater New York Blood Program. She reported that 5.5 per cent of male donors under thirty-five years of age were core antibody positive, as were 7.7 per cent of those over thirty-five years. The estimated cost of the test was three dollars, but the cost of discarding the units as well as recruiting efforts to replace the donor required further evaluation. Data from testing 8,049 donors at Irwin Memorial Blood Bank were also discussed. They demonstrated that donors living in an area of homosexually active men were likely to be positive for anti-HBc and that the test could identify 89% of those most at risk of contracting AIDS. The committee members asked whether these data constituted *'sufficient evidence to substantiate testing for anti-HBc,'* and expressed concern about the potential cost of such testing.
>
> Although Dr Donohue, the director of the Food and Drug Administration's division of blood and blood products, had recommended to the committee that anti-core testing be implement, Dr Michael Rodell, a representative of Armour, suggested that a task force be struck to consider the potential application of the anti-HBc test as an additional risk-reduction measure and to report within three months. This suggestion met with universal approval from the committee members; many representatives of the blood products manufacturers had met the previous evening and agreed that the task force would *'provide a delaying tactic for the implementation of further testing,'* which they expected would become a requirement later that year."

171. The reference to the meeting of the fractionators appears to come from a note of the meeting prepared by Dr Ojala of Cutter **[UCSF0000034, ep.2]**. Dr Ojala also recorded that it was expected that the introduction of anti-HBc testing would eliminate approximately 15% of plasma donors, and 6-7% of whole blood donors. He added that Dr Donohue was *"not completely satisfied with the task force approach,"* but had agreed to it.

172. Dr Ojala also noted that Cutter had already begun anti-HBc core testing. He and Dr Hink recommended [ep.2]:

> "That the implementation of core testing be accelerated to the maximum degree possible to obtain a competitive advantage in the market place. The approval of our heat-treat submission, in conjunction with core-screened plasma could present us with a potential marketing advantage. We made no mention of our plans to the others."

Summary of the position at the end of 1983

173. 1983 saw the introduction by all fractionators of enhanced donor screening processes. Following the publication of the FDA recommendations in March 1983, blood banks also introduced further steps, though they remained less robust than those adopted in plasmapheresis centres. The five firms that supplied the UK gave undertakings to the DHSS that, going forward, they would only supply products that had been manufactured from plasma obtained after the introduction of their new screening processes. However this commitment was, again, prospective. Products that had already been produced were not affected and were not withdrawn. Nor did the DHSS insist upon their recall or destruction.

174. The wider issue of when products should be recalled had been discussed, at length, but no consensus had emerged. The fractionators argued that a policy of automatic recall would jeopardise supply and even the continuing existence of firms. Their arguments were effective in that the FDA was not advised to, and did not, take formal regulatory steps. Instead, recall would continue to be considered on a case-by-case basis.

175. On surrogate testing, the fractionators had successfully argued for further consideration through a task force, something that Dr Ojala saw as a *"delaying tactic"*. His company, Cutter, unilaterally (and at this point, secretly) had begun anti-HBc testing, something that Dr Ojala thought would steal a march on their rivals in the market place.

176. 1983 also saw the first heat treated product being licensed by the FDA, Hyland's Hemofil-T. Armour, Cutter and Alpha had all applied for licences for such products by the end of the year, and these were granted in early 1984. The development of heat treatment is discussed in greater detail below.

177. Meanwhile, products continued to be recalled, and the number of cases of AIDS among haemophilia and transfusion patients grew.

1984

Events in January and February 1984

178. January 1984 saw the publication in the *New England Journal of Medicine* of a study of 18 AIDS cases where the only risk factor identified was exposure to blood components within five years of the onset of the illness **[PRSE0001931]**. The lead author was Dr Curran of the CDC. The Krever Report quoted the testimony of Dr Thomas Zuck of the FDA who said that the article *"put the whole medical community and perhaps the world on notice that AIDS is transmitted by blood transfusions … the debate [was] over"* **[KREV0000001, ep.749]**.

179. The same month saw Alpha recall factor concentrates as the result of a donor later developing AIDS **[KREV0000001, ep.778]**. By early February, there had been four such withdrawals of product **[PRSE0003071, ep.6]**.

180. Cutter (Koate HT, pasteurised) and Armour (Factorate HT) received FDA licences for heat treated products in January. The following month licences were granted to a different Cutter method (Koate HT, dry heat) and Alpha (Profilate HT). As is noted above, Hyland's Factor VIII product (Hemofil T) had already received its licence in March 1983.

The meeting at NIBSC of US and UK fractionators and officials: 9 February 1984

181. On 9 February 1984, a meeting was held at the UK's National Institute of Biological Standards and Control ("NIBSC"). It was entitled *"Meeting on the Infectious Hazards of Blood Products"* and was attended by UK and US fractionators and officials. Among those present from the UK side were: Joseph Smith of the Committee on the Safety of Medicines, Duncan Thomas of NIBSC, Dr Craske, Dr Richard Tedder, Dr Richard Lane (Director of the Blood Products Laboratory) and Dr Brian McLelland and Dr John Cash of the Scottish National Blood Transfusion Service. US attendees included Dr Petricciani, and representatives of Cutter (Dr Ashworth), Armour (Dr Rodell) and Alpha (Dr Carr). A European representative of

Hyland/Travenol attended (Mr J. Van Kalster), as did Dr Eibl of Immuno. **[PRSE0003071; CGRA0000610]**

182. The Inquiry has two main sources for the events at the meeting. The first is a set of draft minutes prepared by Dr Thomas **[PRSE0003071]**. These were circulated to attendees, and in general were agreed to be accurate, subject to one or two points of detail.[24] The second source is a detailed internal memorandum prepared by Dr Carr of Alpha **[CGRA0000610]**. Some of the papers and speaking notes from the meeting have also been identified, including those of Dr Smith **[MHRA0000076_022]**, Dr Petricciani **[BAYP0005158]**, and Dr Terry Snape of the Blood Products Laboratory **[BPLL0001808]**. The Agenda of the meeting survives **[MHRA0000076_018]**, and Dr Thomas provided a summary of it in the NIBSC Yearbook for 1984 **[WITN4461083, ep.19]**.

183. Among the issues discussed at the meeting were the following:

a. The benefits of factor concentrates were assessed against the *"well recognised side-effect"* of hepatitis, and of AIDS. Dr Smith stated that it had been shown that the first exposure to concentrate, from any source, was associated with a 100% infectivity with non-A non-B hepatitis. The meeting recorded that 21 Haemophiliacs in the US and eleven in Europe, including two in the UK, had contracted AIDS. Dr Cash and Dr Thomas stated that the same infectivity rate had been seen in patients receiving commercial concentrates or blood products from the SNBTS. **[PRSE0003071, ep.1-2]**
b. The discussion included an examination of pool sizes, concluding that they may range anywhere from 1,000 to 20,000 litres of plasma **[PRSE0003071, ep.3]**.
c. There was some discussion of the causative agent of AIDS. Dr Tedder mentioned two principal theories, an infective agent (presumably a virus), or the possibility that the immune system was overwhelmed by repeated infusion of foreign proteins. He suggested that the *"true explanation may lie between the two extremes, namely that there may be a transmissible agent, which only becomes infective when certain conditions are met in the host."* **[PRSE0003071, ep.4]**.

[24] See **MHRA0000076_003, MHRA0000076_002, MHRA0000076_003, MHRA0000076_007, MHRA0000076_006**.

d. Dr Petricciani set out the strategies that had been considered by the FDA. He summarised them as (i) voluntary limitation by high risk groups, (ii) exclusion of high-risk donors, (iii) laboratory testing, and (iv) a combination of the above. There was also discussion of AIDS research in the United States. **[PRSE0003071, ep.4]**

e. Dr Ashworth described the methods taken by four main US plasmapheresis centres to reduce the risk of infection. These included: avoiding high risk communities, detecting clinical abnormalities by examination and careful questioning, excluding the high risk donors, and heat treatment. This led to an outline of the approach in the UK to reduce infection in blood products **[PRSE0003071, ep.6]**.

f. At one point in the meeting, Dr Cash commented that paid donors were perhaps less likely to be truthful about their activities than volunteer donors. This was disputed by Dr Rodell, who pointed out that in three of four cases of blood donors contracting AIDS, leading to subsequent withdrawal of product, the donors were volunteers. It was also noted that both Cutter and Alpha had found donors from Texas had developed AIDS, indicating that it was not sufficient to exclude donors from known "high risk" areas.[25] **[PRSE0003071, ep.6]**

g. Dr Lane and Dr Snape provided an overview of fractionation and processing techniques, including in respect of testing for hepatitis B surface antigen and the hopes for heat treatment. **[PRSE0003071, ep.7-9]**

184. The meeting concluded with open discussions, including about what to do with infected blood products, when and if they were discovered **[PRSE0003071, ep.10**, emphasis added**]**.

> "Dr Thomas asked Dr Petricciani whether the FDA had specifically requested the manufacturer to withdraw batches that had been made from an affected pool. Dr Petricciani replied that no formal instruction had been issued by the FDA, but the withdrawal had taken place as a result of informal discussion and agreement. The general feeling of the meeting was that if the diagnosis of AIDS in a donor is definite, then products prepared from pools to which the donor had contributed should be withdrawn. If a donor is found to have symptoms and signs, such as lymphadenopathy, which were associated with incipient AIDS, but were neither diagnostic nor specific for the condition, the recall of material to which the subject had previously contributed plasma was not justified. **It was recognised that the scientific rationale for this course**

[25] It is not known if this reference to the donor from Dallas who was discussed at the Alpha meeting of 18 February 1983, discussed above.

of action left much to be desired, but that no other action could be taken which would not imperil the supply of Factor VIII."

185. On surrogate testing, Dr Thomas' minutes record **[PRSE0003071, ep.10]**:

> "[I]t was generally agreed that, on present evidence, only the test for hepatitis B core antibody was thought likely to be of value. However, there was no general agreement that such testing for core antibody should be part of the routine screening carried out on all donors."

186. There was also *"much discussion about the optimal size of plasma pools, but no agreement that reduction of pool size would be either a practicable or a successful way to reduce the transmission of either hepatitis of AIDS."* **[PRSE0003071, ep.10]**

187. Dr Carr's note of the meeting gives a different perspective on some of the later discussions. On the issue of recall, her note recorded **[CGRA0000610, ep.6]**:

> "The decisions [to recall products] were not being made based on scientific information but simply because of emotional and political considerations."

188. On the issue of small pools, Dr Carr recorded that following a lengthy discussion **[CGRA0000610, ep.6]**:

> "We [presumably a reference to the US fractionators] were finally able to show them that even with a small pool size because of the fact that they are collecting individual donations the exposure of the hemophiliac to numerous donors would still be there. Dr Smith summed up this discussion by stating that they should encourage the development of fractionation and processing controls for lowered infectivity, i.e. physical and chemical inactivation."

189. On surrogate testing, Dr Carr noted that Dr Smith summed up the item *"with practically no discussion at all stating for the attendees that no laboratory test procedures can be recommended at this time."* **[CGRA0000610, ep.7]**

190. Dr Carr also noted a private conversation that she had with Dr Thomas, who expressed his view that he did not think that Alpha should have withdrawn its product. **[CGRA0000610, ep.7]**

The meeting of the Study Group on anti-HBc testing

191. The Task Force (or Study Group) on anti-HBc testing that had been established in December 1983 met on 6 March 1984. Dr Rodell was in the Chair. While the full report would not be presented until July 1984, the group provided an interim report and recommendations following the meeting. These were **[MHRA0000076_010]**:

a. The group comprised representatives of the commercial and non-commercial fractionation industry, the plasmapheresis community, and the FDA.
b. *"The Study Group was divided in its position on testing for anti-HBc as a means of identifying AIDS high risk group members, with the majority believing that such testing was not appropriate for that purpose."*
c. The group recognised that anti-HBc was a surrogate test and was not necessarily indicative of AIDS.
d. It was the *"prevailing opinion"* of the group that if testing were to be employed, it should be employed for whole blood as well as plasmapheresis collection.
e. The group unanimously recommended the initiation of pilot studies in at least two metropolitan areas allowing donors to provide a private written indication that their plasma should not be used in the manufacture of products for haemophilia treatment (as was done in the New York Blood Centre).
f. The group unanimously supported further studies on beta-2 microglobulin levels, as this may correlate more closely with AIDS.

192. A more detailed account is contained in a memorandum prepared for Cutter by Dr Hink **[CGRA0000319]**. He recorded that the meeting took place over 5 hours, and culminated in a vote in which three of the eleven members of the Group voted in favour of anti-HBc testing, one abstained, and the others voted against. Those in favour were Dr Donohue of the FDA, Dr Srigley of Hyland and Dr Hink of Cutter. Dr Hink thought that Dr Gerety of the FDA abstained. Those opposed included Dr Rodell, Dr Carr (Alpha), and representatives of various blood banking organisations.

193. The account of the discussion at the meeting showed Dr Hink speaking in favour of testing. He argued that it would reduce both the costs of product recalls and the threat to supply that such recalls represented. In his view, testing could be carried out if it were deemed desirable. He cited a CDC figure that 75% of high risk groups for AIDS were anti-HBc positive, and suggested that the test could also cut infections of non-A non-B hepatitis. Dr Srigley agreed, but thought that of the seven donors

Hyland had identified as having AIDS, only three or four were anti-HBc positive. [ep.2]

194. Those speaking against the introduction of testing raised various points. Various figures were cited, including that only 15% of self-excluded donors in New York, and only 38% of known gay donors, were anti-HBc positive. It was also claimed that Dr Evatt of the CDC had told one participant that *"only 50% of key blood donors (suspected of transmitting AIDS) were found to be anti-HBc positive."* Dr Carr suggested that there would be a plasma shortage if the test were implemented. Dr Rodell presented figures *"showing anti-HBc testing and rejection of positive donors should cost several million $ per year."* It is not clear if that was intended to indicate the cost to Armour, or the cost to all organisations involved. It is notable, though, that the claim of a cost of $100,000,000 per annum, which had been made by an unknown source in January 1983, was not repeated. [ep.2-3]

195. Following the meeting, and in light of the discussion that had taken place on this issue at NIBSC on 9 February, Dr Rodell provided a copy of his summary report to Dr Thomas. **[MHRA0000076_009]**

Cutter's testing programme for anti-HBc, 2 April 1984 to 30 October 1984

196. Dr Hink's note of the Study Group's minute suggested that efforts were made at the meeting to persuade all fractionation companies to refrain from introducing anti-HBc testing. Dr Carr was stated to be *"adamant"* that Alpha would not begin to test, and Dr Rodell said that Armour would not do so unless *"a competitor was using it to competitive advantage"*. Dr Hink and Dr Srigley both said that they could not speak for their companies on this topic. **[CGRA0000319**; see also **CGRA0000646]**

197. As we have seen, Cutter had already commenced some form of anti-HBc testing, and Dr Hink had (with Dr Ojala) recommended that it be introduced more widely. Dr Ojala considered that this would lead to a competitive advantage. On 2 April 1984, Cutter announced publicly that it would commence testing all donated plasma for anti-HBc. The company declared that: *"Until a specific test for any AIDS agent has been discovered … Cutter intends to take these precautionary measure to protect those with haemophilia who depend on our products."* **[CGRA0000240]**

198. Counsel to the Inquiry do not know how other fractionators reacted to this news. There is no reference to any of them adopting the same approach in the Krever Report, the IOM Report, or in the documents that Counsel to the Inquiry have seen.[26]

199. Cutter reviewed the decision in May 1984, with reference to an internal paper setting out the advantages and disadvantages of the test **[CGRA0000362]**. In summary, these were [ep.2-4]:

Advantages

a. The reduction of risk of future product withdrawals.
b. *"Cutter has an obligation to use all reasonable means to provide safe effective products"*. This point was made with reference to non-A non-B hepatitis as well as other viruses.
c. Testing should result in higher customer acceptance and sales. It was noted that Cutter needed a way to differentiate itself from its rivals.
d. Separation of anti-HBc plasma would allow for more efficient identification of plasma with other hepatitis markers.
e. Start-up costs were already sunk and testing costs were not significant – the exclusion of plasma was the *"real expense"*
f. The testing may allow for stronger claims to be made about non-A non-B hepatitis reduction.

Disadvantages

a. Cost: the costs already incurred amounted to some $100,000, and continuation would add $0.3 to each litre of plasma procured. 15% of plasma tested had proved to be anti-HBc positive. Exclusion of that plasma and any resulting concentrates would have *"significant but indeterminate costs"*.
b. The test was not AIDS-specific, and hence the risk of needing to withdraw product because of AIDS remained.
c. More specific AIDS tests would be available in the future. Press announcements had suggested that this may be by October 1984 (on which, see below).

[26] A Cutter memorandum of 23 May 1094 indicated that no other fractionator had introduced anti-HBc testing as of that date. It was also noted that the effect of the testing would not be known for many years. **[BAYP0005288]**

d. Heat treatment may inactivate the AIDS agent, meaning that testing and heat treatment would be considered *"a belt and suspenders redundancy"*.
e. Removing anti-HBc plasma should also reduce the prevalence of hepatitis B surface antibody, which could have the unintended consequence of rendering a plasma pool at greater risk of transmitting hepatitis B virus (because of the low prevalence of antibodies).
f. Flexibility of plasma production was considerably reduced, and many suppliers were unable or unwilling to comply with the necessary procedures.
g. The identification, separation and isolation of anti-HBc plasma had placed *"a large burden on Cutter employees and staff."*

200. The paper also cited the CDC's figures for anti-HBc positivity among known risk groups for AIDS: 88% of homosexual/bisexual males, 96% of intravenous drug users, and 76% of people with AIDS prodrome (i.e. early symptoms associated with AIDS) [ep.2].[27]

201. Having considered the paper, the company agreed the continuation of the testing procedures at a meeting on 25 June 1984. The same minutes recorded that an insurance claim for $4.9 million had been made in respect of the previous year's withdrawal of 16 lots of Koate and Konyne. **[BAYP0005319; KREV0000001, ep.778]**

202. Cutter continued to test for anti-HBc antigen until the end of October 1984, by which time it considered there was sufficient confidence in the heat treatment process to justify the cessation. It was also noted that a specific test for HTLV-III was soon expected to be available. **[BAYP0005454_005]**

The isolation of HTLV-III, 23 April 1984

203. The isolation of HTLV-III by Dr Robert Gallo and his team was announced at a press conference by the Secretary of Health and Human Services, Margaret Heckler, on 23 April 1984. She said that it was anticipated that a blood test would be available within six months. **[DHSC0001581; KREV0000001, ep.773]**

Events in June and July 1984

[27] A later study published by the CDC in 1985 stated that 62% of donors to whom the CDC had traced a transfusion-related AIDS case had tested positive for anti-HBc. **[KREV0000001, ep.772]**

204. By June 1984, 49 cases of AIDS in people with haemophilia had been identified **[JREE0000019, ep.78]**. The following month, on 13 July 1984, the MMWR published a preliminary report using the first generation of LAV tests. 18 of 25 asymptomatic people with haemophilia tested positive, as did two-thirds of a larger sample size **[KREV0000001, ep.779]**.

205. On 16 July 1984, the Study Group on anti-HBc testing presented its final report. The majority continued to oppose the introduction of the test. They cited the lack of specificity, the 6-20% rejection rate for plasma, an increased risk of hepatitis B transmission, plasma shortages, and price increases. The minority argued that the tests would have identified 60-80% of homosexual men, but they accepted that it would no longer be worth implementing anti-HBc testing in light of the identification of HTLV-III and prospect of a specific screening test. **[KREV0000001, ep.771]**

206. Later that month, at Cutter's initiative, there were discussions between Cutter, Hyland and Alpha about an industry-wide public relations campaign to stimulate the use of Factor VIII. Armour had also expressed an interested, but were unable to attend the meeting. Reference was made to engaging two public relations firms. The Inquiry has a proposal from one of those firms, Hill-Knowlton, but it is not known whether (or how) this matter progressed further. **[CGRA0000548; BAYP0005366]**

Summary of the position by July 1984

207. The debate about the safety of blood products in the first half of 1984 had predominantly been about anti-HBc testing. A coalition of two of the fractionation companies, Armour and Alpha, and a number of blood banking organisations had successfully resisted the calls from the FDA to introduce such testing, and had done so until a point in time when even advocates of testing were resigned to waiting for the emergence of a specific test for HTLV-III/LAV. However, two companies, Hyland and Cutter, had taken a contrary view, with the latter unilaterally introducing anti-HBc screening, despite pressure not to do so.

208. Product withdrawals had continued, as had the increased number of AIDS cases identified among people with haemophilia. Initial results on patient testing had also provided evidence of devastating rates of infection in the United States.

209. The year had, though, seen the announcement of the isolation of HTLV-III, the promise of a specific test for the virus, and the granting of licences for heat treated Factor VIII products. This set the scene for the two issues that would be of most significance in the months that followed: the introduction of an HIV screening test for blood and plasma donors, and the validation and adoption of heat treated factor concentrates. These topics are best approached thematically.

HEAT TREATMENT

The development of heat treated factor concentrates

210. It is outside the scope of this presentation to seek to present a full account of the development of heat treated factor concentrates in the United States. The story is historically and scientifically complex. The Inquiry holds many thousands of pages of documentation that are of relevance to the issue, but these are very far from amounting to a complete – or even adequate – archive from which to undertake a comprehensive, forensic investigation. Instead, Counsel to the Inquiry seek to present an overview of the main narrative events, while identifying some gobbets of material that may help to provide an insight into the topic. The Inquiry will hear further evidence on fractionation, heat treatment and viral inactivation, and the Chair will wish to consider all such evidence before coming to his conclusions.

211. There is an abundance of evidence that, during the 1970s, Factor VIII and Factor IX were considered to be highly heat labile proteins, such that they would not survive the sort of heat treatment that was used as a method of viral inactivation on albumin products: see, for example, the evidence of Sarah Middleton **[Transcript, 1 October 2021, p.125]**. Yet, in 1977, the German company Behringwerke AG commenced work on heat treatment studies, with a view to providing factor concentrates with lower risks of hepatitis transmission **[JREE0000019, ep.100]**.

212. By the following year, Hyland had begun some form of research on heat treatment of Hemofil: an internal memorandum dated 26 April 1978 stated that the work required additional funding and manpower if it were to progress **[CGRA0000215]**. Hyland's parent company, Travenol, appears to have obtained information from its German subsidiary about the Behringwerke process, which encouraged further efforts in this field **[CGRA0000218; CGRA0000219; CGRA0000220]**. By September 1979, hepatitis removal via heat treatment was listed as the second item on Hyland's "Division Priority List", behind the development of Autoplex, the product intended for patients with Factor VIII inhibitors **[CGRA0000222; CGRA0000223]**.

213. Behringwerke obtained a German license for its product, which was pasteurised 60°C for 10 hours, in early 1981 **[KREV0000001, ep.762; JREE0000019, ep.101]**.[28] It was not, at that time, licensed or marketed either in the USA or the UK. At about the same time, Hyland were proceeding to clinical trials in humans of Hemofil T, as its heat treated Factor VIII product had come to be called **[CBLA0000011_005, ep.16, §45]**.

214. Other companies had also commenced work on heat treated products **[JREE0000019, ep.102]**. A Cutter budgeting document from 1983 provides some evidence of the sums that the company were spending, or were estimating or budgeting to spend, on heat treatment work in 1981, 1982 and 1983 **[BAYP0004331]**.

a. In 1981, the total amount spent on research and development by the Drug R&D Division was $4.271 million [ep.4]. Of this, $293,000, or 6.9% was spent on the *"hepatitis free product development"* project.
b. In 1982, an estimated $558,000 of the same budget was estimated for the project, 9.2% of the total [ep.4]. In addition, an estimated $102,000 was estimated to be spent by the Technical Operations Division (5.1% of that total budget). The notes to the budget described the project as *"a defensive move necessary to maintain AHF market share"* [ep.14]
c. The 1983 budget included an estimate for $632,000 under the International Division budget (36% of the total budget) [ep.16]. The notes refer to the need to apply for a Japanese license, and for testing in the first quarter of 1983 [ep.18].

215. It is possible, and indeed likely, that further sums were spent on the project in this period, which are not evident from this analysis of the budget documents that the Inquiry holds.

The licensing of heat treated Factor VIII concentrates in the United States

216. Hyland were the first company to apply for a licence for its heat treated product from the FDA. It submitted its application in June 1982 **[BAXT0000001_001]**. The licence would be granted in March 1983. Other companies followed thereafter.

[28] The secondary literature contains conflicting dates of February and May 1981.

The IOM Report provided a helpful table setting out when licences were applied for and obtained, which is reproduced here. **[JREE0000019, ep.106]**

Manufacturer and Product	**Application**	**Grant**
Hyland – Hemofil T *Dry heat, 60°C for 72-74 hours*	June 1982	March 1983
Armour – Factorate HT *Dry heat, 60°C for 30 hours*	December 1982	January 1984
Alpha – Profilate HT *Heated in suspension, 60°C for 20 hours*	December 1982	February 1984
Miles/Cutter – Koate HT *Pasteurised, 60°C for 10 hours*	August 1983	January 1984
Miles/Cutter *Dry heat, 68°C for 72 hours*	November 1983	February 1984

217. Immuno do not appear to have sought an FDA licence for their heat treated Kryobulin. Their application to the UK Licensing Authority to vary their licence for Kryobulin to allow for heat treatment was made in December 1984, and approved in February 1985 **[SHPL0000271_011]**.[29]

218. The initial work undertaken on heat treatment of Factor VIII products was done for the purposes of inactivating hepatitis, not AIDS. As has been noted above, the FDA convened a meeting *"to discuss certain technical problems with regard to heat inactivation of viruses, particularly non-A non-B hepatitis in plasma derivatives"* on 9 September 1982. The focus of the meeting remained on hepatitis, and AIDS was not mentioned in the record of the meeting. **[SBTS0000313_101; BAYP0004178_001]**

a. Among the topics discussed at the meeting were: the principles of heat inactivation (and the importance of the realisation that residual infectiousness of a material is directly related to the infectious level of the treated material); difficulties in plasma protein denaturation; the difficulties with chimpanzee experiments (*"slow and fraught with inherent problems"*); whether to change inactivation processes known to inactivate HBV in order to seek to inactivate non-A non-B hepatitis; the use of marker viruses for non-A non-B hepatitis, and the difficulties involved in using them (*"no consensus could be reached*

[29] See Counsel to the Inquiry's Presentation on Immuno, Transcript of 23 September 2021.

on the usefulness of this approach"); and the use of clinical trials, including following chimpanzee trials.

The use of heat treated factor concentrates

219. The early heat treated products were treated with some scepticism by haemophilia clinicians. There were (justified) doubts about their effectiveness in inactivating hepatitis. More importantly, doctors were concerned that the heat treatment could give rise to the development of inhibitors, meaning patients could no longer be treated with Factor VIII concentrates, heated or unheated. Cost was also a factor. Dr Evatt, in his *Tragic History,* wrote that *"Because of the high cost and feared risk, the [Hyland] product did not achieve widespread use."* **[CVHB0000042, ep.7;** see also Dr Kingdon's assessment at **CBLA0000011_005, ep.19, §53]** Similar doubts were expressed in the United Kingdom: see, for example Dr Gunson's letter to Dr Walford of 29 June 1983 **[DHSC0002229_056]**, and the subsequent discussion at the 13 July 1983 meeting of the Biologics Sub-Committee of the Committee on the Safety of Medicine **[ARCH0001710]**.

220. As late as June 1984, Dr Aledort, who by then was working for the World Federation of Hemophilia, *"strongly opposed the industry's inclination to stop manufacturing non-heat-treated FVIII and FIX concentrates. He cites the possibility of neo-antigen formation with HT products the extra costs involved, and the fact that there is no direct evidence that heat treatment eliminates or reduces the risk of AIDS to haemophiliacs."* **[BAYP0005319]**

221. Although the products were originally developed to tackle hepatitis, it was the AIDS crisis that led to them becoming rapidly licensed and accepted in use. As the table above shows, the time lapse between an application for a licence from the FDA and the licence being granted shortened considerably as time passed. The presentations given in September and October 2021 by Counsel to the Inquiry contained evidence that the UK authorities were also prepared to encourage and expedite applications for product licences for heat treated products.

222. The work done by the CDC on developing an assay to measure viral load in factor concentrates was an important catalyst. In his *Tragic History*, Dr Evatt wrote that he presented the results of CDC studies that showed LAV/HTLV-III inactivation

by heat treatment at the World Hemophilia Congress in Rio de Janeiro in August 1984. At that time, clinicians still expressed scepticism, but further experiments took place the following month. Dr Steve McDougal, Dr Evatt's colleague at the CDC, was able to demonstrate that large quantities of virus that had been deliberately placed in Cutter (and later Alpha) concentrate was inactivated by heat treatment **[CVHB000042, ep.7]**. Experiments on inactivating mouse retrovirus by heat treatment were reported by Dr Jay Levy in *"The Lancet"* the same month **[KREV0000001, ep.763; CBLA0000011_005, ep.32, §96]**.

223. Events then moved rapidly. Still in September 1984, a conference was held between haemophilia clinicians and CDC officials at which there was agreement that physicians should consider changing to heat-treated factor concentrates, even though there was as yet insufficient proof that AIDS was inactivated. The majority left it to individual clinicians and centres to manage the transfer, though the Krever Report described a *"very vocal minority"* who advocated for a recall of non-heat treated factor concentrates **[KREV0000001, ep.764, ep.766, ep.771]**.

224. In October 1984, the Medical and Scientific Advisory Committee of the NHF advised physicians to *"strongly consider"* changing to heat treated products **[KREV0000001, ep.779; BART0002308]**. The CDC published the results of Dr McDougal's experiments in MMWR on 26 October 1984, **[BART0002308]**. The same edition recorded 52 cases of AIDS in people with haemophilia

225. The Groningen Conference took place on 1 and 2 November 1984, where further presentations were made on the efficacy of heat treatment in inactivating AIDS **[PRSE0000807; PRSE0002692]**. In December 1984, an editorial in *"The Lancet"* advised that it was reasonable to take a pragmatic approach and switch haemophilia A patients to heat treated products, notwithstanding the lack of clinical evidence of their efficacy against AIDS. In the context of a call for additional funding to purchase such products, the editorial suggested that it would be *"indefensible to allow prescription and home use of material known to be at risk from HTLV III when apparently safer preparations are available."* **[CBLA0001964]**.

226. According to Dr Kingdon, Hyland ceased the sale of all non-heat treated Factor VIII concentrates in the USA in January 1985 **[CBLA0000011_005, ep.33, §99]**. The following month, the first published reports appeared in *"The Lancet"* showing, as a result of a clinical trial rather than a laboratory test, that Hemofil-T did

not appear to transmit HTLV-III **[CBLA0000011_005, ep.20, §57; SHPL0000371_036]**. This was the first such clinical evidence of the efficacy of heat treatment **[CBLA0000011_005, ep.24, §70]**.

227. A letter dated 13 March 1985 from Cutter to Dr Geoffrey Savidge at St Thomas' Hospital stated that Cutter felt that it was *"prudent to no longer effect sales of non-heat-treated product for use in the United Kingdom."* **[BAYP0000024_113]**

228. Heat treatment of factor products was endorsed and recommended by the World Health Organisation following a conference and meeting held in Atlanta from 15 to 19 April 1985 **[SHPL0000245_013, ep.5]**. During the conference, the position that non-heat treated products should not be used had been advocated, although it is not clear from the documents whether this represented a consensus of opinion at that time **[BAYP0005758, ep.2]**. In the same month, the NHF revised its treatment recommendations to recognise that heat treated factor concentrates *"may be the preferred products"* for infants and children with severe haemophilia, and for newly identified and previously untreated severe haemophilia patients. It continued to advise the use of desmopressin or cryoprecipitate in patients with mild or moderate haemophilia **[KREV0000001, ep.779]**. It was not until December 1985 that NHF advised that only heat treated product be provided for all patients with severe haemophilia **[KREV0000001, ep.779]**.

Product recall and the approach to non-heat treated factor concentrates

229. Heat treatment led to a change in approach to the recall of products that were known to have been contributed to by a patient who later developed AIDS. In April 1985, the NHF reversed its previous position and declared that it no longer recommended the recall of such concentrates if they had been treated with a licensed heat-treated process, on the basis that the virus would have been *"adequately killed"* with such procedures **[KREV0000001, ep.766]**. This recommendation was cited by Alpha in a letter to the FDA on 30 April 1985, in which it explained that it did not intend to withdraw vials of factor concentrate that had been produced using plasma from a donor who was later diagnosed with AIDS. The letter set out viral inactivation calculations that led it to conclude that its heat treatment would have been sufficient to inactivate a hypothesised *"worst case scenario"* for the viral load in the products. The proposed action (or lack of action) had been discussed

with an official of the Bureau of Biologics **[BAYP0005761]**. The Inquiry has not identified any subsequent correspondence on this point from the FDA.

230. Non-heat treated concentrates that were still in circulation did continue to be withdrawn, including seven batches of Armour product just three days later, on 3 May 1985 **[BAYP0005877]**. Hyland announced a withdrawal in June 1985 **[KREV0000001, ep.778]**.

231. There is some evidence that Cutter sought to sell non-heat treated products – including stock held in Britain – to overseas markets that had not, at that time, adopted heat treated products. An internal memorandum dated 10 April 1985 referred to a trip report given by Jack Wood **[CGRA0000583]**. Mr Wood was, in his own description, the main Cutter contact person for distributors in Europe **[CGRA0000553, ep.8]**. The April 1985 memorandum recorded that Mr Wood had reported that the stock of non-heat treated Koate in the UK was worth approximately $395,000. The memorandum continued:

> "As you know we are attempting to sell some of this merchandise into Hong Kong and Taiwan. Jack indicated that Brian Dyos [of Cutter] will be discussion with Trevor Barrowcliffe [of NIBSC] a dating extension allowing for relabel and continuous selling into markets not yet converted to the heat-treated Factor VIII products.
>
> I'll keep you posted as we progress in this project."

232. A few days earlier, on 15 April, Mr Wood had sent a memorandum to another employee expressing the appreciation of Cutter UK for *"the effort you have made in marketing to other countries their inventory of non-heat-treated Koate."* The memorandum suggested that 4,000 vials of such product had recently been sold, and that this would *"significantly help in reducing this inventory"*. Other material remained and, wrote Mr Wood, *"We will do everything possible to sell this product in European countries not yet converted to heat-treated product"* **[CGRA0000581]**. Mr Wood sent a similar memorandum to another employee on the same day. In this he noted that Cutter UK would be willing to subsidise the sale of the remaining product on the basis that it was better to have a lower profit than a total loss **[CGRA0000582]**.

233. Such an approach is evident within the UK in this period as well. In a letter dated 15 May 1985, Linda Frith of Cutter UK offered what was described as *"Koate regular product"* to Dr Edward Tuddenham at the Royal Free hospital at the discounted price of 4.75p per i.u. The description of the product, its price, and the

stated expiry date of 13 July 1985, all suggest that this was non-heat treated product. The Inquiry has not identified any further documentation revealing Dr Tuddenham's response to this offer **[CGRA0000561]**. A later memorandum, dating from 1987, recorded that Cutter sold *"both heat treated and non-heat treated products in parallel [in the UK] until October of 1985"* **[CGRA0000558]**. A formal letter subsequently sent by the company to a solicitors' firm stated that after February 1985, non-heat treated product was supplied *"only in response to specific requests for it from Haemophilia Centres"* **[SBTS0000416_030]**.

234. On 30 May 1985, a meeting took place between the FDA and fractionators on the question of what, if any, regulatory action should be taken on non-heat treated product. Dr Ojala of Cutter made a note of the discussion, which he circulated in an internal memorandum. According to that note, Dr Meyer (Director of the National Center for Drugs and Biologics) requested voluntary statements from the companies that they would not distribute non-heat treated products **[BAUM0000025]**:

> "He explained that although the FDA could revoke these through the regulatory process, he did not want any attention paid to the fact that the FDA had allowed this situation to continue for so long, and he would like the issue quietly solved without alerting the Congress, the medical community and the public. Implicit in the discussion was the concern that the FDA felt that this action was long overdue. He wanted a date (such as June 1) for the letter from us.
>
> Industry responded with a list of reasons why they had particular problems with the proposal, including the value of the inventory in our control, the lack of inhibitor indication for PTC, Alpha's pending dry-heat approval, Hyland's non-approval for Autoplex etc. Everyone had a reason and Hyland mentioned an 18 million unit AHF inventory that would have to be reworked to heat-treat product.
>
> The industry position was that we would need rapid review of pending submissions and some time to review the situation with our management. Several proposed a staggered elimination of non-heat license, starting with AHF and moving into other areas as feasible, and the international situation was reviewed extensively.
>
> Meyer replied that he understood the situation and could sympathize with the difficulties but that did not remove the overriding concern that no one in the world should be allowed continued exposure to HTLV-III for any of the reasons mentioned … he would assist with rapid review and approval for submissions, but the de-licensure of all products had to occur soon."

235. Dr Ojala's note indicates some tension between fractionators about the different heat treatment techniques used, with the representative of Hyland stating that *"Cutter had made it difficult for the rest of the industry by using such 'extreme' temperatures for so long a duration and thus established precedent."* The Cutter process used dry heat at 68°C for 72 hours. [ep.2]

236. The attendees agreed to meet again on 17 June 1985. Dr Ojala's view was that Dr Meyer clearly intended to solve the problem quickly, with or without the co-operation of the industry.

237. Some of the fractionators took steps before that meeting. On 3 June 1985, Hyland announced that it was discontinuing production of non-heat treated Hemofil and Proplex, and that it would recover any unused units and replace them with heat treated products. The public statement commented that this was being done despite there presently being *"no clear scientific evidence that either [of the products] is involved"* in the transmission of AIDS. **[CGRA0000363]**[30]

238. The Inquiry has not identified a record of the meeting of the 17 June 1985, although it is clear from other documents that it did take place and that the FDA sought information from each company about their policies on non-heat treated products. Dr Rodell of Armour wrote in response on 12 July 1985. He stated that Armour was *"no longer manufacturing or distributing untreated Antihemophilic Factor (Human) for domestic utilization."* It continued to export unheated product to its affiliate company in Germany *"for heat treatment at that site"*. There was no reference in the document to withdrawing or replacing non-heat treated product that had already been distributed **[CGRA0000471_001]**

239. A Cutter document entitled *"Coagulation Update"*, 28 June 1985, set out Cutter's position **[CGRA0000396, ep.2]**:

> "Effective 21 June 1985 all non-heat treated Koate and Konyne were discontinued for sale in the United States. A letter was sent to all customers who had purchased those products in 1984 and 1985, announcing action and recommending return of any existing product. Internationally, a telex and bulletin were sent to all distributors and all affiliates announcing similar action. We are not requesting return of existing inventories of non-heat product internationally due to difficulties in customs, licenses etc."[31]

[30] In his draft statement from 1990, Dr Kingdon stated that Hyland stopped the sale of all non-heat treated Factor VIII concentrate in the USA on 31 January 1985 **[CBLA0000011_005]**. It is possible that no such product was sold before 3 June announcement, but that the company (i) had not made a public commitment not to sell non-heat treated Hemofil, and/or (ii) unheated Proplex was still being sold in the USA until 3 June. It is perhaps notable that Hyland was the earliest company to obtain a licence for a heat treated Factor VIII product, and had stated in May 1983 an intention to switch all production to heat treatment as expeditiously as possible **[PRSE0004496]**.

[31] A sample of the letter sent on 21 June 1985 to Cutter's customers can be found at **[BAYP0005844]**.

240. The same document commented on the praise Cutter had received for its approach from the NHF and World Federation of Hemophilia, and from customers. The document contains the company's understanding of its rivals' positions [ep.2]:

a. Hyland announced similar action on 11 June but did not remove non-heat treated Proplex of Autoplex. (This is not consistent with the Hyland document of 3 June considered above with regard to Proplex, the Factor IX product. It is possible that a change of approach took place on that product, or that the Cutter understanding of the position was wrong.)
b. Armour, reportedly, were not withdrawing any non-heat treated product. (This is consistent with the Armour letter of 12 July.)
c. Alpha had reportedly sold all of its existing non-heat treated Profilnine (Factor IX) product to the New York Blood Centre, leaving it with no inventory and no plans to make an announcement. (This statement would seem to imply that all of Alpha's Factor VIII product, Profilate, was being heat treated at that time.)

241. Counsel to the Inquiry have not been able to identify any documents from Alpha setting out its position and actions at that time.

242. It appears that the steps taken by the fractionators were sufficient to avoid the imposition of further regulatory requirements. Dr Kingdon, in his draft statement from 1990, stated that so far as he was able to recall there was no general product recall **[CBLA0000011_005, ep.23, §66]**. The Krever Report recorded that it was not until 1989 that the FDA required the recall and destruction of all non-heat treated factor products. **[KREV0000001, ep.766]**

AIDS seroconversions via heat treated products

243. In his *Tragic History*, Dr Evatt wrote that by the beginning of 1985, little non-heat treated Factor VIII was being used anywhere, and that as a result, *"The AIDS epidemic in the hemophilic patients thus suddenly ceased."* He cited a study that demonstrated that no hemophilic patients born in 1985 or later was infected with HIB. *"Tragically, during the period 1981 to 1984, more than 50% of the population of hemophilic patients in the USA had already become infected."* **[CVHB0000042, ep.7]**

244. While the epidemic of AIDS cases may have been brought to an end by the use of heat treated products, there were still a number of seroconversions that were associated with the use of heat treated product. In a review article from 1995, Professor Pier Mannucci referred to 18 *"well documented"* cases of HIV transmission through concentrates that were subject to dry heat treatment **[DHSC0038508_045, ep.2]**.[32] Many of these were patients who used batches of Factorate HT that had been subjected to heat treatment, but which contained plasma that had been obtained before the HTLV-III screening test was introduced. Armour withdrew such products from the UK market following consultation with the DHSS in September 1986 **[ARMO0000217]**.

245. The Inquiry will hear further evidence on this matter, and for that reason Counsel to the Inquiry make no further comment on it in this presentation. There is, however, an appendix that provides a brief overview of the controversy concerning research conducted on Armour's behalf by Dr Alfred Prince, head of virology ay the New York Blood Centre.[33]

246. As the Inquiry has heard, while the first generation heat treated products were, in most cases, effective in inactivating HIV, they did not, in general, prevent hepatitis infections. By the 1980s, most such infections were of non-A non-B hepatitis, but there were still cases in which heat treated products were implicated in infections of hepatitis B: see, for example, the evidence and letter to *"The Lancet"* of Dr Vivian Mitchell of the Leicester Haemophilia Centre **[WITN3174003, ep.12, §67; ISPN0000156_089]**.

[32] Pier Mannuccio Mannucci, "Viral safety of plasma-derived and recombinant products used in the management of haemophilia A and B", *Haemophilia* (1995), **1**, (Suppl.1), 14-20, at 15.
[33] This appendix will be disclosed to Core Participants as a separate document.

SCREENING TEST FOR HTLV-III (HIV)

247. The Inquiry will in due course hear evidence about the introduction of an HTLV-III screening test in the United Kingdom in 1985. This part of the presentation does not seek to pre-empt that evidence. Instead, it provides a brief overview of the introduction of such tests in the United States, and the response of the main fractionators to it.

The development of the test

248. As we have seen, when Secretary Heckler announced the isolation of HTLV-III on 23 April 1984 she said that she anticipated that a blood test would be available within six months **[DHSC0001581; KREV0000001, ep.773]**. If this was intended to refer to a nationally available test for use on blood donors, it was to prove optimistic.

249. In June of that year, the United States authorities announced that five firms had been invited to develop and distribute an HTLV-III antibody test. They were Abbott Diagnostics, Electro-Nucleonics Inc, Litton-Bionetics Inc., Travenol/Genentech Diagnostics, and du Pont de Nemours and Co. Inc in association with Biotech Research Laboratories. The first application for a licence for a test was made in December. This application was for an enzyme linked immunosorbent assay (ELISA). **[KREV0000001, ep.774; JREE0000019, ep.73]**

The response of the fractionation companies

250. The fractionation companies were, of course, aware of these developments. In September 1984 a conference call took place between representatives of the main US companies, at which a common position was sought on issues including informed consent, information to be provided to rejected donors, and the ever-contentious matter of the recall of product previously fractionated from the plasma of such donors. Dr Hink's memorandum of the call recorded that, *"There was a lot of talk … which led to nothing conclusive."* **[BAYP0005395_001]**

251. An industry position did emerge in the form of a letter sent on 15 February 1985 from Robert Reilly, Executive Director of the trade body the American Blood

Resources Association, to Dr Petricciani. The letter recorded that it was estimated that between 0.5% and 1% of *"normal donors"* would react positively to the new test; it is unclear to Counsel to the Inquiry who Mr Reilly was defining as a *"normal donor"*. He went on to say that as plasma pools used in fractionation comprised at least 1,000 donations, this made it reasonable to assume that *"all lots of product produced contain plasma with anti-HTLV III."* However, in his view, *"the risk of transmitting the AIDS virus through plasma products is nearly non-existent with the exception of non-heat treated coagulation products."* Dr Reilly therefore proposed that **[BAYP0005650]**:

a. *"Intact units of plasma collected from donors subsequently found to be anti-HTLV-III reactive"* be destroyed.
b. No action be taken on affected *"in process products"* for reasons of product supply.
c. No action be taken on lots of heat treated coagulation factors already manufactured from a pool including a *"confirmed AIDS patient"*.

252. In short, the proposal was that there should be no recall of heat treated products either when a donor tested positive for HTLV-III antibody, or where a donor was diagnosed with AIDS. (This letter was sent before the NHF changed its position on product recall in April 1985, as is discussed above.)

253. On 22 February 1985, a public meeting took place on the issue of HTLV-III screening. Dr Ojala attended and wrote a memorandum summarising the meeting. In his view, the meeting was *"almost a press conference rather than a scientific meeting, and I believe this approach was intentional"*. The purpose, he thought, was for the FDA and CDC to use the occasion to overcome the negativity towards the test that had been expressed by representatives of the blood banking industry and *"special interest groups"* (presumably a reference to gay rights organisations). As far as the fractionators were concerned, *"Bob Reilly spoke for the plasma industry and did not say very much specific other than we thought prompt approval of the test was a good idea."* **[BAYP0005659, ep.1-2]**

254. At the request of the fractionators, a meeting took place between them and the FDA on 26 February 1984. This was preceded by an industry-only meeting. According to a Cutter memorandum, there was *"no enthusiasm or desire"* among their competitors to contest the HTLV-III screening test, although none wished to be

burdened with administering the confirmatory Western blot test: *"an individual testing positive [to the antibody test] would be told he was rejected as a donor, in that industry cannot afford to deal with running confirmation tests."* The meeting also discussed the imposition of ALT testing for the German market. Dr Rodell suggested that the industry might pledge to the FDA that they would not prepare coagulation factors out of *"ALT positive plasma"* for the purpose of avoiding regulatory action that mandated such tests for the US market (on which, see below) [ep.2].

255. At the meeting with the FDA, the industry proposal that was contained in Dr Reilly's letter of 15 February was discussed, with Dr Petricciani reserving the FDA's position. [ep.2]

256. Following this formal meeting, an informal one took place, at the request of Dr Carr. Dr Ojala of Cutter had, by this point left to catch a plane. Dr Carr used the meeting to float the idea that heat treatment and HTLV-III testing had altered the landscape in such a way that the decision not to use plasma from prisoners might now be revisited, They discussed an ongoing study being undertaken by the FDA about the level of infectivity of blood obtained from prisoner, and the possibility that the FDA's guidelines might be relaxed if this were to show that prison blood was not distinguishable from non-prison blood. Dr Carr's memorandum recorded that Armour had *"absolutely no interest"* in the matter, Hyland were interested but did not participate in the discussion, while Dr Reilly considered it a *"potential bombshell"* and did not want to push it further as it did not represent a majority of his constituency. Marginalia on the memorandum asked, *"Do we want to pursue?"* In answer was a note stating: *"Pete, How much material do we get currently (prison plasma)? Could this represent an opportunity to source substantial increased amounts? If yes, we probably do want to pursue. Vaughan, 3/15/85."* **[CGRA0000312]**

257. On 2 March 1985 the Department of Health and Human Services announced that the first HTLV-III antibody test kit, manufactured by Abbott, had been licensed by the FDA **[KREV0000001, ep.776]**. In his 1990 draft witness statement, Dr Kingdon stated that the seven months between the approval of the five companies seeking to develop tests and the granting of the licence was *"in scientific terms … a remarkably short period"* **[CBLA0000011_005, ep.44, §134]**. Dr Ojala, in his memorandum on the 22 February meeting, had referred to the perception among CFC and FDA staff that *"Herculean efforts"* had been made to licence the test so quickly **[BAYP0005659]**.

258. Armour and Hyland began testing donors that month **[PRSE0001754; CBLA0000011_005, ep.34, §102]**. However, according to Dr Kingdon's 1990 draft statement, there were insufficient test kits available to satisfy US demand until June **[CBLA0000011_005, ep.44-45, §135]**.[34] The Krever Report recorded that HTLV-III testing became available in all centres by July 1985, having been available in the vast majority of centres by May 1985 **[KREV0000001, ep.776]**. Immuno appear to have been screening all plasma used in their therapeutic and diagnostic products by October 1985 **[IPSN0000246_003]**.

259. Representatives of the four main US fractionators met again on 12 April 1985, ahead of a Blood Products Advisory Panel meeting. Dr Ojala produced a memorandum reporting the meeting **[CGRA0000261]**. The principal point of discussion was the approach to be taken to the introduction of ALT testing, which was to be instigated in response to the requirements of the German regulators that any plasma with ALT levels at more than twice the normal level should be excluded from plasma pools for factor products. It is apparent from the discussion that it was estimated that only around 20% of US plasma would be tested in this way (and thus be available for the German market). The issues for the fractionators were, first, what was to be done with plasma that was *"positive"* for being twice the normal ALT level, and, second, how best to avoid an unwelcome introduction of ALT testing for <u>all</u> US plasma. The memorandum recorded the following discussion [ep.1]:

> "The Ojala script for an industry position was accepted with enthusiasm from Alpha and some reluctance from the others. Gerety [Robert Gerety, FDA] (or someone) will express concern to the Advisory panel that use of ALT positive plasma in domestic products will change the character of those products. Our formal presentation will state that we are simply hand selecting (via ALT screening) special plasma for a particular customer (the German market) and that all remaining plasma remains licensed source plasma which may be utilized in other products. The ALT test is not required by the FDA, nor do we want it to become so. We will state that any plasma 2 times normal will not be used for the particular customer. We will further offer that any plasma with 5 times the upper limit of normal will not be used in domestic product <u>and</u> the donor will be deferred until the ALT levels fall back to normal. We will use the argument that 5 times normal may indicate a donor health problem. This may not please all of you, but it was the only way to achieve industry consensus. Further, plasma in the over 2 but not less than 5 range will be used <u>randomly</u>

[34] Dr Kingdon expressed his view that: *"Until there were sufficient kits available to meet the US demand it is unlikely that any of the test kit manufacturers would have been willing to export their tests abroad."* **[CBLA0000011_005, ep.45, §135]**

in the production so as not to concentrate this plasma in any particular lots.[35] All coagulation products will be heat-treated for an extra margin of safety. We will endeavour to call German plasma 'special' or some other term to nullify the idea that greater than 2 times normal plasma is 'positive' or other negative connotations.

In practice, Armour will discard all 2x cryo and Hyland will discard all 2x plasma from coagulation products and Fraction II products, We estimate that approximately 20% of total US plasma will be screened, but will vary between manufacturers. Armour requirements are modest,[36] and Hyland will screen all plasma for the interim to 'fill the pipeline'. Alpha will screen only A and B plasma from select centres. Hyland's conservative position is due to Armour's decision (i.e. that want to be perceived as conservative in any subsequent litigation) and because they had two patients develop Non A/Non B in a clinical trial of their IVIG in Seattle."

260. The memorandum made clear that the proposal in the *"Ojala script"* was for plasma with more than 5 times the normal ALT levels to be discarded, with the donor deferred [ep.2].

261. The meeting went on to discuss prison plasma, which was said to illicit *"even more diverse viewpoints"*.

> "Cutter and Alpha believe that science has progressed to the point that we can screen this plasma through testing (HTLV-III etc) and we now heat treat the products. Hyland says they have no current prison plasma sources (!) and Armour states they will never have any. Reilly is perpetually gloomy on the entire subject, and feels we are destined to fail. Nevertheless, we agreed to hang together for a try with the FDA. We will propose to begin using prison plasma cryo and abandon our 'Gentleman's agreement' unless the FDA takes issue and threatens regulatory action."

262. Reference was also made to the FDA's response to the fractionators' letter on product recall. No-one at the meeting was said to like the response. The Inquiry has not yet identified the FDA's letter, but from Dr Ojala's memorandum, it appears to involve some form of three year period for such recalls. The fractionators were to lobby for a change to three or six months [ep.3]. As is discussed above, the NHF changed its position on recall later that month, and it appears that from late April the FDA were content with proposals that heat treated product would not be recalled even when a donor was later diagnosed with AIDS.

[35] Counsel to the Inquiry understand this to mean that such plasma would be mixed with non-tested US plasma, and thus distributed across all resulting products. It would not form a distinct plasma pool, which would, inevitably, have elevated ALT levels when compared to non-tested plasma.
[36] Presumably as a result of a limited market share in Germany.

263. A Cutter representative, Jack Ryan, followed up the approach about prison plasma at a conference call with Dr Charles Carman and Dr Peter Levine of the NHF on 1 May 1985. Dr Levine, speaking personally but reflecting what he believed the NHF's viewpoint would be, expressed opposition. Despite heat treatment, *"he still feels that … we are taking risks that are not justified. Specifically, increased risks for hepatitis non-A and non-B as well as hepatitis B."* Dr Ryan informed him that Cutter would continue the dialogue with the FDA as it thought is position was *"safe … and justified."* **[CGRA0000311]**

264. Counsel to the Inquiry have not identified further documents in which the use of prison plasma was raised. Dr Ryan's comments would suggest that such discussions did continue, but Counsel to the Inquiry are unable to comment on what – if any – changes in practice were made.

265. Similarly, it is not clear from the documents seen by Counsel to the Inquiry what decisions were reached on ALT testing. It appears that such testing became more widely used across the industry in the years to come. In a letter to the NHF in 1987, Carl E. Brook, then President of Hyland, stated that his company had been the *"first manufacturer to screen all plasma in compliance with the German BGA requirements in 1985,"*[37] implying that other companies followed. He also claimed that Hyland had behaved in a responsible fashion by not using material rejected for Germany's ALT requirement in any other market as several other US manufacturers did.' **[CGRA0000290]**

266. Further examination of these issues is outside the scope of this presentation.

Summary of the position by July 1985

267. By July 1985, all US fractionators were producing heat treated factor concentrates produced from plasma screened for HTLV-III/HIV anti-bodies. Donors were subjected to screening regimes intended to exclude high risk donations, including from gay donors. This led to a high level of protection against transmission of HIV but not, in most cases, against non-A non-B hepatitis.

[37] Emphasis added.

268. The protection against AIDS afforded by these measures had led to the reversal of the previous approach to withdrawing batches of factor concentrate that were known to have been contributed to by donors who were later diagnosed with AIDS. This measure had the support of the NHF and, seemingly, the FDA.

269. Some fractionators were considering going further, by opening a dialogue with the FDA with a view to reintroducing the fractionation of plasma from prison donors. This, though, was an issue that split the pharmaceutical companies, not least because of the anticipated increased risk of hepatitis.

270. The introduction of ALT testing in respect of plasma destined for the German market posed a new problem for the fractionators. A consensus was forged to put forward a proposal that was intended to ward off mandatory testing of all US plasma for ALT levels. That proposal, if implemented, would have meant that products exported to Germany would be produced from plasma specifically selected as being relatively low in a marker for hepatitis, whereas domestic products would be drawn from plasma that either had not been tested or was known to have higher ALT levels.

Jenni Richards Q.C.
Matthew Hill
Counsel to the Inquiry