Witness Name: Dr Brendon Gray
Statement No.: WITN6984001
Exhibit: WITN6984002 - WITN6984137
Dated: 21 December 2021

INFECTED BLOOD INQUIRY

WITNESS STATEMENT OF DR BRENDON GRAY

I, Dr Brendon Gray, of Bayer AG, Mullerstr. 178, 13353 Berlin, Germany, WILL SAY AS FOLLOWS:

1. I was UK Medical Director at Bayer plc ("Bayer")[1] from 20 May 2019 to 31 August 2021. I am authorised to make this statement on behalf of Bayer to provide information to assist the Inquiry in relation to the regulation and history of blood products prepared from pooled plasma and supplied by Bayer and associated companies to the National Health Service ("NHS") in the UK between 1970 and 1993.

2. I am a medical doctor. My medical qualifications are MBChB, MPH, MRCGP, FAFPHM (RACP), FACLM. I have not maintained my membership or fellowships since leaving clinical practice. I gained full registration with the Medical Council of New Zealand on 22 December 1994 and with the UK General Medical Council ("GMC") on 14 September 1995. I am currently registered with the GMC (registration number 4241346), but I do not hold a licence to practise. Between 1994 and 2001, I held various house officer and registrar hospital posts in a number of specialties including paediatrics and neonatal intensive care in New Zealand, the UK and Australia. Between 2002 and 2013, I worked in public health and general practice roles in the UK and New Zealand before joining Bayer New Zealand Limited in July 2013. Within the Bayer group I have held posts of increasing seniority in the medical affairs

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[1] As explained at paragraph 4 of the witness statement of Mark Wilkinson dated 14 September 2021 ("Wilkinson") (**WITN2988001**), Bayer plc was first registered in the UK under registration number 935048 as Bayer (UK) Limited. The name was later changed to Bayer UK Limited, and then again to Bayer plc. "Bayer UK" is used throughout this witness statement to refer to the UK company registered under number 935048, regardless of its name at the relevant time.

and pharmacovigilance department. I am currently employed by Bayer AG as Vice President, Head of Pharmacovigilance Regions. I was appointed to this role effective 1 August 2021. I am responsible for the activities of all Bayer AG's country affiliate pharmacovigilance teams around the globe.

3. I therefore joined the Bayer group many years after the period of interest to the Inquiry and have no direct knowledge of the subject matter. However, I am aware that, on 23 September 2021, at the commencement of presentation of evidence to the Inquiry regarding the pharmaceutical companies, Junior Counsel to the Inquiry indicated that the counsel team recognised that others might identify other documents and other themes that they considered to be important and this was welcomed.[2] Furthermore, Bayer wishes to provide what assistance it can to the Inquiry and therefore, while there is no person employed at the company who was present at the relevant time, this statement is intended to provide information in response to the questions set out in the Rule 9 Request dated 21 July 2021 addressed to an ex-employee of Bayer, Mrs Linda Frith, insofar as she is unable to address such matters, based principally on documents which have been disclosed to the Inquiry by Bayer or Bayer HealthCare LLC or are in the public domain.[3]

4. References in this statement are either to publicly available documents or documents that have been provided by Bayer and Bayer HealthCare LLC to the Inquiry. Where reference is made to a document which Bayer or Bayer HealthCare LLC provided to the Inquiry, the document number, file number and schedule is stated in the footnote in the form **[Schedule/file/document]**. For example, **[Reg/3/185]** refers to the 185th document in the 3rd file of regulatory correspondence. An index of the schedules and corresponding references used in this statement is at **Annex E**. Documents referred to are attached as Exhibits **WITN6984002 - WITN6984137** and the Exhibit number referenced in the text, save for when Bayer has been made aware of the Inquiry's Unique Reference Number ("URN") for a document. In which case, the URN is stated in the text.

5. In addition, the following documents are annexed to this witness statement:

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[2] 23 September 2021, Transcript of the hearing, page 53, lines 18 - 21

[3] Miles Laboratories Inc (now called Bayer HealthCare LLC) was a defendant in product liability proceedings in Ireland in the 1990s. The defence was coordinated by an Irish law firm and Bayer's current legal advisors, now at Arnold & Porter, taking instructions from the in-house lawyers at Cutter Inc in the US. Bayer UK Ltd (later Bayer plc) was not a defendant in those proceedings and Bayer plc was not involved in conducting the defence of them. However, Arnold & Porter still held a set of documents belonging to Cutter Inc that were potentially relevant to the issue in that litigation in their offices in London, to the order of Bayer HealthCare LLC, a company incorporated in the US. Bayer informed the Inquiry of these documents (Letter of 11 April 2019) and the Inquiry requested that they should be disclosed (Letter of 13 May 2019). After careful consideration, Bayer HealthCare LLC agreed to disclose the documents that were held within the jurisdiction (Letter of 3 July 2019).

5.1 **Annex A** - Regulatory Legislative Framework Applicable in the UK from 1970 - 1993

5.2 **Annex B** - Regulations and Procedures Relevant to the Operation of Plasma Collection Centres in the US

5.3 **Annex C** - Schedule of Warnings

5.4 **Annex D** - Table of Bayer / Associated Companies' Blood and rDNA Products

5.5 **Annex E** - Index of Schedules

6. This statement is structured as follows:

A. Knowledge of and response to risk

Haemophilia and its treatment

7. The Inquiry is familiar with haemophilia as a blood disorder and has received substantial evidence regarding its effects. While I do not propose to duplicate such material, I set out below limited information regarding haemophilia and its treatment in order to provide context for the later information in this statement regarding the involvement of Bayer and the supply of relevant blood products. The history of haemophilia treatment and responses to the transmission of hepatitis and the human immunodeficiency virus ("HIV") through blood and blood products is also summarised in the timelines attached to the statement

of Mrs Linda Frith **[WITN6407002]**.[4]

8. Haemophilia is a serious and potentially devastating disorder. Long before effective treatments became available, most haemophilia patients died of intracranial or other haemorrhages and did not reach adolescence **[WITN6984002]**.[5] Between 1943 and 1957, patients with severe disease on average would survive only into their early 20s **[WITN3289052]**.[6] By 1962, the median life expectancy for a severe haemophilia patient in Britain was 37 years of age **[HSOC0001285]**.[7]

9. In 1964, the first effective treatment for patients with haemophilia, cryoprecipitate, a concentrated preparation of plasma, was developed **[WITN6984003]**.[8] However, it was effective only in the treatment of haemophilia A and not haemophilia B, the yield of factor VIII in a single unit of cryoprecipitate was variable and unpredictable, the preparation contained many other proteins as well as the required coagulation factors, administration was time-consuming and frequently associated with allergic reactions, and it had to be stored in freezers (a draw back to its use at home) **[BAYP0000022_050]**,[9] **[WITN4461001]**.[10] Treatment in practice required administration in hospital, often associated with long, expensive journeys and time lost from work and school **[BAYP0000020_071]**.[11]

10. In these circumstances, shortly after cryoprecipitate was developed, factor concentrates began to be developed. The original factor concentrates were concentrated preparations of (freeze dried) lyophilised factor VIII or factor IX obtained from pools comprising donations of plasma obtained from many donors **[WITN3901009]**.[12] Plasma, the non-cellular portion of blood, and therapeutically active derivatives are isolated from the pooled plasma through

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[4] A Chronology and Timeline of Events, submitted by Bayer to the Archer Inquiry,**WITN64070002**

[5] Oldenburg *et al*. Haemophilia care then, now and in the future. Haemophilia (2009), 15 (Suppl. 1), 2–7 [**WITN6984002**]

[6] Mejia-Carvajal *et al*. Life expectancy in hemophilia outcome. J Thromb Haemost 2006; 4: 507–9, **WITN3289052**

[7] Jones. Acquired immunodeficiency syndrome, hepatitis, and haemophilia. British Medical Journal 1983; 287: 6407: 1737 [**Other/7/483**], **HSOC0001285**

[8] Aronson. The development of the technology and capacity for the production of factor VIII for the treatment of hemophilia A. Transfusion 30:748-758 (1990) [**Other/18/1952**], [**WITN6984003**]

[9] Biggs. 'Can hemophiliac patients be adequately maintained with cryoprecipitate? Or is it desirable or even necessary to manufacture and administer highly concentrated AHF products?' Vox. Sang., 22: 554-565 (1972) [**Other/1/30**], **BAYP0000022_050**

[10] **WITN3437002**, Written Statement of Dr Mark Winter, paragraph 35.3; Transcript of hearing of Dr Mark Winter on 1 October 2020, pages 30 - 31 and 86 - 89

[11] Anon. Home treatment for Haemophilia, Drug and Therapeutics Bulletin 1978, Vol. 16, No. 13 [**Other/2/134**], **BAYP0000020_071**

[12] Jones *et al*. AIDS and haemophilia, morbidity and mortality in a well-defined population, BMJ, 291, 695 (1985), **WITN3901009**

a process of fractionation i.e., partitioning the components of plasma into various fractions. Through such a process, many therapeutically important medicinal derivatives are obtained:

10.1 Albumin products, which are used as volume expanders and for maintaining colloidal osmotic pressure in shock.

10.2 Immunoglobulin products, which are the concentrated antibody portion of plasma and are used therapeutically in prophylaxis and treatment of infectious disease.

10.3 Coagulation factor concentrates such as factor VIII that are used to treat people with haemophilia who are deficient in those clotting factors.

10.4 The proteinase inhibitors, e.g. Alpha 1 proteinase inhibitor and Antithrombin III, which are used to treat individuals who have a congenital or acquired deficiency of the respective inhibitor **[WITN6407003]**.[13]

11. In contrast to cryoprecipitate therapy, each bottle of factor concentrate contained a quantifiable number of units of factor VIII or factor IX and produced a more predictable coagulation effect when used to treat patients; concentrates could be stored in a refrigerator and allergic reactions following use were rare **[BAYP0000022_050]**,[14] **[BAYP0000020_071]**.[15]

12. The introduction of such therapy was considered a substantial improvement in the treatment that could be provided to haemophilia patients **[WITN6984004]**.[16] Patients with severe haemophilia, for the first time in history, could treat themselves at home and manage the 30-50 bleeding episodes they experienced every year. Bleeding related mortality decreased substantially with the new treatment enabling people to enjoy *"lifestyles that allowed full and productive lives"* **[PRSE0002607 pp3-4]**.[17] Their life expectancy also increased rapidly, approaching that of unaffected persons **[HSOC0001285]**.[18]

13. Between 1982 and 1984, when evidence progressively emerged that the acquired immune deficiency syndrome ("AIDS") was transmitted by a blood-

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[13] October 1994, Statement of Dr Milton Mozen, **WITN6407003**

[14] Biggs. 'Can hemophiliac patients be adequately maintained with cryoprecipitate? Or is it desirable or even necessary to manufacture and administer highly concentrated AHF products?' Vox. Sang., 22: 554-565 (1972) [**Other/1/30**], **BAYP0000022_050**

[15] Unknown author. Home treatment for Haemophilia, Drug and Therapeutics Bulletin 1978, Vol. 16, No. 13 [**Other/2/134**], **BAYP0000020_071**

[16] Heimburger *et al*. Hepatitissicheres Faktor VIII-Konzentrat, Blut 42: 129(1981), English translation - Factor VIII concentrate which is safe with respect to hepatitis, from Microcirculation and prostaglandin metabolism [**Other/4/182**], [**WITN6984004**]

[17] Lusher and Brownstein. Haemophilia and HIV. J Thromb Haemost 2007; 5: 609-10 (2007), **PRSE0002607 pp3-4**

[18] Jones. Acquired immunodeficiency syndrome, hepatitis, and haemophilia. British Medical Journal 10 December 1983; 287: 6407: 1737 [**Other/7/483**], **HSOC0001285**

borne agent, a few clinicians urged patients to convert from factor concentrates to cryoprecipitate **[PRSE0002410]**.[19] However, in view of the benefits associated with concentrates, many physicians and patients were reluctant to abandon their use **[DHSC0001228]**.[20,21]

14. During the period of time of interest to the Inquiry, Bayer UK Limited ("Bayer UK") and, a sister company of Bayer UK, Cutter Laboratories Limited, later Miles Laboratories Limited,[22] supplied to the NHS, on either a licensed or a named-patient basis, the following factor concentrate products:

- Koate - factor VIII
- Koate HT - factor VIII
- Koate HS - factor VIII
- Koate HP - factor VIII
- Konyne - factor IX
- Konyne HT - factor IX

15. A full list of the products supplied in the UK, with product licence numbers and the legal entity that was the marketing authorisation holder is attached as **Annex D**.

16. At all times the products were prepared by Cutter Laboratories Inc, which later became a division of Miles Laboratories Inc, in the United States of America ("US"), referred to throughout this statement as "Cutter Inc".

Knowledge of HIV and hepatitis infections and transmission though blood and blood products

17. The fact that administration of blood and blood products could transmit hepatitis has been known for many years **[PRSE0000403]**,[23] **[WITN6984003]**.[24]

18. From the late 1960s, there were reports of jaundice after cryoprecipitate use in people with haemophilia. The frequency of post-transfusion hepatitis increased in the 1970s and after the isolation of the hepatitis A and B viruses it was

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[19] Desforges. AIDS and the preventative treatment in hemophilia, The New England Journal of Medicine, 13 January 1983, Vol. 308, No.2, page 94, **PRSE0002410**

[20] 4 May 1983, Communication from the Haemophilia Society concerning recent reports of AIDS which appeared in the press [**Other/6/376**], **DHSC0001228**

[21] Transcript of hearing of Dr Mark Winter on 1 October 2020, pages 30-31, 90-92.

[22] The corporate history of the companies is set out in Wilkinson, **WITN2988001**. For ease throughout this statement the companies Cutter Laboratories Limited and Miles Laboratories Limited will be referred to as "Cutter UK".

[23] Beeson. Jaundice occurring 1-4 months after transfusion of blood or plasma. JAMA 1943; 121: 1332-1334, **PRSE0000403**

[24] Aronson. The development of the technology and capacity for the production of factor VIII for the treatment of hemophilia A. Transfusion 30:748-758 (1990) [**Other/18/1952**], [**WITN6984003**]

recognised that at least one other infective agent termed non-A, non-B ("NANB") hepatitis was involved. By the early 1980s, most people exposed to pooled plasma-derived concentrates were infected with NANB hepatitis. In the 1990s, it was shown that most transfusion related NANB hepatitis was caused by hepatitis C ("HCV") **[WITN6984005]**.[25] The incidence of hepatitis in patients with haemophilia, was monitored by the UK Haemophilia Centre Directors Organisation ("HCDO") **[HCDO0000248_010]**,[26] **[PRSE0000642]**.[27] In most cases of NANB hepatitis, the acute infection was relatively mild and even asymptomatic, and was therefore rarely recognised in haemophilia patients during the HCV epidemic **[WITN6984005]**.[28] In view of the apparently benign nature of NANB hepatitis **[WITN6984006]**,[29] doctors generally concluded that the benefits associated with factor concentrates far exceeded the risk of clinical hepatitis, particularly for patients who had already received many blood and plasma infusions and had therefore already been exposed to the causative agent **[GFYF0000127]**.[30]

19. Research into the effects of NANB hepatitis was hampered by the fact that the causative agent had not been isolated and there was no specific test to confirm or exclude infection **[NHBT0000025_021]**,[31] the reluctance of clinicians to perform liver biopsies in patients with bleeding disorders due to the risk of haemorrhage **[PRSE0003089]**[32] and the fact that, in most patients, long term complications were not manifest for 12-25 years after infection **[WITN6984007]**.[33] It was not until the late 1970s-early 1980s, that a recognition slowly developed that NANB hepatitis infection was potentially associated with more serious chronic liver consequences than had previously been understood

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[25] Isfordink *et al.* Viral hepatitis in haemophilia: historical perspective and current management. British Journal of Haematology, 2021, 195, 174–185 [**WITN6984005**]
[26] 1986, UK Haemophilia Centre Directors' AGM [**Other/13/1077**], **HCDO0000248_010**
[27] May 2007, Review of Documentation Relating to the Safety of Blood Products 1970 - 1985 (Non A Non B Hepatitis) by the Department of Health [**Reg/6/505**], **PRSE0000642**
[28] Isfordink *et al.* Viral hepatitis in haemophilia: historical perspective and current management. British Journal of Haematology, 2021, 195, 174–185 (page 176) [**WITN6984005**]
[29] Sherlock. Diseases of the Liver and Biliary System, 1981, Blackwell, Oxford, page 259 [**WITN6984006**]
[30] 2006, Department of Health, Self-Sufficiency in Blood Products in England and Wales, A Chronology from 1973 to 1991 [**Other/21/2092**], **GFYF0000127**
[31] Choo *et al.* Isolation of a cDNA clone derived from a blood borne non-A, non-B viral hepatitis genome. Science. 1989; 244:359-361 [**Other/17/1836**], **NHBT0000025_021**
[32] Aledort *et al.* A Study of Liver Biopsies and Liver Disease Among Hemophiliacs, Blood 1985; 66 (2): 367-372, **PRSE0003089**
[33] Papadopoulos *et al.* Hepatitis C infection in patients with hereditary bleeding disorders: epidemiology, natural history, and management. Ann Gastroenterol. 2018; Jan-Feb; 31(1): 35–41 [**WITN6984007**]

[**WITN6984003**],[34] [**PRSE0003622**].[35]

20. However, even in the mid-1980s when it was apparent that NANB hepatitis was associated with liver failure, cirrhosis and hepatocellular carcinoma, the consensus medical opinion was that clinicians should continue using factor concentrates. Patients, their physicians and the Haemophilia Society all maintained that the improvement in quality of life and dangers of bleeding outweighed the potential risks of treatment [**GFYF0000127**].[36]

21. However, while the existence of NANB hepatitis was recognised from the mid-1970s, the first description of AIDS was in 1981. The causative virus was isolated in 1983, but this was not properly understood or recognised until 1984 (see paragraph 43 below). The first report of this new, previously unknown condition was published by the US Centers for Disease Control ("CDC") in its publication, Morbidity and Mortality Weekly Reports ("MMWR") on 5 June 1981 [**CGRA0000242**].[37] This report described five cases of pneumocystis carinii pneumonia ("PCP"), a condition previously almost exclusively seen in severely immune-suppressed patients, between October 1980 and May 1981 in Los Angeles. The CDC issued a follow-up report on 3 July 1981, describing cases of Kaposi's sarcoma, an uncommonly reported malignancy previously seen primarily in elderly men, in 26 homosexual men over a 30-month period in New York and California. An additional 10 cases of PCP were also reported, bringing the total number of PCP cases among homosexual men in California to 15 since September 1979 [**OXUH0002849**].[38] The CDC alerted doctors to be vigilant and to report cases of PCP, Kaposi's sarcoma and other opportunistic infections associated with immunosuppression in homosexual men. At this stage, the disorder was referred to as "gay-related immune deficiency" or "GRID" and no risk groups other than homosexual men had been identified [**PRSE0000748**].[39]

22. Subsequently, cases of profound immune-suppression were identified in

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[34] Aronson. The development of the technology and capacity for the production of factor VIII for the treatment of hemophilia A. Transfusion 30:748-758 (1990) [**Other/18/1952**], [**WITN6984003**]

[35] Preston. Percutaneous Liver Biopsy and Chronic Liver Disease in Haemophiliacs. The Lancet, September 16, 1978 592-594 [**Other/2/137**], **PRSE0003622**

[36] 2006, Department of Health, Self-Sufficiency in Blood Products in England and Wales, A Chronology from 1973 to 1991 [**Other/21/2092**], **GFYF0000127**

[37] Pneumocystis Pneumonia--Los Angeles. Morbidity and Mortality Weekly Reports (MMWR). 5 June 1981; 30: 250-2 [**Other/4/217**], **CGRA0000242**

[38] Kaposi's Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California. MMWR. 3 July 1981; 30: 305-8, **OXUH0002849**

[39] Perkins and Busch. Transfusion-associated infections: 50 years of relentless challenges and remarkable progress, Transfusion, Volume 50, October 2010, **PRSE0000748**

intravenous drug users and in Haitians, living in the US [**WITN6984008**].[40]

23. The CDC first reported the occurrence of PCP in three patients with severe haemophilia A, in July 1982 [**BAYP0000018_063**].[41] These patients had clinical symptoms that had developed between October 1980 and July 1981; two had laboratory evidence of cellular immune-deficiency and two had already died at the time of the report. Subsequent research has shown that the earliest seroconversion was in 1978 and infections peaked in October 1982, around the time of these first reported cases in MMWR [**PRSE0000099**].[42] Furthermore, research in the UK using retained serum samples has demonstrated that the first British patient with severe haemophilia A was infected in 1979 [**BAYP0000012_007**].[43] The HIV epidemic in the US may have begun as early as 1969, with HIV-1 circulating in the US for 12 years before the initial recognition of AIDS in 1981 [**PRSE0003804**].[44] A study conducted in the mid-1980s demonstrated that among a cohort of 6875 homosexual men from the San Francisco area, 2.4% of the men had developed AIDS. Prevalence of serum antibodies to HIV increased from 4.5% in 1978 to 67.4% in 1984 [**PRSE0001611**].[45] The prevalence of HIV seropositivity in a cohort of homosexually active men in New York City was 6.6% in sera from 1978 or 1979, and the subsequent annual incidence of seroconversion among susceptible men ranged between 5.5% and 10.6% [**WITN6984009**].[46] These results suggest that several thousand individuals were already infected in the US in 1978 [**PRSE0003804**].[47]

24. In November 1982, the US National Haemophilia Foundation ("NHF") wrote to the fractionators in the US stating that:

> *"In view of the relatively high incidence of AIDS in certain groups (specifically homosexuals, intravenous drug abusers, and those who have recently*

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[40] Johnson *et al*. Acquired immunodeficiency syndrome among patients attending hemophilia treatment centers and mortality experience of hemophiliacs in the United States. American Journal of Epidemiology. 1985; 121: 797 [**WITN6984008**]

[41] Pneumocystis carinii Pneumonia among Persons with Hemophilia A. MMWR 1982; 31:365-7 [**Other/5/268**], **BAYP0000018_063**

[42] Kroner *et al*. HIV-I infection among persons with haemophilia in the United States and Western Europe 1978 - 1990. J of Acquired Immune Defic Synd 1994; 7(3)279 [**Other/20/2060**], **PRSE0000099**

[43] Lee *et al*. The natural history of human immunodeficiency virus infection in a haemophilic cohort, British Journal of Haematology 1989 73; 228-234, **BAYP0000012_007**

[44] Gilbert *et al*. The emergence of HIV/AIDS in the Americas and beyond, PNAS November 20, 2007 104 (47) 18566-18570, **PRSE0003804**

[45] Jaffe *et al*. The Acquired Immunodeficiency Syndrome in a Cohort of Homosexual Men. Annals of Internal Medicine. 1985;103:210-214, **PRSE0001611**

[46] Stevens *et al*. Human T-Cell Lymphotropic Virus Type III Infection in a Cohort of Homosexual Men in New York City. JAMA. 1986;255(16):2167–2172. doi:10.1001/jama.1986.03370160065028 [**WITN6984009**]

[47] Gilbert *et al*. The emergence of HIV/AIDS in the Americas and beyond, PNAS November 20, 2007 104 (47) 18566-18570, **PRSE0003804**

resided in Haiti) and, in view of the potential risk of transmission of this syndrome by transfusion of blood products, it is considered prudent at the present time to urge all sources of Factor VIII products to exclude from plasma donation all individuals who belong to these groups"

NHF clarified:

"We recognize that this request is made on the basis of incomplete information, but in our view it is prudent as a precautionary measure until we get a better understanding of the nature of this disease. As you know, NHF is working with the CDC in a nationwide surveillance study that may help to clarify whether or not the spread of AIDS is related to blood product use." **[BAYP0000018_083]**[48]

25. In December 1982, the CDC, in an editorial in MMWR, published a report demonstrating a link between blood transfusion and AIDS with the case of a twenty-month old infant from the San Francisco area who died following unexplained cellular immune-deficiency and opportunistic infections after multiple transfusions: including a transfusion from a donor, subsequently found to have AIDS **[PRSE0003276 (pp.4-6)]**.[49]

26. In January 1983, a letter to the editor was published in the Lancet reporting that 11 of 16 English haemophiliacs who were tested showed altered cellular immunity, which appeared similar to the syndrome affecting homosexual men in the US, known as AIDS **[DHSC0002351_004]**.[50] However, the authors commented that the immunological changes seen in their patients could represent temporary altered immune status and a normal defence mechanism to antigenic load. They noted none of the patients showed features of AIDS and highlighted the need for continued surveillance.

27. Uncertainty regarding the aetiology of AIDS was demonstrated by a joint statement issued by the American Association of Blood Banks, the American Red Cross and the Council for Community Blood Centres, with assistance from the American Blood Commission, National Gay Task Force, the NHF and representatives from the American Blood Resources Association, the CDC and the Food and Drug Administration ("FDA"),[51] in January 1983. The statement reported that the predominant mode of transmission of AIDS seemed to be from

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[48] 2 November 1982, Letter from the National Hemophilia Foundation to Cutter Inc [**Miles Inc/9/770**], **BAYP0000018_083**

[49] Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) - California. MMWR. 1982; 31: 652-54, **PRSE0003276 (pp.4-6)**

[50] Jones *et al.* Altered Immunology in Haemophiliacs. Lancet 1983: 120, **DHSC0002351_004**

[51] The FDA is a federal agency of the Department of Health and Human Services, which is a cabinet-level executive branch department of the US federal government.

person to person, probably involving intimate contact and concluded "*we realise there is no absolute evidence that AIDS is transmitted by blood or blood products and we understand the difficulty in making recommendations based on insufficient data…*". The statement advised that blood and blood products should be used with caution and reasonable attempts should be made to limit blood donation from individuals or groups with an unacceptably high risk of AIDS [**OXUH0000824**].[52]

28. In a follow up to an earlier editorial, a publication in the Lancet on 2 April 1983 questioned the inference that AIDS was linked to transfusion of factor VIII concentrates, commenting that, if the syndrome was transmitted through concentrates, it would have been likely to have affected greater numbers of American and West German recipients who had received far more factor VIII concentrate infusions of US origin than haemophiliacs in other developed countries. The publication concluded that reported cases *"do not constitute a strong argument for a change of treatment policy"* [**PRSE0002723**].[53]

29. On 4 May 1983, the Haemophilia Society in the UK wrote to its members incorporating a statement from Professor Bloom, then Chairman of the HCDO, advising haemophilia patients not to alter their treatment programme. The letter stated:

> *"haemophiliacs, their parents and doctors have always balanced the quality of life and the dangers from bleeding against the risk of treatment. We are no strangers to infective diseases, such as hepatitis, which can be transmitted by factor concentrates. Recent evidence indicates that in this respect at any rate concentrates prepared from British blood are not necessarily safer than those prepared in the United States…"* [**DHSC0001228**].[54]

30. An extraordinary meeting of the Haemophilia Reference Centre Directors [**DHSC0002179_070**][55] was held on 13 May 1983 and attended by Dr Diana Walford for the Department of Health and Social Security ("DHSS") (who also attended subsequent meetings [**WITN4461001**],[56] [**HCDO0000413**]).[57] At the

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[52] March-April 1983, Joint statement on acquired immune deficiency syndrome (AIDS) related to transfusion. Transfusion; 23 (2): 87-88 [**Other/6/360**], **OXUH0000824**

[53] Acquired Immunodeficiency in Haemophilia. Lancet. 1983; 745, **PRSE0002723**

[54] 4 May 1983, Communication from the Haemophilia Society concerning recent reports of AIDS which appeared in the press [**Other/6/376**], **DHSC0001228**

[55] Haemophilia Reference Centres were responsible for the provision of an advisory clinical and laboratory service to the other haemophilia centres (Department of Health and Social Security memorandum (HC(76)4), **DHSC0002179_070**)

[56] **WITN4461001** dated 5 July 2021, Dr Diana Walford, page 34; and Transcript of the hearing of evidence from Dr Diana Walford on 19 July 2021, pages 71 and 77

[57] 19 September 1983, Minutes of the Seventeenth Meeting of Haemophilia Reference Centre Directors, **HCDO0000413**

meeting, it was noted that many directors had restricted their use of NHS concentrates to children and mildly affected haemophilia patients and it was agreed that this policy should be continued. It was also agreed that there was insufficient evidence to warrant restriction of the use of imported concentrates in other patients in view of the immense benefits of therapy **[HCDO0000003_008]**.[58]

31. In May 1983, a dry heat-treated factor VIII concentrate was licensed in the US by another fractionator **[PRSE0000099]**.[59] However, in view of the absence of clinical trial evidence confirming any benefit associated with use of this product, Hemofil-T, in terms of the risk of hepatitis or AIDS, the US FDA would not permit any claims of improved safety to be made **[BAYP0004647]**[60] and following poor published study results, I understand the product was not widely used **[HSOC0001563]**.[61]

32. Nevertheless, in June 1983, the World Federation of Hemophilia ("WFH") issued its own recommendations to haemophilia patients and doctors; these were consistent with the views previously expressed by the Haemophilia Society and the UK HCDO. The WFH stated:

> *"there is insufficient evidence to recommend at the present, any change in treatment; therefore, present treatment, of hemophilia should continue with whatever blood products are available, according to the judgment of the individual physician"* **[PRSE0001351]**.[62]

33. On 24 June 1983, Professor Bloom and Dr Rizza, the Chairman and Secretary of the HCDO, wrote to the Haemophilia Centre Directors, reporting on a meeting of the directors the previous month. The directors were advised that the Licensing Authority had been asked to consider any implications for clinicians as a result of the FDA's guidelines on donor screening issued on 24 March 1983 to the American Plasma Collecting Agencies (see paragraph 64 below). The issue of so-called "hepatitis reduced" factor VIII concentrates was also considered. The view expressed by the directors was that there was no evidence that the processes involved in the manufacture of such concentrates would inactivate any viruses other than those causing hepatitis. Furthermore,

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[58] 13 May 1983, Minutes of extraordinary meeting of the Haemophilia Reference Centre Directors, **HCDO0000003_008**

[59] Kroner *et al*. HIV-I infection incidence among persons with haemophilia in the United States and Western Europe 1978 - 1990. J of Acquired Immune Defic Synd 1994; 7(3)279 [**Other/20/2060**], **PRSE0000099**

[60] 1983, Hemofil T label, [**Miles Inc/13/1261**], **BAYP0004647**

[61] Colombo *et al*. Transmission of Non-A, Non-Hepatitis by heat-treated factor VIII Concentrate, Lancet 1985; ii 1 - 4 [**Other/12/933**], **HSOC0001563**

[62] 30 June 1983, Resolutions by the World Federation of Hemophilia General Assembly on 29 June 1983 [**Miles Inc/13/1251**], **PRSE0001351**

they stated the effectiveness of such concentrates, in terms of reducing the risk of transmission of hepatitis, should be subject to formal clinical trials in "mild" haemophilia patients. Directors were therefore urged not to use "hepatitis reduced" concentrates randomly on a "named patient" basis, under exemptions from the normal licensing requirements, but to reserve such treatments for formal clinical trials, so that the results could be collected and analysed in a structured way [**HCDO0000270_004**].[63]

34. The dilemma facing all those involved in the treatment of patients with haemophilia during this period was summarised in a report by Dr John Craske, a virologist who was Chairman of the HCDO Hepatitis Working Party, in July 1983. He pointed out that, at that stage, while AIDS appeared likely to be due to an infective process, the nature of the agent was not known and it was unclear whether it would be inactivated by any of the processes attempted (all unproven) for hepatitis. He referred to the ethical difficulties associated with the assessment of heat-treated products:

> *"[s]ince the only way of ensuring the susceptibility to non-A, non-B viruses is by using patients who have not previously received Factor VIII or IX concentrate, [previously unexposed patients, (PUPs)], a choice will have to be made between heat treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate which appears to carry a 100% chance of transmitting non-A, non-B hepatitis"* [**HCDO0000135_012**].[64]

35. A meeting of the UK Licensing Authority's Committee on Safety of Medicines ("CSM") was held on 13 July 1983, to consider the risk of AIDS (and other infections transmitted by blood products) against the benefits of use of concentrates, noting that, in the case of haemophilia patients, such products were life-saving. The CSM considered the possibility of withdrawing factor concentrates from supply and replacing them with cryoprecipitate. However, it was concluded that this was not feasible in the UK on the grounds of insufficient cryoprecipitate supply. Finally, the CSM commented that the perceived level of risk associated with the use of factor concentrates did not at that time justify serious consideration of such solutions [**DHSC0001208**].[65]

36. In October 1983, a paper was published in the British Medical Journal, reporting on immunological abnormalities in Scottish haemophilia patients, most of whom

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[63] 24 June 1983, Letter from Professor Bloom and Dr Rizza to the Haemophilia Centre Directors, **HCDO0000270_004**

[64] 11 July 1983, Report of Dr John Craske, Chairman of the HCDO Hepatitis Working Party, **HCDO0000135_012**

[65] 13 July 1983, Meeting of the UK Licensing Authority's Committee on Safety of Medicines, **DHSC0001208**

had received no American factor VIII concentrate for over two years. The authors stated that these patients were found to have immunological abnormalities similar to those observed in American haemophilia patients and concluded that these results argued against a causative agent specific to US blood products [**PRSE0001121**].[66]

37. A further meeting of the HCDO took place in October 1983. The availability of NHS factor VIII was considered. The directors were informed that the new NHS Blood Products Laboratory ("BPL") with increased capacity for production of domestic concentrates would be opened in 1985-1986. In the meantime, it was agreed that patients should not be encouraged to transfer to cryoprecipitate but should continue to receive available NHS concentrates or commercial concentrates in the usual way. In particular, Professor Bloom advised the directors that patients should not stop using commercial concentrates, in view of the fact that there was no proof that these were the cause of AIDS. The directors also considered Dr Craske's report ([**HCDO0000135_012**][67]) regarding the factors to be taken into account in the selection of "hepatitis reduced" products for clinical trials including evaluation of residual infectivity (with respect to hepatitis viruses) and the possibility that factor VIII concentrate prepared from US plasma might be contaminated with the putative infective agent associated with AIDS, creating ethical problems when investigating such products in previously untreated patients [**PRSE0004440**].[68]

38. In answer to a Parliamentary question in November 1983, the Secretary of State for Health and Social Services, Lord Kenneth Clarke, stated:

> *"[t]here is no conclusive evidence that acquired immune deficiency syndrome (AIDS) is transmitted by blood products. The use of Factor VIII concentrates is confined almost exclusively to designated haemophilia centres whose directors and staff are expert in this field. Profesional [sic] advice has been made available to all such Centres in relation to the possible risks of AIDS from this material"* [**WITN6984010**].[69]

39. By the end of 1983, two UK patients with haemophilia A had developed AIDS (no UK patient with haemophilia B had yet developed the disease). An editorial in the British Medical Journal in December 1983 reported on these cases and commented that throughout the world the "*opinion of the majority is that the risk*

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[66] Froebel *et al*. Immunological abnormalities in haemophilia : are they caused by American Factor VIII concentrate? BMJ 1983; 287:1091 [**Other/7/452**], **PRSE0001121**

[67] 11 July 1983, Report of Dr John Craske, Chairman of the HCDO Hepatitis Working Party, **HCDO0000135_012**

[68] 17 October 1983, Meeting minutes of the HCDO, **PRSE0004440**

[69] 14 November 1983, Parliamentary question given by Lord Kenneth Clarke [**WITN6984010**]; see para 4.19 of the Statement of Lord Kenneth Clarke to the Inquiry dated 1 July 2021, **WITN0758011**

of haemorrhage and its complications far outweighs the risk of developing AIDS or chronic liver disease". However, the author recommended that it was *"sensible"* to treat very young, severely affected children with cryoprecipitate rather than factor concentrate **[HSOC0001285]**.[70]

40. In March 1984, the HCDO sent a memorandum making the Haemophilia Centre Directors aware of the result of a study using Hemofil-T, the heat-treated factor VIII concentrate referenced at paragraph 31 above, which indicated a 63% infection rate for NANB hepatitis in patients who had not previously been exposed to factor concentrates. The HCDO did not give a recommendation to transfer to heat-treated products at this time **[CBLA0001831]**.[71] However, I note evidence to the Inquiry from Dr Winter that both he and Dr Savidge had decided to use heat-treated products by the spring of 1984 **[WITN3437002]**.[72]

41. By this stage, although not definitely confirmed, it seemed likely that AIDS in haemophilia patients was most probably caused by an infective agent in blood products **[PRSE0001131]**.[73] However, a US paper published by authors from the US CDC in April 1984 highlighted the dilemma for patients and doctors and referred to the fact that the incidence of AIDS in patients with haemophilia was low (1 in 1,000 patients) and that the interim recommendations of the US NHF (i.e. to exercise control in the use of blood products and to make reasonable attempts to limit blood donations from individuals or groups that might have an unacceptably high risk of AIDS) were reasonable: "*they are all anyone can do until the situation is clarified* " **[WITN6984011]**.[74]

42. In December 1983, a questionnaire concerning the occurrence of AIDS and possible related clinical syndromes in people with haemophilia, was sent by Professor Bloom to directors of 201 European haemophilia centres. One hundred and thirty five replies were received covering an estimated 65% of treated patients from 18 countries and eight cases of AIDS were identified. The report of this survey concluded it was noteworthy that no cases of AIDS in haemophilia patients, definitely related to the transfusion of blood products, were reported from Germany where very large amounts of US factor VIII concentrates had been used for many years. Professor Bloom stated these

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[70] Jones. Acquired immune deficiency syndrome, hepatitis and haemophilia. BMJ 1983; 287:1737 [**Other/7/483**], **HSOC0001285**

[71] 29 March 1984, Memorandum from the Oxford Haemophilia Centre to the UK Haemophilia Centre Directors, **CBLA0001831**

[72] Statement of Dr Mark Winter dated 6 August 2020, **WITN3437002**, paras 35.7 and 35.9; and Transcript of the hearing of evidence from Dr Mark Winter on 1 October 2021, pages 132, 133, 136, 140

[73] Gallo *et al*. Frequent detection and isolation of cryopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984; 224: 500 [**Other/8/504**], **PRSE0001131**

[74] Evatt *et al*. The acquired immune deficiency syndrome in patients with hemophilia, Ann. Int. Med. 1984:100 499 [**Other/8/559**], [**WITN6984011**]

data suggested that the role of US concentrates in the causation of AIDS in European haemophilia patients should be regarded as unproven **[WITN6984012]**.[75]

43. In 1983, Luc Montagnier's team at the Pasteur Institute in Paris isolated a retrovirus (a virus that uses RNA as its genetic material) from a homosexual patient with lymphadenopathy. They were able to infect T cells (a type of immune cell) from a healthy donor with this retrovirus. The group concluded that this patient at risk for AIDS was infected with a retrovirus belonging to a family of T-lymphotropic retroviruses that are horizontally transmitted in humans, although the role of this virus in the etiology of AIDS remained to be determined **[PRSE0004469]**.[76] A retrovirus was later isolated from a group of patients with AIDS and persons at risk of AIDS by Robert Gallo and colleagues at the National Cancer Institute in the US and the data were published in May 1984 **[PRSE0001131]**.[77] This retrovirus was subsequently confirmed to be the same as that previously identified by Montagnier **[BAYP0000012_006]**.[78] However, there continued to be some doubts about the implications of immunological abnormalities seen in haemophilia patients and any link to a potential viral cause in the aetiology of AIDS. By way of example, a paper published in the Lancet in June 1984 demonstrated immunological abnormalities in haemophilia patients treated exclusively with factor VIII concentrate or cryoprecipitate prepared by the Scottish National Blood Transfusion Service (none had been exposed to commercial factor VIII concentrate in the previous five years and most had never received any during their lives). The authors stated that they had not identified the cause of the abnormalities they had observed in the T lymphocyte population but concluded they were unlikely due to a specific AIDS virus in the blood products but rather were "*more likely to result either from an as yet unidentified component of the therapeutic concentrates or from a non-specific effect of foreign protein infused intravenously"* and went on to state that *"it seems that some patients are more susceptible to this immunological disturbance than others*" **[OXUH0002842]**.[79]

44. In September 1984, the first report of anti-HTLV[80] antibody status in UK patients

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[75] Bloom. Acquired immunodeficiency syndrome and other possible immunological disorders in European haemophiliacs. Lancet 1984; 1452 [**Other/9/600**], [**WITN6984012**]

[76] Barré-Sinoussi *et al.* Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 1983; 220, 868–871, **PRSE0004469**

[77] Gallo *et al.* Frequent detection and isolation of cryopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984; 224: 500 [**Other/8/504**], **PRSE0001131**

[78] Barker and Dodd. Viral Hepatitis, acquired immunodeficiency syndrome, and other infections transmitted by transfusion. Clinical practice of transfusion medicine, second edition, chapter 29, 1989; 667-712, by transfusion. [**Other/17/1777/21**], **BAYP0000012_006**

[79] Carr *et al.* Abnormalities in circulating lymphocyte subsets in haemophiliacs in an AIDS - free population. Lancet 1984; i:1431, **OXUH0002842**

[80] Human T-lymphotropic virus

was published [**BART0000871**].[81] The survey, based on assays using HTLV-III[82] provided by Gallo's laboratory and LAV-I[83] provided by Montagnier's laboratory, included 184 haemophilia patients who had received factor concentrates and found that 34% of these patients had anti-HIV antibodies. The authors stated, however, that this high prevalence had to be set against the relatively low prevalence of disease among patients with haemophilia, stated to be *"roughly one per thousand haemophiliacs"*. A statement issued by the Haemophilia Society the same month apparently commenting on these results and this apparent "low" prevalence of AIDS suggested that the presence of antibodies could suggest immunity to infection [**WITN6984013**].[84]

45. The results of a study conducted by Dr Levy from the University of California jointly with the CDC, and in collaboration with Cutter researchers, confirmed the heat sensitivity of certain retroviruses and was published in September 1984 [**CBLA0001898**].[85] The study results were available to Cutter ahead of publication and described in an internal memo in May 1984 [**BAUM0000003_001**].[86] The study used factor concentrate purified from cryoprecipitate mixed with mouse retrovirus (the AIDS virus had not been isolated at the time the study was conducted), which was subsequently fractionated and heat-treated at 68°C. Samples were then assayed for the presence of the retrovirus after fractionation and at time periods up to 96 hours after heating. The results suggested that mouse retroviruses could survive the fractionation and freeze-drying processes and that heating for several hours was necessary before substantial quantities of infectious virus became inactivated. The authors concluded that the results supported the hypothesis that retroviruses could be the aetiological agent in AIDS and indicated that factor VIII concentrates must be heated to inactivate these viruses. The study did not investigate factor VIII activity in the heat-treated product.

46. Prior to the publication of this study, the implications of infection with the AIDS agent remained uncertain and there continued to be concerns regarding the use of heat-treated concentrates. These were summarised in an editorial published in Vox Sang in June 1984 [**BAYP0000026_007**].[87] The author

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[81] Cheingsong-Popov *et al*. Prevalence of antibodies to human T lymphotropic virus III in AIDS and AIDS - risk patients in Britain. Lancet 1984; ii:477, **BART0000871**
[82] Human T-lymphotropic virus type III
[83] Lymphadenopathy-associated virus
[84] September 1984, A statement issued by the Haemophiliac Society [**WITN6984013**]
[85] Levy *et al*. Recovery and inactivation of infectious retroviruses added to Factor VIII concentrates. Lancet 1984; ii:722 [**Other/10/640**], **CBLA0001898**
[86] 17 May 1984, Internal Cutter Inc memorandum [**Miles Inc/21/2117**], **BAUM0000003_001**
[87] Soulier. Diseases transmissible by blood transfusion. Vox Sang 1984; 47(1):1 [**Other/8/508**], **BAYP0000026_007**

concluded that:

> *"the risk for hemophiliacs to be contaminated by several viruses should restrict prophylactic treatment, or may require the use of heated fractions. However, if such heated material is now available, it is not yet known if the inactivation of all viruses is obtained and if the heating of globulins is not carrying a risk of immunogenicity".*

47. In summary, during the summer of 1984, the benefits of heat treatment of factor concentrates in terms of prevention of transmission of the AIDS virus had not definitively been established in view of the difficulty carrying out clinical trials and the fact that no antibody test for the virus identified by Montagnier and Gallo was generally available. Furthermore, the natural history of AIDS was not at that time understood. Some clinicians were also concerned that heat treatment of plasma proteins would reduce efficacy of the product, increase the risk that antibodies to factor VIII (inhibitors) would be produced or increase thrombogenicity, with devastating consequences for the patient [**PRSE0003980**].[88]

48. By September 1984, it was noted at a meeting of the HCDO that while the UK Licensing Authority had not licensed any heat-treated factor concentrates, some directors had entered patients into clinical trials of such products [**PRSE0003659**].[89]

49. In October 1984, the US NHF recommended for the first time that use of heat-treated concentrates should be considered "Because heat-treated products appear to have no increase in untoward effects attributable to the heat treatment, we now recommend that treaters using coagulation factor concentrates should strongly consider changing to heat-treated products, with the understanding that the protection against AIDS is yet to be proven. We again urge a prospective national study of the use of these and other materials in patients not previously exposed to pooled blood products" [**DHSC0001273**].[90]

50. In December 1984, the Haemophilia Reference Centre Directors prepared an AIDS advisory document which I assume was sent to all haemophilia centres in the UK [**HCDO0000270_007**].[91]

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[88] Bird *et al*. Haemophilia and AIDS. Lancet 1985; i:162 [**Other/11/749**], **PRSE0003980**
[89] 27 September 1984, Minutes of the 15th meeting of UK Haemophilia Centre Directors, extract, **PRSE0003659**
[90] 13 October 1984, NHF Hemophilia Information Exchange [**Other/10/653**], **DHSC0001273**
[91] 14 December 1984, AIDS advisory document from the Haemophilia Centre Directors Organisation, **HCDO0000270_007**

50.1 The advisory document concluded that the options for haemophilia A patients in probable decreasing order of safety from AIDS were as follows:

> *"1. Heated U.K. concentrate (note: still NANB hepatitis risk)*
> *2. Single donor cryo or FFP*
> *3. Heated, imported conc. (note: still NANB hepatitis risk)*
> *4. Unheated U.K. conc.*
> *5. Unheated, imported conc. - almost certain to be contaminated.*
> *Note: Heated concentrates may still transmit hepatitis. Some of the distinctions e.g. between 3 and 4 are debatable and the long-term effects (e.g. immunogenicty) (sic) of using heated plasma proteins in this way are unknown…".*

50.2 The overall recommendations for treatment of haemophilia patients issued by the Haemophilia Reference Centre Directors at that time were as follows:

> *"1. Concentrate is still needed, bleeding is the commonest cause of disability and death.*
> *2. Use DDAVP in mild Haemophilia A and vWd if possible.*
> *3. For Haemophilia A needing blood products*
> *(a) "Virgin" Patients those not previously exposed to concentrate, and children use cryo or heated NHS Factor VIII (if available).*
> *(b) Severe and Moderate haemophiliacs previously treated with Factor VIII, use heat treated NHS Factor VIII, if available, or heat treated US commercial.*
> *4. Haemophilia B*
> *(a) Mild Christmas Fresh frozen plasma if possible (otherwise NHS Factor IX).*
> *(b) "Virgin" Patients and those not previously exposed to concentrate use fresh frozen plasma (or NHS factor IX concentrate if essential)*
> *(c) Severe and Moderate Christmas Disease previously exposed to factor IX concentrate continue to use NHS Factor IX."*

50.3 The advisory document referred specifically to the continued use of unheated NHS concentrates:

> *"In general heated concentrate appears to be the recommendation of virologists consulted but individual Directors may wish to make up their own minds. This is particularly true of unheated NHS material. The evidence that heated US factor VIII is safer than unheated NHS is debatable and some Directors may wish to continue using unheated NHS material until all supplies are heated. This is valid for carefully selected patients but must be on individual decision based on the assumption that some batches of NHS materials will be contaminated with HTLVIII."*

51. In December 1984, the Haemophilia Reference Centre Directors also agreed

that heat-treated concentrates should be given to all patients *"if freely* available*"* including those who were found to be antibody positive. It was stated that treatment for antibody negative patients must be with heat-treated material *"from now on"* **[HCDO0000394_117]**.[92] The directors noted that the use of heat-treated products would create financial difficulties for treatment centres, however the basis for the advice was reinforced in the following months, when two batches of NHS factor VIII concentrate (one English and one Scottish) were linked to subsequent HIV infections in people with haemophilia **[HSOC0002656]**,[93] **[BAYP0000003_292]**.[94]

52. However, while there was, by this stage general agreement that heat treated factor VIII concentrates were preferred, the HCDO continued to express concern regarding the risk of immunogenicity (development of inhibitors) and thrombogenicity induced by heating factor VIII concentrates **[HCDO0000394_117]**.[95] In circumstances where the clinical benefits of heat treatment were said to be *"unproven"* the potential risks associated with heat treatment (including the possibility of inhibitor development, which would be irreversible) were even felt by some clinicians to outweigh the potential benefits **[PRSE0003980]**.[96] Therefore, despite the availability of heat-treated commercial concentrates, some haemophilia centre directors continued to use non heat-treated NHS concentrates. Furthermore, some clinicians were reluctant to use heat-treated concentrates in mildly affected patients or young children, rather than cryoprecipitate or fresh frozen plasma, because of the high incidence of NANB hepatitis in patients treated with multi-donor products **[WITN3901009]**.[97]

53. In September 1985, the NHS BPL commenced production of its dry heat-treated factor VIII concentrate, 8Y (heated at 80°C for 72 hours) **[GFYF0000127]**.[98] A study published in 1989 described the challenges of investigating whether the process used in 8Y production was successful in eradicating HIV and NANB hepatitis. These included: the limitations of experiments in chimpanzees and requirement for studies in previously

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[92] 10 December 1984, Notes of the Haemophilia Reference Centre Directors meeting, **HCDO0000394_117**

[93] Ludlam *et al*. Human T-Lymphotropic Virus Type III (HTLV-III) infection in seronegative haemophiliacs after transfusion of factor VIII, The Lancet, 3 August 1985, page 233 [**Other/12/958**], **HSOC0002656**

[94] Blood donations and AIDS: Statement from Department of Health, The Lancet, Vol 1: no 8419, 5 January 1985:63 [**Reg/3/185], BAYP0000003_292**

[95] 10 December 1984, Notes of the Haemophilia Reference Centre Directors meeting, **HCDO0000394_117**

[96] Bird *et al*. Haemophilia and AIDS. Lancet 1985; i:162 [**Other/11/749**], **PRSE0003980**

[97] Jones *et al*. AIDS and haemophilia: morbidity and mortality in a well-defined population. BMJ 1985;291:695, **WITN3901009**

[98] 2006, Department of Health, Self-Sufficiency in Blood Products in England and Wales, A Chronology from 1973 to 1991 [**Other/21/2092**], **GFYF0000127**

unexposed patients over a period of time long enough to identify the presence of clinical infections (the virus responsible for NANB hepatitis had not been identified); the ethical difficulties associated with conducting clinical trials in young boys, particularly given the need for frequent venepuncture in circumstances where the patients themselves would derive no clinical benefit; and the fact that use of capillary blood samples would pose greater risks than venepuncture to clinical staff [**WITN6984014**].[99] A dry heat-treated factor IX concentrate was produced by BPL from October 1985 [**GFYF0000127**].[100]

54. In November 1985, the US NHF first recommended that clinicians should prescribe "*only heat treated or otherwise virally attenuated coagulation factor concentrates*" for severe patients without inhibitors, but taking into account the fact that "*protection against AIDS is yet to be absolutely proven*" [**DHSC0001278**].[101]

55. As noted by the authors of the 1989 8Y safety study publication, NANB hepatitis had nearly a 100% incidence in patients previously treated with large pool unheated concentrates, whether they were drawn from paid or volunteer donors [**WITN6984014**].[102] The virus was widespread and contaminated all lots of plasma products, whether derived from volunteer or commercial plasma and whether screened by alanine transaminase ("ALT") or not [**WITN6984003**].[103] While the risk of treatment with cryoprecipitate derived from a single blood-donation might have represented a small risk of exposure to hepatitis on any one occasion [**PRSE0003622**],[104] the risk to people with severe haemophilia from using single, small pool cryoprecipitate ultimately was still very high as such people were eventually exposed to the number of donors contributing to large plasma pools [**RLIT0000178**].[105]

56. By 1985, the efforts to develop viral inactivation mechanisms to address NANB hepatitis, although unsuccessful as regards NANB hepatitis, resulted in processes that were seemingly effective in preventing transmission of the AIDS

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[99] Pasi and Hill. Safety trial of heated Factor VIII concentrate (8Y). Arch Dis Child 1989; 64: 1463-1467 [**WITN6984014**]

[100] 2006, Department of Health, Self-Sufficiency in Blood Products in England and Wales, A Chronology from 1973 to 1991 [**Other/21/2092/23**], **GFYF0000127**

[101] November 1985, NHF recommendations concerning AIDS and the treatment of hemophilia [**Other/12/1011**], **DHSC0001278**

[102] Pasi and Hill. Safety trial of heated Factor VIII concentrate (8Y). Arch Dis Child 1989; 64: 1463-1467 [**WITN6984014**]

[103] Aronson. The development of the technology and capacity for the production of factor VIII for the treatment of hemophilia A. Transfusion 30:748-758 (1990) [**Other/18/1952**], [**WITN6984003**]

[104] Preston *et al*. Percutaneous Liver Biopsy and Chronic Liver Disease in Haemophiliacs. The Lancet, September 16, 1978 592-594 [**Other/2/137**], **PRSE0003622**

[105] Barker. "What is the importance of the 'small pool concept' in the preparation of fraction I and cryoprecipitates for the prevention of post-transfusion hepatitis?" Vox Sang. 38: 106-119 (1980), **RLIT0000178**

agent [**HSOC0001563**].[106] However, efforts continued to be made to produce concentrates that did not transmit NANB hepatitis. In the absence of a test for the causative virus, the benefits of such treatments could not be tested, save through clinical studies in previously unexposed patients with the associated ethical difficulties (see paragraph 53) and accordingly many of the later products, for example Koate HS (see paragraph 251), were not granted product licences. In March 1989, the Haemophilia Reference Centre Directors issued a paper containing their recommendations on choice of therapeutic products for the treatment of patients with haemophilia. The paper concluded:

> *"[w]e regard it as self-evident that all patients should be treated with the safest possible therapeutic products. HIV and the hepatitis viruses cause serious and often fatal disease, and every effort should be made to prevent both initial infection and re-exposure. In attempting to meet this ideal, however, there remain several problems:*
>
> *Although it seems probable that different therapeutic products may be associated with different risks of viral transmission, it is not possible to quantitate these risks accurately. The data on which judgements should be based is to a large extent unavailable…*
>
> *Other factors being equal, we favour fully licensed products, or products having CTX [Clinical Trial Exemption Certificate] approval, rather than those which have to be used on a "named patient" basis….*
>
> *Financial considerations inevitably influence the availability of therapeutic products, and it is the responsibility of Haemophilia Centre Directors to make appropriate efforts to obtain adequate funding for therapeutic products…."* **[WITN6984015]**[107]

57. At that stage, the only factor VIII concentrates recommended by the Haemophilia Reference Centre Directors and licensed in the UK or subject to a CTX were the following:

> Koate HT (Bayer UK),
> Profilate HT (Alpha),
> Hemate P (Behringwerke),
> NHS 8Y (CTX) (NHS - Elstree),
> Monoclate P (CTX) (Armour),

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[106] Colombo *et al.* Transmission of Non-A, Non-Hepatitis by heat-treated factor VIII Concentrate, Lancet 1985; ii 1 - 4, **HSOC0001563**

[107] 22 March 1989, The Haemophilia Reference Centre Directors, Recommendations on choice of Therapeutic Products for the Treatment of non-inhibitor patients with haemophilia A, haemophilia B or Von Willebrand's disease [**WITN6984015**]

Hemofil-M (CTX) (Baxter).

58. In addition, the Haemophilia Reference Centre Directors referred to the availability of other products that were unlicensed and not subject to a CTX. Such products could be used on a "named patient" basis only.

59. The efforts made by Cutter Inc to eliminate NANB hepatitis from its blood products during this period are set out in section D.

B. Blood supply and donor pools

60. A summary of the relevant UK legislation governing the placing of blood products on the UK market at the relevant time is provided at **Annex A**. A summary of the relevant US legislation governing the collection of plasma and production of plasma at the relevant time is provided at **Annex B**.

61. The documents that I have reviewed and legislation at the time indicate that at all times relevant to the Inquiry, plasma for use in products placed on the UK market by Miles UK (later Bayer UK) was collected at centres in the US licensed by the FDA and inspected by both the FDA, state authorities and Cutter Inc to seek to ensure compliance with all relevant legislation and guidance.

Compliance by Cutter Inc Centres with FDA Regulations and Procedures

62. The amount of plasma obtained from whole blood was not adequate to meet the needs for raw material to produce plasma derivatives. Therefore, much of the plasma made into factor concentrates was obtained by a process whereby plasma is removed from whole blood with the blood cells returned to the donor during donation allowing for frequent donations ("plasmapheresis") .The collection of plasma through plasmapheresis in the US was subject to regulation and supervision by the US FDA through its Bureau of Biologics ("BoB"). A formal compliance programme for the plasma fractionation industry was established in 1977 and responsibility for annual inspections was transferred from BoB to the FDA field investigation office [**JREE0000019**].[108]

63. **Annex B** explains that from 1973, all US plasma centres were required to hold a licence from, and were inspected by, the FDA in order to operate. In addition, it was necessary for plasma centres to have a medical director/responsible head who was a licensed physician and subject to FDA approval. An FDA plasmapheresis inspection document has been disclosed to the Inquiry and

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[108] Leveton *et al.* HIV and the blood supply : an analysis of crisis decisionmaking. Committee to Study HIV Transmission Through Blood and Blood Products, Division of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, Washington, D.C. 1995. Page 51, **JREE0000019**

demonstrates the depth of investigation and the requirements in terms of donor screening, record keeping etc. that were required of each plasma centre **[WITN6984016]**.[109] If a plasma centre was found to be in violation of the regulations, corrective action memos were issued. In the case of gross violations, the FDA had power to shut down a plasma centre. In addition to FDA inspection, all Cutter-owned and affiliated centres were inspected by relevant state regulatory authorities. No forewarning was given of inspections by State and Federal authorities and all records, techniques in use etc. were subject to scrutiny **[BAYP0004221]**.[110]

64. Following reports of AIDS, and as further information emerged suggesting that AIDS might be caused by a blood borne virus, an FDA Directive of 24 March 1983 mandated new requirements concerning the elimination of donors in the three higher risk groups for AIDS (male homosexuals, intravenous drug users and recent residents of, or visitors to, Haiti) **[BAYP0000002_167]**.[111] However, these requirements had already been included in relevant Cutter procedures dated 1 February 1983 **[BAYP0000026_005]**.[112] On 23 February 1983 Cutter Inc issued a press release announcing a plasma donor screening programme that introduced supplemental screening of donors at all Cutter-owned and affiliated centres **[BAYP0000028_038]**.[113] Some of the screening procedures, such as routine checks for weight loss and generalised lymphadenopathy, had been in use for many years. The new requirements were:

64.1 All donors were required to read and sign a confidential questionnaire, which stated that they were not members of any of the three high risk groups **[BAYP0000026_005]**.[114]

64.2 Posters were displayed at collection centres drawing attention to the risk of AIDS in the high-risk groups **[WITN6984017]**.[115]

64.3 The medical examination given to donors had been expanded to include questions specifically related to AIDS-like symptoms, such as night sweats, drastic and unexplained weight loss and recurrent fever. The physical examination of donors was supplemented to include a check for enlarged lymph

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[109] September 1981, FDA Instruction Booklet for Plasmapheresis Inspection Checklist and Report, Form FDA 2722 **[Miles Inc/7/510]**, **[WITN6984016]**
[110] 31 August 1982, Letter from Cutter Inc to Dr C Tsai **[Miles Inc/9/705]**, **BAYP0004221**
[111] March 1983, Product Licence Application for Koate, attachment 4 **[Reg/2/68]**, **BAYP0000002_167**
[112] See, for example, 1983, Form provided to blood donors regarding AIDS risk **[Other/6/304]**, **BAYP0000026_005**
[113] 23 February 1983, Press release issued by Cutter Inc re 'Cutter Laboratories Announces Plasma Donor Screening Program' **[Other/6/345]**, **BAYP0000028_038**
[114] 1983, Form provided to blood donors regarding AIDS risk **[Other/6/304]**, **BAYP0000026_005**
[115] 1983, Warnings displayed in donor centres regarding AIDS risk **[Other/6/305]**, **[WITN6984017]**

glands and a full body examination for suspicious lesions **[BAYP0000028_076]**.[116]

65. In 1976, Cutter Inc developed the Cutter System of Plasmapheresis ("CSOPs") to provide a step-by-step plasma collection procedure for procuring plasma, through plasmapheresis, from paid donors at Cutter Inc owned and operated plasma centres, in order to apply the FDA's Code of Federal Regulations and good manufacturing practices. The CSOPs were official licensing documents required, reviewed and approved, by the FDA **[WITN6984018]**.[117] Revisions were made by Cutter Inc and resubmitted to the FDA as regulations and science evolved over time **[BAYP0005978]**,[118] **[WITN6984019]**.[119] Any breach of a CSOP was a breach of the plasma centre's licence to operate. In addition to inspection by FDA, I am aware that Cutter Inc's Plasma Procurement department was responsible for inspecting and ensuring that Cutter Inc's owned and contracted plasma centres complied with regulatory requirements and procedures for collection **[BAYP0000011_077]**.[120]

66. Quality assurance plans ("QAPs") were also developed by Cutter Inc and were submitted to the DHSS in product licence applications made in the UK **[BAYP0000002_169]**,[121] **[WITN6984020]**.[122] QAP003 listed the approved suppliers of Source Plasma (Human) **[BAYP0000002_169]**.[123]

67. I am aware that plasma collected from the plasma centres was transported to one of Cutter Inc's two owned and operated fractionation facilities: one in Berkeley, California and the second in Clayton, North Carolina. These sites were responsible for fractionation of the plasma, a process by which:

> *"cryoprecipitate is recovered by centrifugation from thawed pools of fresh frozen human plasma. Soluble proteins may be removed by a wash of cryoprecipitate. Extraneous non AHF protein is removed through pH and temperature adjustment. Prothrombin complex proteins are removed by adsorption with $Al(OH)_3$. The AHF activity is concentrated by alcohol precipitation or ultrafiltration"* **[BAYP0000002_164]**.[124]

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[116] 5 April 1983, Letter from Cutter Inc to the Welsh National School of Medicine [**Other/6/362**], **BAYP0000028_076**
[117] See, for example, 29 December 1982, Letter from FDA to Cutter Inc regarding review of CSOPs [**Miles Inc/10/834**], [**WITN6984018**]
[118] 7 July 1987, Letter from Cutter Inc to the US DHHS [**Miles Inc/30/3057**], **BAYP0005978**
[119] 14 March 1988, Letter from US DHHS to Cutter Inc [**Miles Inc/32/3154**], [**WITN6984019**]
[120] 5 May 1988, Quality Assurance Document - Plasma Sources [**Other/16/1635**], **BAYP0000011_077**
[121] March 1983, Product Licence Application for Koate, attachment 5 [**Reg/2/69**], **BAYP0000002_169**
[122] March 1983, Product Licence Application for Koate, attachment 5 [**Reg/2/69**], **BAYP0000002_169** & March 1983, Product Licence Application for Koate, attachment 6 [**Reg/2/70**], [**WITN6984020**]
[123] March 1983, Product Licence Application for Koate, attachment 5 [**Reg/2/69**], **BAYP0000002_169**
[124] March 1983, Product Licence Application for Koate [**Reg/2/65**], **BAYP0000002_164**

68. Detailed specifications and quality controls for Anti-Haemophilic Factor ("AHF") products produced by the Berkeley and Clayton sites were set out in quality assurance documents. The documents show that a full set of QACs was provided to DHSS as part of a product licence application **[WITN6984021]**.[125] Cutter Inc also maintained batch production records ("BPRs") that were detailed accounts of raw materials and product components comprising the batch and all significant processing details relating to the batch **[BAYP0000004_285]**.[126]

69. It is apparent from the documents available that, at the time period relevant to the Inquiry, Cutter Inc was in frequent contact with the FDA. These frequent communications included submission of product licence applications and amendments, reports on status of donors, donor screening, donor pools, warnings, submission of BPRs and all things having to do with the manufacturing and fractionation process.

Pool size

70. The size of the pools used for preparation of factor concentrates is an area of interest to the Inquiry. The issue appears to be whether haemophilia patients could have likely avoided infection had they been treated with single donor products.

71. Plasma was an important and scarce resource, and it was therefore important that donations were used efficiently. Fractionation permitted the separation and extraction of many useful components of plasma with different therapeutic uses, including albumin and immune globulins as well as the various coagulation factors (as detailed in paragraph 10). FDA/BoB regulations applicable to fractionation mandated large pools (from which immune globulins and factor concentrates were prepared) of at least 1000 different donors for the manufacture of immune globulins to ensure the inclusion of a broad spectrum of antibodies **[WITN6984022]**,[127] **[JREE0000019]**.[128] Increasing the pool size increases the availability of the therapeutic portion of plasma and was more efficient for production in the manufacturing process of factor concentrates because clotting proteins are found in extremely small quantities in plasma

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[125] March 1983, Product Licence Application for Koate, attachments 7-8 **[Reg/2/71-72]**, **[WITN6984021]**
[126] 3 July 1980, Application for a product licence for Konyne page 12 **[Reg/4/225 attachment]**, **BAYP0000004_285**
[127] 1 April 1974, Code of Federal Regulations, Manufacture of Immune Serum Globulin (Human) #640.102(d) **[WITN6984022]**
[128] Leveton *et al.* HIV and the blood supply : an analysis of crisis decisionmaking. Committee to Study HIV Transmission Through Blood and Blood Products, Division of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, Washington, D.C. 1995. Page 31, **JREE0000019**

[**JREE0000019**].[129] Furthermore, concentrates required large pools as a result of the repeated testing required for purity and activity guarantees.[130]

72. Soon after the development of factor concentrates it was recognised that they carried a risk of hepatitis [**JREE0000019**].[131] Nevertheless, insofar as NANB hepatitis was concerned, some commentators expressed the view that it was unlikely that use of small pools or single donor products would have materially reduced the risk of viral transmission. A haemophilia patient would have required multiple units of cryoprecipitate to treat a bleeding episode and a patient with severe haemophilia would require frequent treatment, with the result that he would have been exposed to many infusions from many different donors over a long period of time [**RLIT0000178**].[132] As such, while large plasma pools would seem likely to increase the risk that recipients of the resulting blood products would be exposed to viruses contaminating one or a few units included in the pool, for patients with severe haemophilia requiring frequent treatments involving many units of therapy the risk of exposure to any but the rarest viruses would, in fact, have been only minimally affected, even by large reductions in manufacturing scale.

73. Dr L.F. Barker, the Head of Blood Services for the American Red Cross (formerly with the BoB) summarised the position in 1980 as:

> *"a retrospective analysis of patients with severe hemophilia treated with small pools of cryoprecipitate showed a similar prevalence of hepatitis B markers and elevated levels of SGPT [or ALT] when compared with patients treated with AHF concentrate. As predicted, then, prevention of posttransfusion hepatitis does not appear to be feasible by use of the 'small pool concept' for severe hemophiliacs requiring multiple treatments over many years."* [**RLIT0000178**][133]

74. In January 1983, Alpha wrote to Cutter Inc following a meeting to develop an

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[129] Leveton *et al.* HIV and the blood supply : an analysis of crisis decisionmaking. Committee to Study HIV Transmission Through Blood and Blood Products, Division of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, Washington, D.C. 1995. Page 31, **JREE0000019**

[130] Dr Mozen's statement, section 5.6.2, **WITN6407003**

[131] Leveton *et al.* HIV and the blood supply : an analysis of crisis decision making. Committee to Study HIV Transmission Through Blood and Blood Products, Division of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, Washington, D.C. 1995. Page 31, **JREE0000019**

[132] Barker *et al.* "What is the importance of the 'small pool concept' in the preparation of fraction I and cryoprecipitates for the prevention of post-transfusion hepatitis?" Vox Sang. 38: 106-119 (1980), **RLIT0000178**

[133] Barker *et al.* "What is the importance of the 'small pool concept' in the preparation of fraction I and cryoprecipitates for the prevention of post-transfusion hepatitis?" Vox Sang. 38: 106-119 (1980), **RLIT0000178**

industry position with regard to AIDS. This letter stated:

> *"any attempt to reduce batch size 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."* **[BAYP0004375]**[134]

75. In 1996, Dr Barker, commented on a study by Lynch *et al* **[RLIT0000148]**[135] that looked at pool size in the manufacture of plasma derivatives. Dr Barker stated:

> *"Their study is exemplary of the kinds of analysis needed in considering this and other measures for increasing safety of blood and blood products. These authors show that, except in the case of extremely rare pathogens, a reduction in pool size is not a very promising approach to increasing the safety of pooled plasma products in persons who require frequent treatment over many years, such as persons with moderate or severe clotting factor deficiencies. Very similar conclusions were reached by an earlier group commenting on the small-pool strategy, but with less thorough mathematical modeling."* **[RLIT0000149]**[136]

76. Dr Barker also noted the paper suggested there could be certain circumstances in which attention to pool sizes and sources could confer some benefit, at least temporarily, "*for example if a newly emergent agent is uneven in its geographical distribution*" such that "products *made from local donations in sites where the agent has not yet emerged would have greater safety that [sic] would large pools made from a variety of collection regions, including those where the agent is emerging first".* However, *"the relative advantage of this approach would naturally decline as the prevalence of the agent becomes uniform and widespread*" **[RLIT0000149]**.[137] The impact of the size of plasma pools on the final infectivity of concentrates is still debated **[WITN6984005**.[138]

77. In 1997, Dr Kasper, a haematologist, treating patients with haemophilia in the

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[134] 21 January 1983, Letter from Alpha to Cutter Inc [**Miles Inc/10/895**], **BAYP0004375**
[135] Lynch *et al.* Considerations of pool size in the manufacture of plasma derivatives, Transfusion 1996:36 770-775, **RLIT0000148**
[136] Barker. Plasma pool size and the safety of plasma derivatives. Transfusion. 1996; 36: 768-769, **RLIT0000149**
[137] Barker. Plasma pool size and the safety of plasma derivatives. Transfusion. 1996; 36: 768-769, **RLIT0000149**
[138] Isfordink. Viral hepatitis in haemophilia: historical perspective and current management, British Journal of Haematology, 2021, 195, 174–185 [**WITN6984005**]

US, discussed reasons why large pools might be better than smaller pools:

"Modern fractionation methods require large volumes of plasma for efficiency and cost-effectiveness. Reducing the number of donations per pool from, for example, 20,000 to 5000, would have deleterious effects on production efficiency but give little benefit to patients. It is assumed that most large pools contain donations from a few individuals with low-level, undetected infections. A single undetected infected donor is diluted more in a pool of 20,000 donations than in a pool of 5,000, but exposure to four lots of product each made from a pool of 5000 donors is equivalent to exposure from one lot made from a pool of 20,0000 donors. Most patients with moderate to severe hemophilia receive transfusions from multiple lots, so are exposed to a large number of different pools. Even if a patient could limit his exposure to one lot, he could only hope that he chose a lot free of undetected infection". **[WITN6984023]**[139]

78. The contemporaneous documents from Cutter Inc indicate that the company considered at various times the size of plasma pools and the risk of viral transmission with larger or small sized pools, and also with cryoprecipitate as compared to pooled plasma. The discussions and data focussed on concerns regarding hepatitis as knowledge of HIV was still limited and testing of recipients of blood products and plasma pools for the AIDS virus not possible until 1985. Various examples of the discussions are set out below.

78.1 An internal Cutter Inc note from 1981 stated:

"Theoretically, one can reduce the incidence of hepatitis by using a smaller donor pool. However, the Hasiba study demonstrates no advantage of single donor cryoprecipitate over concentrate after a total lifetime dosage of 100,000 AHF units. This is consistent with the observation by Dr Peter Levine to which I alluded. He has shown that after one year of treatment, there is no advantage for the cryoprecipitate-treated group. After one year of therapy, the frequency of abnormal liver function tests is identical in groups treated with single donor cryoprecipitate or AHF concentrate. Only patients who were treated very infrequently benefited from treatment with cryoprecipitate. As such, only the exceptional haemophiliac who requires only rare treatment will benefit from small-pool AHF. The same logic is valid for factor IX therapy in haemophilia B.

A more persuasive argument can be made for small-pool factor IX for patients requiring only one-time Konyne. As we discussed, Cutter is required by the

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[139] Kasper. Clotting Factor Concentrates in 1997, Paper prepared for meeting of Brazilian Society of Hematology, November 1997 [**WITN6984023**]

Bureau of Biologics to manufacture Konyne from a pool of >1,000 donors, but if this were not in effect, how small should the pool be to significantly reduce the risk of non-A, non-B hepatitis or hepatitis B? All the donors are, of course, HBsAg negative. According to the data of Aach et al, based on the ALT screening test, as many as 10% of the donors fall into the higher risk group (ALT > 30). Thus, even in a small pool of 100 donors, 10 donors will still be considered at risk for transmitting NANB hepatitis. I cannot provide a similar analysis for hepatitis B, since by definition all donors are negative.

Clearly, the best solution will be to develop improved screening tests for hepatitis B and especially non-A, non-B hepatitis. Until these become available we will not be able to eradicate the risk of hepatitis from these products which cannot be pasteurised." **[BAYP0004035]**[140]

78.2 An internal Cutter Inc note from October 1982 enclosed a letter published in the Lancet. The Lancet letter stated:

"We have just completed a series of studies similar to the one reported by Dr Rickard and colleagues from Sydney [..] These results are of great interest because both the Sydney and Edinburgh patients have been treated predominantly with cryoprecipitate prepared from individual voluntary blood donations. They might therefore be expected to have a lower incidence of hepatitis B infection than haemophiliacs who have received commercial factor VIII concentrates prepared from large plasma pools. The very high prevalence of hepatitis B markers in our patients with severe haemophilia suggests that the use of cryoprecipitate instead of factor VIII concentrates does not protect against infection. Prospects for haemophiliacs, in this regard, however, must now be brighter with the potential for immunising patients against hepatitis B". **[BAYP0004257]**[141]

78.3 A further internal note from October 1982 stated:

"It is perhaps of interest that the US Cooperative Hemophilia Study Group has found that when cryoprecipitate was compared with AHF concentrates individuals receiving ≤ 50,000 units over the first six months had a lower incidence of hepatitis if they received cryoprecipitate only, but after this point, the incidence of abnormal liver function was similar in individuals receiving either product. Thus, past a certain point, the risk of hepatitis with a lower risk product, e.g., cryoprecipitate eventually approaches that of concentrates

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[140] 1 May 1981, Cutter Inc note [**Miles Inc/7/467**], **BAYP0004035**

[141] 11 October 1982, Cutter Inc internal memo enclosing letter from The Lancet 2 October 1982 [**Miles Inc/9/745**], **BAYP0004257**

simply because the total number of AHF units received by a patient becomes larger with time." [**BAYP0004267_001**][142]

79. From as early as the first product licence application for Koate in February 1976, the UK DHSS required information regarding the number of donations in each pool of plasma [**BAYP0000001_110**].[143] The UK DHSS was notified, prior to granting the first licence for Koate, that each plasma pool of 2500 litres of plasma was comprised of approximately equal donations from at least 1000 individual donors and that each lot of Koate was generally made up of material fractionated from 3-5 pools [**IPSN0000312_109**].[144]

Voluntary or paid for plasma

80. The majority of the world's plasma was at times relevant to the Inquiry collected from the US. The high demand for plasma products and the lengthy and often uncomfortable procedure of plasmapheresis led to the justification and legalisation of compensation for plasma in the US in order to increase the quantities available [**JREE0000019**],[145] [**WITN6984024**].[146]

81. In June 1984, Professor Kernoff, Head of the Haemophilia Centre at the Royal Free Hospital in London, wrote in a paper published in the British Journal of Haematology that:

"All plasma collected in the United Kingdom is obtained from volunteer, unpaid donors. However, the quantity of factor VIII concentrate fractionated from this plasma by the National Health Service (NHS) is insufficient to meet demand. Treatment of patients with haemophilia A is therefore dependent on imported commercial concentrates, almost all of which are derived from paid donors in the USA".

81.1 Professor Kernoff observed that:

"Although it is well established that the risk of post-infusion hepatitis is higher after commercial than volunteer blood (Hollinger et al, 1981), the evidence that the same holds for clotting factor concentrates prepared from large plasma pools is less substantial. Acute post-infusion hepatitis in patients

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[142] 18 October 1982, Cutter Inc internal memo [**Miles Inc/9/756**], **BAYP0004267_001**
[143] 2 February 1976, Letter from DHSS to Bayer UK 'Anti-Haemophilic Factor (Human) Koate - PL/0010/0061' [**Reg/1/15**], **BAYP0000001_110**
[144] 27 February 1976, Letter from Bayer UK to DHSS [**Reg/1/16**], **IPSN0000312_109**
[145] Leveton *et al.* HIV and the blood supply : an analysis of crisis decisionmaking. Committee to Study HIV Transmission Through Blood and Blood Products, Division of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, Washington, D.C. 1995. Page 31, **JREE0000019**
[146] 10 September 1974, Washington DC, National Blood Policy, Notices, page 32702 [**WITN6984024**]

treated with these products is usually in the non-A non-B (NANB) type; and there is a disturbingly high rate of progression to chronicity (Bamber et al 1981; Dienstag, 1983). The overall incidence of acute hepatitis in haemophilia populations has been reported to be only 2-6% of treated patients per year, whether volunteer or commercial products have been used (Biggs, 1974; Kim et al, 1980; Rickard et al, 1982)".

81.2 Professor Kernoff stated that he had produced a report that provided a quantification of the risks of acute hepatitis associated with different blood products obtained from volunteer and commercial sources, concluding:

"Whether prepared from volunteer or commercial donor plasma, clotting factor concentrates carry a very high risk of acute NANB hepatitis in first exposure recipients. Even substantial previous exposure to other blood products may reduce this risk only marginally." **[PRSE0003439]**[147]

82. In 1985, the US Congress, Office of Technology concluded that the risk of developing clinical hepatitis was the same whether plasma of volunteer or paid donors had been used **[WITN6984025]**.[148]

83. A report by Professor Howard Thomas (Emeritus Professor of Hepatology at Imperial College London) prepared for the Penrose Inquiry stated that:

"In 1970-90, there was debate as to whether blood products derived from volunteer blood donations prior to screening tests being introduced in 1991, were safer in terms of transmission of HIV and HCV, than those derived from paid donors particularly those imported from the USA and Central and South America. In the case of HCV where the prevalence of infection in the UK blood donating general community was around 0.5% and several thousand donations were used to make each batch of factor 8 and 9 concentrate, the majority of batches made from volunteer blood donations were infected and the frequency of transmission was similar following use of both English NHS (Kernoff Lu Karayiannis and Thomas 1984, Brit J of Haematology), Scottish NHS (Ludlam Chapman, Cohen and Litton 1989, Lancet) and commercial material." **[PRSE0004640]**[149]

84. As regards HIV, once a test to detect antibodies to HIV ("anti-HTLV-III") was available it was possible to evaluate the prevalence of HIV in products prepared from commercially-sourced plasma as compared to voluntarily-sourced

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[147] Kernoff *et al.* High risk of non-A non-B hepatitis after a first exposure to volunteer or commercial clotting factor concentrates. British Journal of Haematology. 1985; 60: 469-479, **PRSE0003439**
[148] January 1985, Blood Policy and Technology, Washington DC. US Congress, Office of technology Assessment, OTA-H-260, page 25-26 [**Other/11/729**], [**WITN6984025**]
[149] 2015, Penrose Inquiry - Professor's Thomas report on Hepatitis C, **PRSE0004640**

plasma. In 1985, Dr Peter Jones and colleagues from Newcastle published the results of their examination of 143 multi-transfused patients for evidence of disease related to AIDS **[WITN3901009]**.[150] Seventy six of the 99 patients with severe haemophilia A were seropositive to HTLV-III. All except one of these seropositive patients had received factor VIII commercial concentrates at some time. The few patients with haemophilia B within the population had been exposed to only NHS factor IX concentrate from volunteer donors and all were seronegative. However, it was stated that *"seroconversion and, in one case, full blown AIDS have occurred in similar groups of patients with haemophilia B in the UK, indicating that the UK donor panel has included HTLV-III infected donors."*

Prison plasma

85. In the Rule 9 Request of 21 July 2021 to Mrs Linda Frith, the Inquiry asked for Mrs Frith's understanding of Cutter Inc's use of prison plasma and cited documents **BAYP0004952**, **BAYP0005729** and **CGRA0000545**. However, I understand that Mrs Frith has no knowledge of this area.

86. In order to manufacture gammaglobulin products such as hepatitis, rabies, and tetanus immune globulins, fractionators needed a steady and constant supply of high titre (high in antibody to a particular virus) plasma. Prison centres served as a specialised and major source of hyperimmunised donors **[BAYP0004303].**[151] Cutter Inc collected from three prison centres. In an internal Cutter Inc memo of 9 March 1983, it is stated these centres were not in *"high risk states, ours being in Arizona and Nevada…where almost no, or no AIDS is reported."* **[BAYP0004477_005]**[152]

87. The licensing requirements set out in **Annex B** applied as much to prison plasma centres as any other plasma centre. The centres therefore required an FDA licence to operate and were regulated and subject to regular inspections from the FDA, Cutter Inc and relevant state regulatory authorities. The same donor qualifications applied to both prison and non-prison donors. Prison donors underwent testing before being allowed to donate plasma; after initial screening, repeat prison donors were monitored at regular intervals.

88. The FDA never issued specific regulations regarding the use of prison plasma. However, a US DHHS meeting was held in July 1982, during which the potential for prison plasma to contain the causative agent in AIDS was

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[150] Jones *et al.* AIDS and haemophilia, morbidity and mortality in a well-defined population, BMJ, 291, 695 (1985), **WITN3901009**
[151] 13 December 1982, Cutter Inc internal note [**Miles Inc/9/811**], **BAYP0004303**
[152] 9 March 1983, Cutter Inc internal memo [**Miles Inc/11/1021**], **BAYP0004477_005**

discussed [**WITN6984026**].[153] In December 1982, Dennis Donahue from the FDA asked if Cutter Inc and the other fractionators would be willing to exclude plasma from prisons which, at the time, only accounted for 2% of collected plasma. It was pointed out that prison plasma was the source of Cutter Inc's hyperimmunised donors and Cutter Inc suggested that prison plasma continue to be collected. Dennis Donahue then suggested that Cutter Inc exclude prison plasma from AHF production [**BAYP0004303**].[154] It was reported internally that Dennis Donahue acknowledged that the actual risk of plasma collected from prisons was less important than the perceived risk [**BAUM0000009**].[155]

89. Meeting minutes of Cutter Inc's Biological Management Committee, dated 5 February 1983, stated: *"it was decided that we will no longer release Koate from prison plasma"*. A Cutter Inc Quality Assurance Document dated 16 March 1983 confirms that Cutter Inc had, by that date, discontinued the use of prison plasma in factor concentrates [**WITN6984027**].[156] Remaining stocks of factor concentrate product that had been produced from prison plasma were used for research and development purposes only [**BAYP0004434**].[157] The product licence applications in the UK made for Koate in March 1983 [**WITN6984028**][158] and Konyne HT in March 1985 [**WITN6984029**][159] included a list all Cutter Inc owned or affiliated centres. Three prisons were present on the list because plasma received from prisons continued to be used for production of rabies antibody [**BAYP0004798**].[160]

90. The Rule 9 Request to Linda Frith asked Mrs Frith to consider three documents concerning the use of prison plasma. Document **BAYP0004952**, meeting minutes of the Cutter Inc Biological Coordinating Committee dated 14 November 1983, stated in light of potential product shortage that *"it may also be possible to produce AHF-HT from prison plasma"*. The minutes contained no further comments regarding this proposal [**BAYP0004952**].[161] Document **BAYP0005729**, meeting minutes of the Cutter Inc Biological Coordinating Committee dated 4 April 1985, stated under the heading "*Update of Plasma*

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[153] 3 August 1982, Letter from Travenol Laboratories to the Pharmaceuticals Manufacturers Association [**Miles Inc/9/680**], [**WITN6984026**]
[154] 13 December 1982, Cutter Inc internal note [**Miles Inc/9/811**], **BAYP0004303**
[155] 21 December 1982, Cutter Inc internal note [**Miles Inc/9/825**], **BAUM0000009**
[156] 16 March 1983, Cutter Inc Laboratories Quality Assurance Document [**Miles Inc/11/1038**], [**WITN6984027**]
[157] 15 February 1983, Minutes of Cutter Biological Management Meeting [**Miles Inc/11/967**], **BAYP0004434**
[158] 9 March 1983, Attachment 4 to the UK product licence application PL 1605/0004 [**Reg/2/65**], [**WITN6984028**]
[159] March 1985, Abridged Product Licence Application for Konyne HT - Part II - Pharmaceutical data [**Reg/3/205**], [**WITN6984029**]
[160] 27 September 1983, Cutter Inc internal memorandum [**Miles Inc/15/1458**], **BAYP0004798**
[161] 14 November 1983, Biological Coordinating Committee [**Miles Inc/17/1675**], **BAYP0004952**

Procurement", "S. Ojala and other manufacturers will be meeting with FDA regarding prison plasma for AHF" **[BAYP0005729].**[162] Document **CGRA0000545**, an internal Cutter Inc note reporting on a meeting between fractionators on 12 April 1985, stated under the heading *"Prison Plasma":*

> *"This subject illicits [sic] even more diverse viewpoints. Cutter and Alpha believe that science has progessed [sic] 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. We will further agree to do whatever testing the FDA deems necessary to answer any academic concerns. Sam Anderson will contact the NHF to insure there are no major obstacles there, and I recommend Jack Ryan do likewise. It will not serve our purposes to effect change with the FDA and offend our customers. The argument for using prison plasma is the additional testing (HTLV-III) and heat treatment which provides product safety. [Cutter Inc employees] will try to discuss this with Petricciani in Atlanta this week, on a preliminary basis".*

91. I have not identified any further information in the documents available in relation to the proposal that prison plasma should once again be used to produce factor concentrates for commercial supply.

Donor screening

92. Bayer UK informed DHSS in the first product licence application for Koate in February 1976 that all plasmapheresis donors had to be acceptable according to the criteria described in the US Code of Federal Regulations and all centres from which source material was obtained had to be licensed by the US FDA **[WITN6984054]**,[163] **BAYP0000001_113**.[164] The FDA therefore ensured that all donors and units of human source plasma were handled according to the Regulations which stipulated that only hepatitis B surface antigen ("HBsAg") screened units of source plasma from healthy donors could be used in the manufacture of licensed biological products such as Koate. It is clear from the documents available that plasma was being HBsAg screened from as early as

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[162] 4 April 1985, Biological Coordinating Committee [**Miles Inc/27/2691**], **BAYP0005729**
[163] 25 February 1976, Letter from Cutter Inc to Bayer UK re 'Product Licence Application for Koate in the UK' [**Other/2/82**], [**WITN6984054**]
[164] 4 March 1976, Letter from Cuter UK to DHSS [**Reg/1/17**], **BAYP0000001_113**

1974 **[WITN6984030]**.[165]

93. CSOPs dating from 1981 are available in the documents I have reviewed and set out the checks that were required to be performed on plasma donors. These are CSOP 402 "Pre-donation History" **[WITN6984031]**[166] and CSOP 403 "Medical History and Physical Examination" **[BAYP0000019_094]**.[167] These forms stated that:

93.1 Donors were required to be assessed by a physician. The details on the forms were given as a guide. The physician's medical judgement was to prevail.

93.2 Any history of hepatitis prevented donation and clinical jaundice from an unproven cause was to be considered indicative of a positive history of hepatitis. Contact with a person who had hepatitis caused donation to be deferred for six months without any signs or symptoms of hepatitis. Contact meant cohabitation and routine use of the same eating and sanitary facilities.

93.3 If the donor had been tattooed or had piercings since the last donation, the donor was to be rejected until six months without evidence of hepatitis had elapsed.

93.4 If the donor had received a blood transfusion since the last donation, it was required that donation was deferred for six months without hepatitis symptoms.

93.5 Donors were not to be under the influence of drugs or alcohol on the day of donation.

93.6 The physician was required to check the donor's temperature, pulse, respiration, blood pressure, weight and height, as well as their general appearance and nutrition and to look for unexplained needle marks.

94. On 1 February 1983, in light of reports concerning AIDS, Cutter Inc put in place additional measures to ensure the suitability of donors and to protect Cutter Inc's products from contamination, to the extent possible at that time **[WITN6984032]**.[168] The quality assurance documents, CSOP 401 "Donor Card", CSOP 402 "Pre-donation History Form" and CSOP 403 "Medical History and Physical Examination", were dated 14 February 1983. The following additions were made to the "Medical History and Physical Examination" sections of these procedures:

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[165] 15 February 1974, Cutter Inc memo, "Revisions to Cutter System of Plasmapheresis" [**Miles Inc/2/132**], [**WITN6984030**]
[166] 5 December 1981, CSOP - Predonation History - Form 81-9711 [**Miles Inc/7/526**], [**WITN6984031**]
[167] 5 December 1981, CSOP - Medical History and Physical Examination - Form No. 81-9731 [**Miles Inc/7/525**], **BAYP0000019_094**
[168] 17 May 1983, Letter from Cutter UK to DHSS [**Reg/2/78**], [**WITN6984032**]

94.1 Skin - unexplained jaundice was viewed as providing an indication of hepatitis. Recent appearance of brownish, reddish or purplish lesions, nodular or flat, anywhere on the entire body surface was stated to be potentially indicative of AIDS. Chronic eczema, chronic dermatitis and recurring boils could all result in rejection as a donor (section 4.2);

94.2 Skin - Note: Jaundice, chronic eczema, chronic dermatitis, boils. Look for unexplained needle marks on both arms or other areas where narcotic administration might be practised. Skin was to be examined for signs of AIDS (section 6.4); and

94.3 Lymphatic System: enlarged or tender cervical, axillary, supratrochlear or inguinal lymph nodes could be indicative of AIDS (section 6.11).

95. In addition, it appears that a new quality assurance document, "QA Plasma Sources - Acquired Immune Deficiency Syndrome (AIDS)" (the "AIDS information sheet") was issued on 14 February 1983. This stated:

> *"The Cutter System of Plasmapheresis (CSOP) requires rejection of donors with signs or symptoms of AIDS. The CSOP also requires rejection of donors from at risk groups associated with AIDS. This procedure provides the AIDS Information Notice which is to be signed by the donor, a center employee as a witness, and dated. This information sheet is to be filed in the donor record file (donor chart).*
>
> *Plasma centre employees performing donor suitability determination are to be trained in the additional requirements …[of CSOP 401, 402]…*
>
> *In addition, donors must be asked during predonation history questioning if they are members of AIDS at risk groups:*
>
> *(1) Male Homosexuals*
> *(2) Residents of, or visitors to, Haiti within the past 5 years*
> *(3) Intravenous drug users (past and present requirements)*
>
> *Donors may not be accepted for plasmapheresis if they are members of these at risk groups. Record responses in Comments section (rubber stamp additional questions under the word "Comments" on the form)."* **[BAYP0004429_002]**.[169]

96. On 28 July 1983, the AIDS information sheet was revised to ask the donor if they were a sexual partner of an at risk group. On the same day, CSOP 402 was revised to include pre-donation examination of lymph nodes in the neck

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[169] 14 February 1983, Cutter Inc Quality Assurance Document 118 [**Miles Inc/9/726**], **BAYP0004429_002**

and CSOP 403 was revised to includes questions regarding persistent diarrhoea and night sweats [**BAYP0005807_003**].[170]

97. In the latest version of the AIDS information sheet available to me (dated 1985), the definition of the risk groups had been changed to:

> *"ANYONE WHO HAS AIDS OR ANY OF ITS SIGNS OR SYMPTOMS*
> *MEN WHO HAVE HAD SEX WITH ANOTHER MAN, EVEN ONCE, SINCE 1977*
> *PAST OR PRESENT INTRAVENOUS DRUG USERS*
> *RESIDENTS OF, OR VISITORS TO HAITI SINCE 1977*
> *SEXUAL PARTNERS OF THE ABOVE*
> *Signs and symptoms include unexplained weight loss, night sweats, blue or purple spots on or under the skin or on mucous membranes, unexplained swelling anywhere on the body lasting more than one month, persistent which spots or unusual blemishes in the mouth, feverishness for more than 10 days, persistent cough or shortness of breath, persistent diarrhea"* [**WITN6984033**].[171]

98. In late 1983, the screening of donors for hepatitis B core antibody ("HBcAb") began and by 30 March 1984, screening of all donors for HBcAb had been instigated in all Cutter plasma centres [**BAYP0005807_003**].[172] A Cutter Inc press release dated 2 April 1984, announced the introduction of testing for HBcAb at all plasma centres because *"Hepatitis B has been found to be prevalent in the same populations that are at high risk for Acquired Immune Deficiency Syndrome (AIDS)"* and *"the transmissibility of Hepatitis B seems to parallel that of AIDS"* [**CGRA0000240**].[173] Cutter UK appears to have sent a copy of the press release to DHSS on 5 April 1984 [**BAYP0000003_215**].[174]

99. A new CSOP dated 14 March 1984, CSOP 300 - Special Plasma, was created that stated that donors suspected of being at risk for AIDS shall be assigned to a Special Plasma Program at the discretion of plasma centre personnel. In addition, it stated that Cutter Biological Special Testing Lab would identify to the plasma centre those donors whose plasma had tested HBcAb positive (see paragraph 139 below) and who were to be classified as Special Plasma donors, Plasma type S. Positive plasma was to be labelled as Plasma designated for use in manufacturing albumin, Protein Plasma Fraction, or globulin only

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[170] 31 May 1985, Cutter Inc internal memo [**Miles Inc/28/2800**], **BAYP0005807_003**

[171] Undated circa 1985, Dear Donor Letter regarding AIDS risk groups **[Miles Inc/29/2927]**, [**WITN6984033**]

[172] 31 May 1985, Cutter Inc internal memo [**Miles Inc/28/2800**], **BAYP0005807_003**

[173] 2 April 1984, Cutter Inc news release [**Other/8/560**], **CGRA0000240**

[174] 5 April 1984, Letter from Cutter UK to DHSS [**Reg/3/125**], **BAYP0000003_215**

[CGRA0000326_003].[175]

100. On 29 May 1984, Cutter Inc sent to the managers of Cutter affiliated plasma centres a revised version of CSOP 300. This version is not present in the documents available to me. However, the cover letter stated that:

> *"[a]fter almost two months experience with collecting, testing, segregating and receiving Special Plasma, some ideas have surfaced which should make things simpler and, hopefully, more error free". One such change was stated to be that "[a]ll plasma collected from donors whose HBc Antibody status is unknown whether first-timers or not, will be listed together under new temporary plasma type U - "Unknown" [**BAYP0005297**].*[176]

101. A later version of CSOP 300 dated 30 August 1984, stated: "New donors and donors returning after an absence of four month or longer must temporarily be classified as Special Plasma donors, plasma type S, until results of HB_c antibody testing are known **[CGRA0000326_010]**.[177] In addition, it noted the following precautions:

> *"1. If HBc antibody testing is incomplete or a test sample is missing and a back up sample is unavailable, the donor's plasma is to be shipped as Type S until the donor's status with regard to this test dan be determined.*
>
> *2. Should a HBc Antibody positive unit be inadvertently shipped as HBc Antibody negative, i.e. other than as Plasma Type S, promptly report by phone to the National Plasma Centre Operations Manager (415) 420-5151. Report must include Control Number, Donor Number, Date Drawn, Week Number, Plasma Type, Donor Code, Case Number, date shipped and destination".*

102. HBcAb screening of donors was discontinued in 1984, as notified in a Cutter Inc marketing bulletin dated 12 November 1984, which stated that *"[a]s a result of the success of our heating process against viral contaminants, the anti-hepatitis B core tests will no longer be performed."* **[BAYP0005475_001]**.[178] A Cutter Inc Plasma Procurement newsletter from November 1984 stated a decision had been made:

> *"to discontinue hepatitis B core antibody testing and the segregation of hepatitis B core positive plasma into the Special Plasma type.*

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[175] 14 March 1984, Cutter Inc Quality Assurance document CSOP 300 [**Miles Inc/19/1999**], **CGRA0000326_003**

[176] 29 May 1984, Cutter Inc internal memo [**Miles Inc/21/2144**], **BAYP0005297**

[177] 30 August 1984, Cutter Inc Quality Assurance document CSOP 300 [**Other/10/630**], **CGRA0000326_010**

[178] 12 November 1984, Cutter Inc marketing bulletin [**Miles Inc/24/2365**], **BAYP0005475_001**

In addition, Cutter is participating in the development of the HTLV III antibody test which will be much more specific for AIDS than the hepatitis core antibody test and will have a very low incidence of positives. We hope to have this tool by mid-1985." **[BAYP0005501]**[179]

C. Communication and notification of risks

Adverse event reports

103. The legislation and guidance relating to the handling and reporting of adverse events to the regulatory authorities in the UK at the relevant time is contained within **Annex A**.

104. Available documentation suggests that suspected adverse reactions to Cutter's factor concentrates that were notified or confirmed to the UK company were recorded on a "Customer Service Report" and "Medical Information Report" form and the circumstances were investigated. The details of the suspected adverse reaction were reported by the UK company to Cutter Inc, and there is evidence that the Director of Medical Services or the drug safety unit of Cutter Inc would contact the reporting clinician directly **[BAYP0000008_102]**,[180] **[BAYP0000011_093]**.[181] A document entitled "Customer Service "Desk" Procedure" sets out the procedure to be followed by Cutter Inc when a Customer Service Report form was received **[BAYP0004912_005]**.[182] Investigation of suspected adverse reactions might include reviewing the manufacturing and quality assurance records for the particular batch of concentrate and testing of retained samples from that batch by Cutter Inc.

105. There is evidence from the documentation I have seen that following investigation, the following actions were to be taken:

105.1 Suspected adverse reactions notified or confirmed by a doctor, dentist, pharmacist or coroner in the UK and suspected serious adverse reactions from abroad, were reported to the DHSS and, in some cases, the NIBSC **[WITN6984034]**.[183]

105.2 In cases that appeared to implicate a particular batch of product, other centres that had also received the batch were informed (both in the UK and in other

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[179] 1 November 1984, Plasma Procurement newsletter [**Miles Inc/24/2395**], **BAYP0005501**
[180] 28 February 1986, Letter from Cutter Inc to Dr Mitchell [**Other/13/1118**], **BAYP0000008_102**
[181] 18 May 1988, Letter from Cutter Inc to Queen Elizabeth Hospital [**Other/16/1647**], **BAYP0000011_093**
[182] Undated, Customer Service "Desk" procedure [**Miles Inc/16/1622**, **attachment 4**], **BAYP0004912_005**
[183] 20 May 1988, Note of a meeting at the NIBSC to discuss Cutter products [**Reg/5/377**], [**WITN6984034**]

countries where product from the same batch had been supplied) **[BAYP0000004_401]**.[184]

105.3 Where a serious concern was raised in relation to a particular batch of product, consideration would be given as to whether the entire batch should be recalled (paragraph 110).

106. Where suspected adverse reactions involved possible infection, it was necessary to consider whether the virus was likely to have been transmitted by one of Cutter's products, another blood product or contracted from some other source. Often patients had received blood products from various sources over time (including other company's products and NHS product). In cases where all tests and inquiries regarding the suspected batch came back negative, and where no other reports were received, it appears that Cutter staff considered it unlikely that Cutter's products were implicated rather than some other cause. There is evidence that DHSS did not require a recall following one or two isolated cases associated with a single batch of product **[WITN6984035]**.[185]

107. There is evidence that cases of hepatitis associated with factor concentrates notified to the product licence holder were reported to the DHSS by the company. However, the available documentation is incomplete. The documents also indicate that it was unusual for healthcare professionals to report such cases to DHSS, but would instead add cases to the Haemophilia Centre directors' computerised surveillance unit based in Oxford. There is evidence that physicians treating haemophiliacs seemingly reported any occurrences to this centre rather than to the DHSS **[WITN6984035]**.[186]

Particular adverse event reports identified by the Inquiry

108. I am aware that four particular adverse event reports were identified by the Inquiry in the Rule 9 Request sent to Mrs Linda Frith. I have no further information to provide to the Inquiry beyond that set out by Mrs Frith in her statement dated 16 November 2021, in relation to the adverse events reported with Konyne HT - lot 20N028, Koate HT - lot 50P069 and Koate HT - lot 50R004. However I have identified some further details in relation to the adverse events reported with respect to Koate HT - lot 50S021, which may be of assistance to the Inquiry.

109. In February 1988, Cutter UK received a report from Dr Copplestone, of the Plymouth Haemophilia Centre about three patients who had been treated with

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[184] 23 December 1986, Letter from Cutter UK to DHSS [**Reg/4/327**], **BAYP0000004_401**
[185] 18 May 1988, Note of a telephone conversation between Bayer UK and DHSS [**Other/16/1649**], [**WITN6984035**]
[186] 18 May 1988, Note of a telephone conversation between Bayer UK and DHSS [**Other/16/1649**], [**WITN6984035**]

Koate HT lot 50S021 and who had developed clinical hepatitis B. Three other patients had been treated with the lot but were immune **[BAYP0000011_014]**.[187] On 25 February 1988, it was noted that Cutter Inc reported that it had seen no adverse reports of any kind for lot 50S021 **[BAYP0000011_021]**.[188] On 7 March 1988, Cutter Inc informed Dr Copplestone that a review of the manufacturing and quality assurance records for the lot showed that all plasma used in its manufacture was HBsAg screened and found to be negative. All release tests were negative. As was the testing of the lot itself **[BAYP0000011_027]**.[189]

110. On the basis of the information from Dr Copplestone that lot 50S021 was the only common factor **[BAYP0000011_035]**,[190] as stated by Mrs Frith at paragraph 141 of her statement, Bayer UK recalled the batch in March 1988 and informed DHSS that it would contact every customer who had been supplied with the batch, inform them of possible hepatitis B transmission and request the immediate return of any unused product **[BAYP0000005_056]**.[191]

111. The incidents were reported to the CSM by the Yellow Card system and both DHSS and NIBSC were notified of the recall by Bayer UK **[BAYP0000005_056/BAYP0000005_057]**,[192] **[BAYP0000005_058]**.[193]

112. Mrs Frith also referred to an internal memo, which stated that Dr Mooney of Liverpool Royal Infirmary and Dr Parapia of Bradford Royal Infirmary had patients with possible hepatitis B infections, possibly due to Koate HT lot 50S021 **[BAYP0000011_056]**.[194] However, as regards the patient in Liverpool, the possible transmission of hepatitis B via Koate HT was excluded; Dr Mooney and Dr Hay consulted the patient's notes and discovered that the patient had not in fact received lot 50S021 **[WITN6984036]**.[195] There is no further information regarding the patient in Bradford in the materials available to me.

113. In May 1988, the Director of Clinical Research at Cutter Inc visited Dr Copplestone, who completed a special drug incident questionnaire devised by the Director of Clinical Research. The Director of Clinical Research then wrote up a report regarding each patient **[BAYP0000011_097 -**

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[187] 5 February 1988, Cutter UK memo [**Other/16/1581**], **BAYP0000011_014**
[188] 23 February 1988, Cutter UK memo [**Other/16/1588**], **BAYP0000011_021**
[189] 7 March 1988, Letter from Cutter UK to Derriford Hospital [**Other/16/1592**], **BAYP0000011_027**
[190] 17 March 1988, Interoffice Communication [**Other/16/1600**], **BAYP0000011_035**
[191] 24 May 1988, Letter from Bayer UK to DHSS [**Reg/5/380**], **BAYP0000005_056**
[192] 24 May 1988, Letter from Bayer UK to DHSS [**Reg/5/380**], **BAYP0000005_056 & BAYP0000005_057**
[193] 24 May 1988, Letter from Bayer UK to NIBSC [**Reg/5/381**], **BAYP0000005_058**
[194] 12 April 1988, Cutter Inc internal memo [**Other/16/1617**], **BAYP0000011_056**
[195] 4 May 1988, Bayer UK internal memorandum [**Other/16/1634**], [**WITN6984036**]

BAYP0000011_111].[196]

114. According to a file note dated 6 June 1988, on the 3 June 1988 Dr Thomas of NIBSC requested confirmation as to whether the patient in Plymouth (discussed at paragraph 109) had in fact contracted NANB hepatitis. Bayer UK confirmed that the patient had contracted hepatitis B. NIBSC replied that this eased the situation since hepatitis B was a *"known hazard with this product"*, although it was questioned why the patient(s) had not been vaccinated. NIBSC noted that owing to the sensitivity of the current assays, it was not possible to detect hepatitis B in the final product, however, following the occurrence of hepatitis B in Ireland in 1986, it had been understood that all plasma pools would be tested for hepatitis B. The document stated that this would be confirmed following a visit by Cutter Inc to the UK on 20 June 1988 **[BAYP0000005_198]**.[197]

115. On 1 July 1988, Dr Thomas of NIBSC telephoned Bayer UK about the hepatitis reports with Koate HT, lot 50S021. A report of the conversation stated:

> *"I told him we reviewed all the records. Every unit was tested and negative for HBsAg, as was the plasma pool. He asked whether we could rule out human error. Of course, we could not. I told him there were unusual features about this incident: only one centre had problems, the patients were all old, only in one case could we not find other risk factors, the patients had not been immunised for Hepatitis B even though this is the practice in the UK. Unlike the previous incident where the pool was positive, the Factor IX made from some of the same pool also resulted in Hepatitis; with lot [illegible], this is not the case. No reports have been received from [illegible]. He asked where else this lot went and I said it only went to U.K. This was because the order was large enough to include a complete lot. The lot had been released by the FDA."* **[WITN6984037]**.[198]

116. Dr Thomas asked for a sample of the pool and also whether it was intended to take the product off the market. Bayer UK responded that this was not the case as there were patients to whom the product represented no additional risk. The company had withdrawn and replaced the lot, which was treated as a withdrawal rather than a recall, a strategy approved by Dr Thomas **[WITN6984037]**.[199]

117. On 12 August 1988, Bayer UK provided DHSS with Cutter Inc's report on the

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[196] 20 May 1988, Interoffice Communication [**Other/16/1651**], **BAYP0000011_097- BAYP0000011_111**
[197] 6 June 1988, Note of telephone conversation between Bayer UK and NIBSC [**Reg/4/388**], **BAYP0000005_198**
[198] 1 July 1988, Visit to Bayer UK trip report [**Other/16/1689**], [**WITN6984037**]
[199] 1 July 1988, Visit to Bayer UK trip report [**Other/16/1689**], [**WITN6984037**]

matter, which it had submitted to the FDA **[WITN6984038]**.[200] Cutter Inc's investigation of the lot revealed no abnormalities: there were no HBsAg positive donors in the pool; both the pool and final container test for HBsAg were negative; and a thorough check of customer service files did not indicate reports of hepatitis B transmission for factor VIII or factor IX manufactured from pooled material contained in lot 50S021. The Director of Clinical Research at Cutter Inc's review of the patients' medical histories showed:

- Three of the six patients receiving lot 50S021 were already seropositive prior to receipt of the lot (patients AL, CU and JA, ages 49, 39 and 28 respectively);
- Patient FT (age 67) received only lot 50S021 in August 1987 and developed acute hepatitis B in December 1987; no other causative factors could be determined;
- Patient AW and FN (both 54), one with Von Willebrand disease and the other with mild haemophilia A, also developed acute hepatitis B. These two patients both received factor VIII manufactured by Cutter but were also concurrently treated with factor VIII from another manufacturer licensed in the UK.

118. At the completion of the investigation, no clear conclusions could be drawn. The Director of Clinical Research concluded that "the source of hepatitis B was not clear due to the medical histories of these hemophiliacs. Only the hepatitis B contracted by Patient FT appears to be related to lot 50S021" **[BAYP0000011_180]**.[201]

Product labels

119. The requirements pursuant to UK legislation as regards what must be stated on product packaging and labelling, including the warnings to be provided, are set out in **Annex A**.

120. It is apparent from the documents available that where identical products were placed on the UK and US markets, matching text was used on the labelling and package inserts (where approved by the competent regulatory authorities) save for the name of the licence holder or distributor and the national product licence number. The UK company would therefore submit to DHSS the labelling and package inserts used by Cutter Inc for supply in the US and over print it with the name of the UK distributor and the UK product licence number

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[200] 12 August 1988, Letter from Bayer UK to DHSS [**Reg/5/412**], [**WITN6984038**]
[201] 29 June 1988, Letter from Cutter Inc to FDA [**Reg/5/398**], **BAYP0000011_180**

[BAYP0000001_097].[202]

121. All of the plasma products placed on the UK market, at all times, presented a warning about the risk of viral transmission on the label and in the package insert. Warning statements were updated as knowledge increased regarding the risk of viral transmission. A table showing the development of the warning text over time for Koate and Koate HT is attached as **Annex C.**

122. The first approved package insert for Koate, submitted to DHSS on 16 October 1975, stated:

"Antihemophilic Factor (Human)

Koate™

SEE SECTIONS ENTITLED "INDICATIONS" AND "WARNING" FOR DESCRIPTION OF HEPATITIS RISK"

Further wording appeared, again in capital letters, at the section headed "Description":

"THIS PRODUCT IS PREPARED FROM UNITS OF HUMAN PLASMA WHICH HAVE BEEN TESTED AND FOUND NON-REACTIVE FOR HEPATITIS ASSOCIATED (AUSTRALIA) ANTIGEN. UNFORTUNATELY THIS TEST DOES NOT WITH CERTAINTY PRECLUDE THE PRESENCE OF HEPATITIS VIRUS. SEE WARNING."

122.1 Under the heading "Indications" the text included the caution:

"CAUTION: BECAUSE OF THE POSSIBILITY THAT ANY LOT OF KOATE™ MIGHT CONTAIN THE CAUSATIVE AGENTS OF VIRAL HEPATITIS, ITS USE MUST BE CONSIDERED IN LIGHT OF THIS HAZARD, PARTICULARLY IN PERSONS WITH FEW PREVIOUS TRANSFUSIONS OF BLOOD AND PLASMA PRODUCTS.

Kasper and Kipnis[4] have concluded that those who had little exposure to blood products had a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild hemophilia, they recommend single donor products. However, for patients with moderate or severe hemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates

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[202] 13 August 1975, Letter from Bayer UK to Cutter Inc re DHSS requirements [**Reg/1/3**], **BAYP0000001_097**

have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients."

122.2 This was followed in the same paragraph by a boxed warning:

"Koāte™ concentrate is a purified dried fraction of pooled plasma obtained from many donors. SINCE THE PRESENCE OR ABSENCE OF HEPATITIS VIRUS IN KOĀTE™ CONCENTRATE CANNOT BE PROVEN WITH ABSOLUTE CERTAINTY, THE PRESENCE OF SUCH A VIRUS SHOULD BE ASSUMED and the hazard of administering Koāte™ concentrate should be weighed against the medical consequences of withholding it."

122.3 The subsequent paragraph stated:

"Since there is this definite risk of hepatitis, we suggest that the physician give consideration to explaining to the patient (or the patient's family) the relative risks of giving or withholding this product. Then, should the patient develop hepatitis, as a result of the injection, it will not come as a surprise, and there is not nearly the likelihood of resentment, which will almost surely follow an unexplained and unexpected infection."

122.4 In a paragraph on the product warranty it was stated:

"[….] and that the risk of transmitting hepatitis be carefully weighed before the product is prescribed."

122.5 The draft labelling for the side panel of the carton stated:

"WARNING: Since the presence or absence of the virus of hepatitis in Koāte™ cannot be proven with absolute certainty, the presence of such virus should be assumed and the hazard of administering Koāte™ should be weighed against the medical consequences of withholding the use of Koāte™."

122.6 The draft labelling for the container stated:

"HEPATITIS DANGER

SEE DIRECTION SHEET". [**BAYP0000001_098**][203]

123. It is apparent from the materials available that by March 1981, the package insert emphasised the risk of hepatitis associated with use, as follows (wording underlined had been added):

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[203] October 1975, Koate; Product Licence Application [**Reg/1/4**], **BAYP0000001_098**

"THIS PRODUCT IS PREPARED FROM HUMAN VENOUS PLASMA. EACH INDIVIDUAL UNIT OF PLASMA AND EACH LOT OF FINAL PRODUCT HAS BEEN FOUND NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN USING A LICENSED THIRD-GENERATION ASSAY. HOWEVER, THIS TEST DOES NOT PRECLUDE THE PRESENCE OF HEPATITIS VIRUS. SEE WARNING."

124. The boxed warning had also been developed as follows:

"Antihemophilic Factor (Human) Koāte™ concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koāte concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood and plasma products.

Kasper and Kipnis[4] have concluded that those who have had little exposure to blood products have a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild hemophilia, they recommend single donor products. However, for patients with moderate or severe hemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients." **[BAYP0000019_025]**[204]

125. In December 1981, the DHSS approved a revision to the Koate package insert. The description of the product was amended as follows (wording added is underlined) and began the format of reference to hepatitis viruses, as opposed to hepatitis virus:

"THIS PRODUCT HAS BEEN PREPARED FROM LARGE POOLS OF HUMAN VENOUS PLASMA COLLECTED FROM MANY PAID DONORS. EACH INDIVIDUAL UNIT OF PLASMA AND EACH LOT OF FINAL PRODUCT HAS BEEN FOUND NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN (HBsAg) USING A U.S. FEDERALLY APPROVED TEST OF AT LEAST THIRD-GENERATION SENSITIVITY. UNFORTUNATELY, THIS TEST DOES NOT PRECLUDE THE PRESENCE OF HEPATITIS VIRUSES. SEE WARNING.

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[204] March 1981, Package insert for Antihemophilic Factor (Human) Koate **[Other/4/199]**, **BAYP0000019_025**

NO KNOWN LABORATORY TEST METHOD CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT HEPATITIS." **[BAYP0000019_087]**[205]

126. In March 1984, the information provided to users of factor concentrates in the package insert for Koate was amended. This included the addition of emerging information about AIDS. The boxed warning was stated as follows:

> *"**Koāte® concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. Although each unit of plasma has** been **found nonreactive for hepatitis B surface antigen (HBsAg) using a U.S. Federally approved test with third-generation sensitivity, the presence of hepatitis viruses in such pools should be assumed.***
>
> *Kasper and Kipnis[5] have concluded that those who have had little exposure to blood products have a higher risk of developing hepatitis after introduction of clotting factor concentrates. For those patients, especially those with mild haemophilia, they recommend single donor products. For patients with moderate or severe haemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe haemophilia that these products should not be denied to appropriate patients.*
>
> *Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophilics who have received blood and/or coagulation factor concentrates, including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, secondary to multiple antigenic exposures or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly."* **[WITN6407005]**.[206]

127. It is apparent from the documents available to me that the addition of an AIDS warning was being discussed with the BoB in the US in November 1983 **[WITN6984039]**[207] and it can be seen from the documents that the paragraph above had been added to the package insert in the US by December 1983

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[205] December 1981, Package leaflet - Koate [**Other/4/236**], **BAYP0000019_087**
[206] March 1984, Package leaflet for Antihaemophilic Factor (Human) Dried Factor VIII [**Other/8/548**], **WITN6407005**
[207] 8 November 1983, Letter from Cutter Inc to NCDB re Antihemophilic Factor (Human) [**Miles Inc/16/1657**], [**WITN6984039**]

[BAYP0000027_080].[208]

Koate HT

128. On 12 November 1984, Bayer UK applied to DHSS for a product licence for Koate HT. The application included the following statement:

"HEPATITIS DANGER - SEE INSERT LEAFLET

This product has been prepared from large pools of human venous plasma collected from many paid donors. Each individual unit of plasma and each lot of final product has been found non-reactive for hepatitis B surface antigen (HB_sAg) using a U.S. Federally approved test with third generation sensitivity.

WARNING: Koate-H.T. Concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administrating Koate-H.T. concentrate should be weighed against the medical consequence of withholding treatment." **[WITN6984040]**.[209]

129. The package insert stated:

"WARNINGS

Antihemophilic Factor (Human), heat-treated, Koate HT** concentrate **is a purified dried fraction taken from large pools of fresh human plasma obtained from many paid donors. Although each unit of plasma has been found non-reactive for hepatitis B surface antigen (HBsAg) using a US Federally approved test with third generation sensitivity, the presence of hepatitis viruses in such pools must be assumed.

Kasper and Kipnis[5] have concluded that those who have had little exposure to blood products have a higher risk of developing hepatitis after introduction of clotting factor concentrates. For such patients, especially those with mild hemophilia, they recommend single donor products. For patients with moderate or severe hemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients.

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[208] December 1983, US Package insert for Koate [**Other/7/475**], **BAYP0000027_080**
[209] 12 November 1984, Application for a product licence [**Reg/3/167a**], [**WITN6984040**]

Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in hemophilics who have received blood and/or coagulation factor concentrates including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly." **[WITN6984040]**[210]

130. The data sheet to be provided to clinicians provided the following information relating to the risks of viral transmission:

Under the heading "*Warnings*":

"Koate-HT concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate-HT should be weighed against the medical consequence of withholding it, particularly in persons who have had few previous transfusions of blood or blood products."

And under the heading "*Further information*":

"Koate-HT has been heated at 68℃ for 72-77 hours and there is no evidence of any adverse effect upon the properties of the product. The heat treatment step has been introduced to reduce the risk of transmission of infectious agents.

Studies have demonstrated that the heat-treatment process used in the production of Koate-HT inactivates potential infectious viruses, including a retrovirus, but it has not yet been established that agents of any major transmittable disease would be inactivated" **[WITN6984041]**.[211]

131. By June 1985, additional wording had been added to the Koate HT label. The warning, at that time then read (additional wording underlined):

"WARNING: KOĀTE®-HT IS A PURIFIED DRIED FRACTION OF POOLED PLASMA OBTAINED FROM MANY DONORS. THE PRESENCE OF HEPATITIS VIRUSES SHOULD BE ASSUMED AND THE HAZARD OF ADMINISTRATING KOĀTE®-HT SHOULD BE WEIGHED AGAINST THE MEDICAL CONSEQUENCE OF WITHHOLDING IT PARTICULARLY IN

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[210] 12 November 1984, Application for a product licence [**Reg/3/167a**], [**WITN6984040**]
[211] 17 April 1985, Interoffice communication enclosing Koate HT Data Sheet [**Other/11/848**], [**WITN6984041**]

PERSONS WITH FEW PREVIOUS TRANSFUSIONS OF BLOOD OR BLOOD PRODUCTS" **[WITN6984042]**[212]

132. In July 1986, the package insert for Koate HT was substantially revised to include details of non-clinical studies on the effect of the heat treatment process on virus inactivation, which had been carried out using a number of viruses including LAV/HTLV-III and AIDS related virus ("ARV") added prior to heating. The boxed warning was changed to state that individual units of plasma had been tested and found to be non-reactive for hepatitis B surface antigen and antibody to HTLV-III by an FDA-approved test. It was also stated that other screening procedures and the heat treatment process were designed to reduce the risk of transmitting viral infection, although available testing methods were not sensitive enough to detect all units of potentially infectious plasma, and treatment methods had not been shown to be totally effective in eliminating viral infectivity. The warning referred, with the publications cited, to the recommendations of Fletcher *et al* and Kasper and Kipnis **[WITN6407007]**.[213]

133. Around the same time, the product label (draft dated 23 May) was updated to include wording that the pools of human plasma from which the product was made might contain the causative agents of NANB hepatitis, hepatitis B and other viral diseases. It stated that each unit of plasma had been tested and found non-reactive for HBsAg and HTLV-III antibody by FDA-approved tests **[BAYP0000008_186]**.[214]

134. On 10 August 1987, Cutter UK submitted to DHSS an application for variation of the Koate HT product licence to revise the wording of the labelling for Koate HT. The revised wording about "Source Plasma (Human)" included the following statement, (revisions underlined):

> *"Source plasma is collected according to the Cutter System of Plasmapheresis which incorporates all the FDA requirements for Source Plasma including testing of samples from all donors for antibodies to ~~HTLVIII~~ HIV.*
>
> *In addition Cutter test each donation for ALT levels. Only units found to have an ALT level less than twice the upper limit of normal for the test are used in the manufacture of KOATE HT."* **[BAYP0000004_453]**[215]

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[212] 4 June 1985, Package insert and labels for Koate HT [**Other/12/908 - 911**], [**WITN6984042**]
[213] July 1986, Koate-HT; published package insert [**Other/13/1231**], **WITN6407007**
[214] 14 May 1986, Package insert for Antihaemophilic Factor (Human) - Koate HT [**Other/13/1180**], **BAYP0000008_186**
[215] 10 August 1987, PL Variation Application - Koate HT PL 0055/0107 [**Reg/4/354**], **BAYP0000004_453**

135. However, the variation was not approved by DHSS until eighteen months later on 27 February 1989 [**WITN6407011**].[216]

136. The data sheet for Koate HT dated August 1988 stated within the section "*further information*":

> *"Koate HT is prepared from pooled units of plasma which have been individually tested and found non-reactive for hepatitis B surface antigen and antibody to human immunodeficiency virus 1 (HIV-1) by approved FDA tests. Each unit used in the manufacture of this product has been found to have an ALT level less than twice the upper limit of normal for the test.*
>
> *Koate HT has been heated at 68℃ for 72-77 hours and there is no evidence if any adverse effect upon the properties of the product. The heat treatment step has been introduced to reduce the risk of transmission of infectious agents.*
>
> *In-vitro studies have demonstrated that the heat-treatment process used in the production of Koate HT inactivates a number of viruses including HIV-1, but it has not yet been established that agents of any major transmittable disease would be eliminated" (underlining denotes change from February 1985 version)* [**BAYP0000011_232**].[217]

D. Cutter Inc's efforts to reduce the risk of infected blood products

Testing of plasma

137. Cutter Inc tested plasma used to prepare its factor concentrates for exposure to hepatitis B using the HBsAg test from the 1970s [**BAYP0000020_007**].[218] This test was mandated by the FDA in 1975 [**BAYP0000012_006**].[219]

138. A Cutter Inc laboratory procedure document dated 12 January 1980, set out the procedure to be followed if a donor was reported to have, or to have had, clinical, serum, or infectious hepatitis or was discovered to have tested HBsAg positive in the past. If the validity of the report was established, the procedure stated to *"record information on Donor Chart and permanently terminate donor;*

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[216] 27 February 1989, DHSS approval to variation application for Koate HT [**Reg/5/443**], **WITN6407011**
[217] 16 September 1988, Data sheet for Koate HT [**Other/16/1745**], **BAYP0000011_232**
[218] See for example, 7 January 1976, Cutter Inc internal note [**Other/2/076**], **BAYP0000020_007**
[219] Barker L and Dodd R (1989). Viral Hepatitis, acquired immunodeficiency syndrome, and other infections transmitted by transfusion, Chapter 29 of Petz & Swisher, Clinical practice of transfusion medicine, second edition, page 280 [**Other/17/1777**], **BAYP0000012_006**

update permanent reject files" [**BAYP0000019_018 (p 89)**].[220]

139. In April 1984, Cutter Inc began screening donated plasma for hepatitis B using the HBcAb test [**BAYP0000010_137**].[221] A CSOP dated 14 March 1984, stated that if the Cutter Biological Special Testing Lab identified HBcAb positive plasma, staff were to report this to the relevant plasma centre such that the donor could be classified as a "Special Plasma" donor (see paragraph 99 above) [**CGRA0000326_003**].[222] On 10 May 1984, Cutter UK submitted an application to DHSS to vary the Koate product licence in respect of the amendments to the CSOP, which had added the requirement for HBcAb testing to all source plasma [**BAYP0000003_334**].[223] A positive test result excluded that individual from donating plasma for use in the production of Koate [**WITN6984043**].[224] Variation of the product licence was granted on 8 June 1984 [**BAYP0000003_334**].[225] In consequence, the specification of source material then read:

> *"Cutter System of Plasmapheresis incorporates all FDA requirements for Source Plasma. In addition, HB_c Antibody test now included in the Cutter System." (emphasis on new wording)* [**BAYP0000003_334**][226]

140. As stated at paragraph 102 above, Cutter Inc ceased HBcAb testing on 12 November 1984.

141. By May 1985, Cutter Inc had introduced screening of all individual donations of plasma for antibody to HTLV-III" **BAYP0000008_124**].[227]

142. A note from Cutter Inc to Cutter UK dated 8 October 1986, stated that from the cut-off date of 14 August 1985, only Koate HT product made wholly from HTLV-III screened plasma was supplied by Cutter Inc [**BAYP0000009_011**].[228] On 6 March 1986, Cutter UK wrote to Professor Bloom at University Hospital Wales stating *"all batches of Koate HT arriving in the U.K. from now on will be HTLVIII-tested material and found to be non-reactive"* [**BAYP0000008_109**].[229] In March 1986, Cutter UK requested confirmation from DHSS that the Electro-Nucleonics

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[220] 12 January 1980, Cutter Laboratories Inc. Procedure 2.5.1.2. [**Miles Inc/7/439**], **BAYP0000019_018 (p 89)**
[221] 16 July 1987, Improvements in Blood-Clotting Product Make Therapy Safer for Haemophiliacs, Draft 2 [**Other/15/1534**], **BAYP0000010_137**
[222] 14 March 1984, Cutter Inc Quality Assurance document [**Miles Inc/20/1999**], **CGRA0000326_003**
[223] 8 June 1984, Approval of variation from DHSS [**Reg/3/138**], **BAYP0000003_334**
[224] 23 May 1984, Letter from Cutter UK to NDAB **[Reg/3/136]**, [**WITN6984043**]
[225] 8 June 1984, Approval of variation from DHSS [**Reg/3/138**], **BAYP0000003_334**
[226] 8 June 1984, Approval of variation from DHSS **[Reg/3/138]**, **BAYP0000003_334**
[227] 19 March 1986, Cutter Inc telex [**Other/13/1137**], **BAYP0000008_124**
[228] 8 October 1986, Cutter Inc note re 'HTLV-III Screened Product' [**Other/14/1357**], **BAYP0000009_011**
[229] 6 March 1986, Letter from Cutter UK to Professor Bloom [**Other/13/1123**], **BAYP0000008_109**

VIRGO Anti-HTLV-III/LAV assay test, which was that used by Cutter Inc, had been evaluated and found acceptable to the authorities in the UK **[DHSC0002478_066]**.[230]

143. In addition, while this was not an FDA or DHSS requirement, from October 1985, all batches of Koate HT were prepared from plasma screened for ALT levels, in addition to HTLV-III antibodies and HBsAg **[WITN6984044]**.[231] ALT is an enzyme produced primarily in liver cells; when these are damaged, the level of ALT in the blood becomes elevated. Elevation of ALT therefore can be an indicator of non-specific liver cell damage, including hepatitis as well as other conditions.

144. In early July 1986, DHSS had general concerns regarding the effectiveness of plasma screening for HTLV-III and ALT levels. They therefore requested further information regarding Cutter Inc's screening tests, including the lower limits of detection and the implications of failure to detect a low positive result **[BAYP0000008_258]**.[232] The response is not present in the documents available to me.

145. The documents indicate that on 5 August 1987, DHSS, acting on the advice of CSM, wrote to all companies holding product licences for blood products stating:

> *"CSM has advised that licence holders for blood products should be required to supply quality assurance and performance evaluation information on the screening procedures currently carried out for antibodies to HIV and HBS antigen. The following information is required:*
>
> *1. Full details of the test procedure used for the testing of blood donations used in the manufacture, including the manufacturer's instructions for test lots or reagents and indicating any deviation from these instructions used in the testing laboratory.*
>
> *2. Quality control procedures carried out in relation to the assays including the frequency of testing of positive and negative controls.*
>
> *3. The criteria by which donor units are excluded from processing.*

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[230] 20 March 1986, Letter from Cutter UK to DHSS [**Reg/4/278**], **DHSC0002478_066**
[231] 24 February 1987, Letter from North West Regional Health Authority, Attachment 5 - Information about source of plasma, page 13 [**Other/15/1465**], [**WITN6984044**]
[232] 4 July 1986, Letter from Cutter UK to Cutter Inc re 'Screening of Donors for HTLV III Antibodies and ALT Levels' [**Other/13/1244**], **BAYP0000008_258**

From 1 January 1988 the information requested above should be supplied to the NIBSC with the protocols normally provided for the batch release procedure. This does not require any variation to the product licences." **[MHRA0033319_041]** [233]

146. Cutter UK replied on 9 December 1987, with details of the procedures used for screening blood donations used in the manufacture of its products, together with the criteria by which donor units were excluded from processing based on the donor's ALT levels. It stated:

"If serum samples from any donor are positive by the ALTAIRE test (ie ALT levels are at least twice the upper limit of normal) the following procedure is used:

- If the donor's ALT levels are between 2 and 5 times the upper limit of normal for the first time in 30 days and the plasma units are non-reactive, no action is taken.

- If the donor's ALT levels are between 2 and 5 times the upper limit of normal for the second time in 30 days the unit is destroyed (even if it has tested non-reactive) and the donor is permanently deferred.

If the second reactive is more than 30 days after the first no action is taken.

- If the donor's ALT levels are more than 5 times the upper limit of normal for the first time the unit is destroyed and the donor permanently deferred." **[BAYP0000004_463]**.[234]

147. Finally, it appears that Cutter Inc introduced anti-HCV testing during the course of 1992 **[WITN6984045]**,[235] **[BAYP0000033_040]**.[236]

Dry heat and wet heat treatment

148. Throughout the 1970s and 1980s, the research efforts of Cutter Inc to develop effective virucidal procedures was driven by the Head of Research at Cutter Inc, Dr Milton Mozen. He is now 92 years old and I understand that he is unable to assist the Inquiry directly. However, I am advised by Bayer's UK lawyers, Arnold & Porter, that in October 1994, Dr Mozen prepared a witness statement that was submitted to the Institute of Medicine in the US and filed at the Krever Inquiry in Canada. Bayer has provided the witness statement to me. The

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[233] 5 August 1987, Letter from DHSS to Cutter UK [**Reg/4/352**], **MHRA0033319_041**
[234] 9 December 1987, Letter from Cutter UK to DHSS [**Other/4/359**], **BAYP0000004_463**
[235] 13 January 1992, Letter from Bayer UK to Cutter Inc [**HP Additional/1/10**], [**WITN6984045**]
[236] 12 November 1992, Cutter Inc internal memo [**Other/20/2034**], **BAYP0000033_040**

statement is attached as [**WITN6407003**][237] to the Statement of Mrs Frith to assist the Inquiry in understanding the research that was conducted by Cutter Inc at the relevant time and the technical difficulties encountered in this field. I am not qualified to address the technical issues involved, but based on my own reading of such matters I believe Dr Mozen presents an objective view of scientific developments at the relevant time.

149. In Section 4 of his statement, Dr Mozen explains the process of plasma fractionation and how factor VIII was purified from cryoprecipitate from the late 1960s onwards. He notes that the coagulation activities of both factor VIII and factor IX were extremely heat labile, and accordingly each purification step resulted in a loss of coagulation activity.

150. Dr Mozen describes the problem of testing final products for the presence of infectious hepatitis virus and the difficulties that scientists faced for many years in inactivating hepatitis B or hepatitis C in coagulation factor concentrates by heating and other methods, without bringing about complete loss of biological effectiveness.[238] As such, loss of efficacy of the product was an ongoing concern to the company as various heat treatment methods were trialled.

151. Against that background, Dr Mozen describes the efforts made by Cutter Inc to develop a heat treatment capable of avoiding transmission of hepatitis. In Section 6.6 of his statement, he notes that viruses vary in their stability and that hepatitis B and C proved less susceptible to virucidal treatments than HIV which, by chance, was found to be inactivated by heat treatment that did not inactivate hepatitis. It was necessary first to discover suitable protective agents (stabilisers) that could be added to the coagulation components and protect them against heat so that their biological potency was not lost. Dr Mozen further explains that the research of such protective agents also required a full understanding of the structure and biological action of factor VIII, which was not achieved until the early 1980s.

152. According to Dr Mozen, proof of effective inactivation presented its own difficulties, as, in the early years, it required injection of the product into chimpanzees, as human hepatitis does not infect laboratory animals other than the chimpanzee.[239] Suitable control samples were not readily available until the latter half of the 1970s and given the incubation periods, the experiments were complex and had to last at least one year.

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[237] A report prepared in 1994 by Dr Milton Mozen, Head of Research at Cutter Inc, for the purposes of a US Institute of Medicine report and also submitted to the Krever Inquiry in Canada, **WITN6407003**
[238] Sections 5.10, 5.14, 6.3, 6.5 and 7.1 of Dr Mozen's statement, **WITN6407003**
[239] Sections 6.11 and 6.12 of Dr Mozen's statement, **WITN6407003**

153. In Section 7 of his statement, Dr Mozen describes the development of heat treatment processes for factor VIII products within Cutter Inc through the 1970s and early 1980s. Initially the company experimented with heating in solution (known as pasteurisation or "wet heat" treatment), which was thought likely to be more effective at inactivating virus than any "dry heat" treatment. This was because experiments led by another company had indicated that their dry heat procedure was not effective in inactivating hepatitis virus in chimpanzees. [240]

154. As described above, the heat lability of factor VIII necessitated the identification and addition of protective agents into the concentrate solution prior to heating. In late 1978, Cutter Inc started to undertake preliminary work into the discovery of protective agents which could stabilise factor VIII.[241] Similarly, Cutter Inc worked to improve the purification protocols and remove other plasma proteins present in the concentrate which prevented effective treating.[242] Cutter Inc found that the addition of certain stabilising compounds allowed factor VIII to be heated to 60°C for 10 hours, whilst retaining adequate levels of clotting activity. Cutter Inc also carried out studies on animals to demonstrate that, to the extent technically feasible, the heating of factor VIII did not lead to structural changes, which if present, could have been detected by the immune system as foreign (neoantigenicity) potentially resulting in anti-factor VIII antibodies (inhibitors) with potentially devastating consequences for the affected patient.[243]

155. Dr Mozen describes how Cutter Inc continued to optimise the pasteurisation and activity yield of factor VIII with various protective agents, in order to try and develop a hepatitis-safe product that could be produced on a larger scale.[244] By 1982, Cutter Inc had scaled up production for a successful preclinical pilot study and continued to work towards larger production for testing in patients.[245] In parallel, Cutter Inc initiated a chimpanzee study to assess whether the heat treatment had successfully inactivated hepatitis, the results of which could not be determined until a suitably long follow up period had passed.[246] Studies in chimpanzees were the only way in which the effectiveness of viral inactivation could be investigated at that time, other than through clinical trials in previously unexposed patients.

156. By 1983, Cutter Inc had developed a wet heat-treated product that was

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[240] Section 7.7 of Dr Mozen's statement, **WITN6407003**
[241] Section 6.7 and 7.2 of Dr Mozen's statement, **WITN6407003**
[242] Section 6.8 and 6.10 of Dr Mozen's statement, **WITN6407003**
[243] Section 7.2 - 7.4 of Dr Mozen's statement, **WITN6407003**
[244] Section 7.4 - 7.5 of Dr Mozen's statement, **WITN6407003**
[245] Section 7.8 of Dr Mozen's statement, **WITN6407003**
[246] Section 7.10 of Dr Mozen's statement, **WITN6407003**

considered to be as safe and effective in inactivating model viruses as products already on the market.[247] At that stage the studies had not, and could not have, addressed the question of hepatitis safety in humans. The manufacture and sale of this product was approved in the US in January 1984. However, major manufacturing problems were encountered. Yields of finished product were poor and many technical problems were encountered in manufacturing the product, including some which prevented consistent process and product.[248] Furthermore, Cutter Inc learned that its pasteurised factor VIII had not prevented the inoculated chimpanzees from becoming infected with hepatitis B, both circumstances precluding further commercial development.[249]

157. From late 1982, the company had also been investigating the potential advantages of heat-treating freeze-dried factor VIII.[250] The first factor VIII product utilising dry heat treatment (from another company) was authorised by the FDA in 1983. Therefore, in 1983 Cutter Inc began to investigate the effectiveness of its own dry heat process by defining the maximum temperature and duration that could be applied without destroying clotting activity.[251] It was shown that heating at 68°C for 72 hours did not cause significant loss of factor VIII activity. Cutter Inc was able to demonstrate that the heating process rendered a number of model viruses inactive.

158. The new product "Koate HT" was approved in the US on 29 February 1984 [**BAYP0000026_067**].[252] At that time the FDA was allowing model virus experiments on inactivation to take the place of chimpanzee experiments.[253] Hence, Cutter Inc did not have definitive clinical studies to demonstrate the effectiveness of the dry heat process in activating hepatitis virus.[254] Furthermore, the virus causing AIDS had not been identified nor isolated.

159. However, once Dr Robert Gallo published his research identifying the causative agent of AIDS in May 1984 [**PRSE0001131**],[255] it became possible to obtain various strains of the AIDS virus and prove whether it could be inactivated when subject to the heating conditions of the Koate HT process. In 1984, Cutter Inc collaborated on two studies, one with Dr Jay Levy of the University of California (see paragraph 45 above) and the other a study with Dr J. S. McDougal at the

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[247] Section 7.8 of Dr Mozen's statement, **WITN6407003**
[248] Section 7.9 of Dr Mozen's statement, **WITN6407003**
[249] Section 7.10 of Dr Mozen's statement, **WITN6407003**
[250] Sections 7.6, 7.7 and 7.11 of Dr Mozen's statement, **WITN6407003**
[251] Sections 7.11 and 7.12 of Dr Mozen's statement, **WITN6407003**
[252] 29 February 1984, Cutter UK internal communication [**Other/8/547**], **BAYP0000026_067**
[253] Section 7.7 of Dr Mozen's statement, **WITN6407003**
[254] Section 7.12 of Dr Mozen's statement, **WITN6407003**
[255] Gallo *et al.* 'Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS.' Sci 224:500-502 (1984) [**Other/8/504**], **PRSE0001131**

CDC, which proved that retroviruses (including the AIDS virus in the McDougal study), could be inactivated by heat **[PRSE0001941]**.[256]

160. In June 1986, at the XVII International Congress of the WFH in Milan, Professor Allain of the Centre National Transfusion Sanguine and the Haemophilia Treatment Centre in Paris, presented the abstract of a study he and colleagues had conducted. Professor Allain concluded that the study demonstrated that Koate HT did not transmit the AIDS virus (then known as HTLV-III) and was associated with a low risk of transmitting NANB hepatitis **[BAYP0000010_173]**.[257]

161. A copy of the full report of Professor Allain's study indicates that no evidence of HTLV-III transmission was seen in any patient, but the study did show evidence of NANB hepatitis in two patients **[BAYP0005892]**.[258]

162. Despite the favourable results in terms of eradication of HIV/HTLV-III, Cutter Inc continued to modify and try to improve its viral inactivation processes in order to develop a product that eradicated hepatitis. It completed its second wet heat treatment process to develop Koate HS and also developed Koate HP, which utilised a solvent/detergent process using try-n-butyl phosphate ("TNPB") and polysorbate 80 to inactivate viruses. Details of the applications for approval of Koate HS and Koate HP in the UK are provided at paragraphs 241 to 248 and 249 to 257, respectively. Cutter Inc also went on to develop its recombinant DNA product, Kogenate. In an internal letter of September 1984, it was said that *"[w]e believe Cutter will have the first commercially available Factor VIII product from recombinant DNA technology"* **[BAYP0005399]**.[259] Kogenate was licensed in the UK in May 1994 (see paragraph 259 below).

Discussion of studies

163. The earliest document I have identified in the materials available to me in which Cutter UK provided information to clinicians regarding viral inactivation studies is a letter of 29 November 1984 to Professor Bloom. The letter states that Koate HT (at that time unlicensed) was available, the price and attaches *"some references relating to viral inactivation studies carried out by Cutter Laboratories"*. However, the references are not present in the materials

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[256] McDougal *et al.* "Thermal inactivation of the Acquired Immunodeficiency Syndrome Virus, Human T Lymphotropic Virus-III/Lymphadenopathy-associated Virus, with Special Reference to Antihemophilic Factor". Journal of Clinical Investigations Volume 76, August 1985: 875-877 [**Other/12/951**], **PRSE0001941**

[257] Allain *et al.* Clinical Evaluation of a heat-treated high purity Factor VIII concentrate, undated [**Other/15/1561**], **BAYP0000010_173**

[258] 30 January 1987, Cutter Inc handwritten note enclosing correspondence and documentation regarding PL for Koate-HT [**Miles Inc/30/2951**], **BAYP0005892**

[259] 11 September 1984, Cutter Inc memorandum [**Miles Inc/23/2258**], **BAYP0005399**

[BAYP0000025_081].[260]

164. By early 1985, Cutter UK was providing to clinicians a "Viral Inactivation Studies" booklet **[NHBT0096602_053]**.[261]

165. Cutter UK also wrote to NHS bodies providing viral inactivation data. For example, on 26 March 1985, Cutter UK wrote to the National Blood Transfusion Service with information about ARV studies in lyophilised AHF concentrates. The information concluded that *"prolonged heating for at least 72 hours would be expected to bring about the inactivation of LAV or AIDS related virus."* **[BAYP0000024_252]**.[262]

166. On 18 February 1986, Cutter UK wrote to Mr Martin of the Bristol Royal Infirmary enclosing a booklet *"on the inactivation of AIDS-associated* viruses *in Factor VIII concentrates and the effectiveness of heat treatment"* and stated that Cutter Inc's heat treatment process (72 hours at 68 degrees) *"adds a considerable margin of safety to Dr. Levy's inactivation times"* **[WITN6984046]**.[263]

167. In October 1986, Cutter UK provided data on virus inactivation by the Koate HT heating process to various clinicians who (according to the cover letters) had probably received Koate HT. In addition to the "Viral Inactivation Studies" booklet, a second booklet the "Inactivation of AIDS-associated viruses in antihemophilic factor products" was attached **[ARMO0000428]**.[264] The two booklets provided were said to *"cover the elimination of the AIDS virus".* In addition, it was stated that *"The study by Professor Allain shows that there is no risk of AIDS transmission and a low risk of transmission of Non A Non B hepatitis (found to be 40%)"* **[BAYP0000009_022]**,[265] **[BAYP0000009_021]**,[266] **[BAYP0000009_035]**. [267]

168. In addition, on 21 October 1986, Cutter UK sent the same letter to Dr Prentice (Plymouth), Dr Lee (Exeter), Dr Smith (Bath) and Dr Gardiner (Bath) enclosing a "Home Treatment Pack", an "Inactivation Booklet", the "Harold book", and a copy of the "Allain abstract". The letter stated:

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[260] 29 November 1984, Letter from Cutter UK to Professor Bloom [**Other/10/682**], **BAYP0000025_081**
[261] 1985, Dr Milton Mozen "Viral Inactivation Studies" [**Other/8/496**], **NHBT0096602_053**
[262] 26 March 1985, Letter from Cutter UK to the National Blood Transfusion Service [**Other/11/822**], **BAYP0000024_252**
[263] 18 February 1986, Letter from Cutter UK to Bristol Royal Infirmary [**Other/13/1110**], [**WITN6984046**]
[264] 1986, Cutter Biological document titled 'Inactivation of AIDS-associated viruses in antihemophilic factor products: The effectiveness of heat treatment' [**Miles Inc/29/2934**], **ARMO0000428**
[265] 15 October 1986, Letter from Cutter UK to Kingston General Hospital [**Other/14/1368**], **BAYP0000009_022**
[266] 14 October 1986, Letter from Cutter UK to Dr Barlow [**Other/14/1367**], **BAYP0000009_021**
[267] 24 October 1986, Letter from Cutter UK to Dr Wylie [**Other/14/1381**], **BAYP0000009_035**

*"**Virus Inactivation Studies: HIV***

It has been demonstrated that an HTLVIII inoculum of 10^6 infectious particles/ml in the pre-lyophilised factor VIII concentrate is eliminated by the process used for production of Koate HT. Following lyophilisation and heat-treatment at 68°C for 72 hours, no virus was detectable in the final product (Ref. McDougal et al, 1986 and J. Levy et al, 1985). Please see the inactivation booklet for a summary of results.

A clinical study conducted by a haemophilia study group in France, under the direction of Professor J.D. Allain provides further evidence that Koate HT carries no risk of transmission of HTLV (LAV). 11 patients with haemophilia A, 6 of whom had not been previously exposed to blood products were entered into this study and followed-up for up to 12 months following the initial infusion of Koate HT. No other blood product was given during the study. After at least 6 months, none of the patients studied for that period had developed antibodies to HTLVIII (LAV). (Abstract of paper presented at XVII International Congress of the World Federation of Haemophilia, Milan, June 1986).

The full report is not yet available but the data presented in Milan indicate that the heat-treatment process used in the production of Koate HT is effective in eliminating HTLVIII and also results in a significant reduction in the incidence of Non-A, Non-B hepatitis in haemophilic recipients.

The initial Non-A, Non-B viral inactivation studies carried out on Koate HT included a study in chimpanzees to demonstrate the effect of the heat-treatment process on the infectivity of non-A, non-B hepatitis. There was no evidence of hepatitis over a period of 15 weeks in animals inoculated with Koate HT which had been spiked with 2500 CID (chimpanzee infective dose) of NANB hepatitis virus prior to lyophilisation.

Further evidence of absence of non-A, non-B hepatitis and HTLVIII infectivity is obtained from clinical use of the product. Since it was first marketed in the USA in February 1984 and in the UK since February 1985, no reports of hepatitis non-A, non-B or HTLVIII antibody seroconversion in patients treated with Koate HT have been received from these or other markets worldwide." **[BAYP0000009_030]**.[268]

E. Named-patient supply

169. The legislative basis that permitted an unlicensed product to be imported into the UK for use by a designated doctor for a specific patient is set out in **Annex**

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[268] 21 October 1986, Letter from Cutter UK to Dr Prentice, et al [**Other/14/1376**], **BAYP0000009_030**

A.

170. At various times, Cutter UK provided Koate HT, Koate HS, Koate HP and Konyne HT to specific clinicians in the UK on a named-patient basis. As set out in section F, where Koate HT, Koate HS and Konyne HT were provided on a named-patient basis, an application for a product licence was promptly made. In cases of Koate HT, Koate HS and Koate HP clinical trials were ongoing.

171. It is apparent from the documents available that health authorities invited tenders for unlicensed products to be provided on a named-patient basis. For example, the letter of 21 December 1984 from Newcastle Health Authority invited Cutter UK to compete in a tender for 3 million lots of heat-treated factor VIII **[BAYP0000025_112]**.[269] In reply, Cutter UK set out the nominal value potencies of Koate HT (at the time unlicensed) that it had available and stated *"Konyne HT, a Factor IX heat treated concentrate is also available. The vial presentation has a nominal value of 500 international units"* **[BAYP0000024_027]**.[270] As set out in **Annex A**, it was permissible to inform a purchaser or clinician of the availability of a product on an unlicensed basis, and the price of the product, so long as no product claims were made.

172. On 18 May 1988, Bayer UK spoke with Dr Rotblat, DHSS Medical Assessor for Biological Products, regarding the named-patient supply of blood products. Seemingly Dr Rotblat said that *"twenty-five doses of a blood product can be imported at a time for named patient supply, in the same way as for any other product according to the import licence exemption scheme"*. One detail Dr Rotblat required was that the *"letter applying for permission to import includes confirmation that the product was sourced from an HGIV[sic]-tested donor"*. Otherwise, there were said to be no extra provisions. Any product specifically imported would apparently not be tested by NIBSC. Dr Rotblat is reported as saying that it would be a good idea to emphasis to the relevant doctor that the product was not licensed and that the doctor had to take full responsibility for any consequences of the treatment, almost more so than for "ordinary" pharmaceuticals. Dr Rotblat was said to have commented that if there was an outbreak of hepatitis B, she would be extremely concerned as this should not be in products nowadays, but with hepatitis A she would not be so concerned. Similarly, she would not be concerned with one or two isolated cases, whereas an outbreak which could be traced to one batch could lead to her asking Cutter

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[269] 21 December 1984, Letter from Newcastle Health Authority to Cutter UK [**Other/10/713**], **BAYP0000025_112**

[270] 14 January 1985, Letter from Cutter UK to Newcastle Health Authority [**Other/11/741**], **BAYP0000024_027**

UK to withdraw that batch **[WITN6984035]**.[271]

F. Withdrawal of Koate and switch to Koate HT

173. On 29 February 1984, Cutter Inc received a licence from the FDA to sell heat-treated Koate ("**Koate HT**") in the US **[BAYP0000026_067]**.[272] The plan in the UK was for a third of all Koate sales in 1984 to be of heat-treated product **[BAYP0000026_008]**.[273] However, in October 1983 it was noted that:

> *"The market is confused at present because of A.I.D.S. The recent death of a haemophiliac.....means that plans to conduct trials with H.T commercial concentrates have been postponed because centres are unwilling to use such products now for treating virgin haemophiliacs....opinions of the leading Directors appear to vary between trying to eliminate the use of commercial concentrate and wanting to switch many patients to a satisfactory heat treated product"* **[BAYP0000026_008]**.[274]

174. Cutter UK's 1984 marketing plan stated that a clinical trial exemption certificate for heat-treated Koate would be obtained and the product would then be sold on a "prescription only" basis (this was presumably meant to refer to supply on a "named-patient" basis) until a full product licence had been granted **[BAYP0000026_008]**.[275]

175. An application for a product licence for Koate HT was made to DHSS on 13 November 1984 **[BAYP0000008_064]**.[276] Cutter UK had anticipated that licensed Koate HT would be launched on the UK market during the second quarter of 1985. However, it made what was described as a "hasty" appearance on a named-patient basis at the end of November 1984, replacing all non heat treated material **[CGRA0000554]**.[277] This escalation in timelines is probably explained by the content of an internal report dated 30 November 1984:

> *"AIDS has finally come to the United Kingdom with a force that has caused a virtual panic in the Department of Health. For one year this department has blocked every application for registration of its heat-treated factor VIII products and now in the space of one week they are in a panic responding to the newspaper demand for action concerning the AIDS risk to hemophiliacs*

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[271] 18 May 1988, Note of a telephone conversation between Bayer UK and DHSS [**Other/16/1649**], [**WITN6984035**]
[272] On 29 February 1984, Cutter Inc received a licence from the FDA to sell heat-treated Koate ("**Koate HT**") [**Other/8/547**], **BAYP0000026_067**
[273] October 1983, 1984 Cutter UK marketing plan [**Other/8/500**], **BAYP0000026_008**
[274] October 1983, 1984 Cutter UK marketing plan [**Other/8/500**], **BAYP0000026_008**
[275] October 1983, 1984 Cutter UK marketing plan [**Other/8/500**], **BAYP0000026_008**
[276] 18 February 1985, Product licence for Koate HT PL 0055/0107 [**Reg/3/199**], **BAYP0000008_064**
[277] January 1985, Cutter UK, Year End Review and Reports [**Other/11/728**], **CGRA0000554**

[…] Following these headlines the Department of Health has advised Cutter that every action will be taken to grant us registration by early December […]The Hemophilia Treatment Centres are now also responding to the newspaper stimulus and requesting heat-treated Koate on a named patient basis. Cutter UK had in inventory 1000 vials of 500 I.U. Koate H.T. which has now been allocated and requests for other sizes have been received from the treatment centres." **[BAYP0000025_087]**[278]

176. It is apparent that in January 1985, Cutter UK was exchanging stocks of Koate for Koate HT and it was expected that this would be, for the most part, complete by the end of February 1985 **[BAYP0000024_090]**,[279] **[BAYP0000026_008]**.[280]

177. By February 1985, the UK market for Koate had been converted to heat-treated product (presumably on a named-patient basis during the period prior to grant of the product licence on 18 February 1985) and therefore presumably no further non-heat-treated Koate was sold **[BAYP0000024_114]**.[281] This is confirmed by a letter dated 13 March 1985, in which Cutter UK refused to sell Koate to the UK market stating *"dramatic changes have taken place in the United Kingdom regarding heat-treated factor VIII products. Therefore, we at Cutter feel it is prudent to no longer effect sales of non-heat-treated product for use in the United Kingdom"* **[BAYP0000024_113]**.[282]

178. A letter dated 31 December 1985, from Cutter UK to Oxford Regional Health Authority said:

"Towards the end of 1984 and the beginning of 1985, (November to February), all the Haemophilia Centres in the U.K. changed from non heat-treated Factor VIII (Koate) to heat-treated material because they realised that the heat-treatment of Factor concentrates inactivates the HTLVIII/LAV (AIDS) virus. Cutter Laboratories were asked by all Haemophilia Centres to henceforward supply only heat-treated product.

The majority of Centres returned their non heat-treated Koate material to us and we replaced with Koate HT on request.

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[278] 30 November 1984, Cutter UK memo [**Other/10/688**], **BAYP0000025_087**
[279] March 1985, Interoffice Communication re 'Cutter UK - Key Indicator Report - January 1985' [**Other/11/792**], **BAYP0000024_090**
[280] October 1983, 1984 Cutter UK marketing plan [**Other/8/500**], **BAYP0000026_008**
[281] 13 March 1985, Cutter Inc/Cutter UK Internal Memorandum [**Other/11/806**], **BAYP0000024_114**
[282] 13 March 1985, Letter from Cutter Inc to St Thomas' Hospital [**Other/11/805**], **BAYP0000024_113**

Communications were made with Oxford Haemophilia Centre and they were informed that the price for Koate HT would be 12 pence per International Unit before they had ordered any.

The material was sold on prescription on a named patient basis until our licence was obtained from the DHSS in April, 1986" (note, this would appear to be an incorrect date stated by the author; the licence was granted in February 1985, see paragraph 177 above) [**WITN6984047**].[283]

G. Interactions with DHSS and NIBSC

179. As stated in Wilkinson, neither Bayer nor any company that Bayer has at any time owned or controlled has manufactured products from pooled plasma [**WITN2988001**].[284] However, as described in Wilkinson, at one time Bayer did apply for a product licence entitling it to place such a product in the UK market and it has supplied services to Bayer group affiliates that have been responsible for the supply of such products in the UK.

180. In summary, the documents show that Cutter UK was in constant communication with DHSS, or the relevant body at the time. From the first licence application for Koate, DHSS was made aware that Cutter Inc only manufactured Koate from plasma collected from donors at Cutter-owned and affiliated donor centres in the US and had a list of all plasma centres used to source plasma. At all times, product for the UK market was to be manufactured by Cutter Inc at either of its sites in Berkeley, California, or Clayton, North California, and these sites were inspected by UK authorities (for examples see paragraphs 197 and 233 below). Cutter UK was in communication with DHSS regarding product licence applications, permission to conduct clinical trials (and arrangements thereof) and importation of product on a named-patient basis. As knowledge of potential viral transmission with blood products increased, and additional precautions were taken by Cutter Inc, Cutter UK updated DHSS, answered questions from DHSS and, where necessary, made variation applications for its product licences. In addition, as set out in section C, Cutter UK also communicated suspected adverse events to DHSS, or the relevant body at the time.

181. Cutter UK was also in communication with the NIBSC regarding the requirements for testing and release of product onto the UK market. All product that reached the UK market was required by law to undergo the batch release

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[283] 31 December 1985, Letter from Cutter UK to Oxford Regional Health Authority [**Other/12/1067**], [**WITN6984047**]
[284] Wilkinson, **WITN2988001**

procedure of NIBSC (see **Annex A**).

Koate

Koate PL 0010/0061 (prior to grant)

182. On 16 October 1975, Bayer UK submitted to DHSS an abridged product licence application (reference number PL/0010/0061 **[WITN6984048]**[285], **[WITN6984049]**[286] for "Antihemophilic Factor (Human) Koate™" ("**Koate**") for the treatment of haemophilia A, cross-referring to published literature reporting on clinical trials and studies. The application included details of manufacture of the product including source material, testing of final product, summary of accumulative clinical experience, clinical evaluation and a summary of individual clinical studies **[BAYP0000001_098]**.[287]

183. Cutter Inc had previously provided undertakings and declarations under section19(3) of the Medicines Act 1968 (a summary of the relevant legislation applicable at the time is contained at **Annex A**) to DHSS approving designated premises for storing or manufacturing medicinal product and the operations carried on in the course of manufacturing and to comply with any conditions attached to the product licence in relation to the manufacture of the product **[BAYP0000001_094]**,[288] **[WITN6984050]**.[289]

184. In addition, prior to the application being made, DHSS had asked Bayer UK for information about the number of donations that were included in the pool from which each preparation of Koate was obtained *"because of the hepatitis risk"* **[BAYP0000001_097]**.[290] The response is not present in the papers, but information on the size of plasma pools is at paragraphs 70-77 above.

185. Cutter Inc provided Bayer UK with further data concerning the occurrence of hepatitis after administration of Koate and a copy of reference number four of the package insert (Kasper CK, Kipnis SA: Hepatitis and clotting-factor concentrates, JAMA, 221:510, 1972). No cases of hepatitis had been reported in any of the 33 patients (166 infusions) administered with Koate in clinical evaluations of the product and Cutter Inc had received no reports attributing hepatitis to Koate since its introduction in the US in February 1974

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[285] 16 October 1975, Letter from Bayer UK to the DHSS **[Reg/1/6]**, **[WITN6984048]**
[286] 23 October 1975, Letter from DHSS to Bayer UK **[Reg/1/7]**, **[WITN6984049]**
[287] October 1975, Product Licence Application (Abridged) File 1 **[Reg/1/4]**, **BAYP0000001_098**
[288] 11 June 1975, Two undertakings and declarations under section 19(3) of the Medicines Act 1968 **[Reg/1/1]**, **BAYP0000001_094**
[289] 31 October 1975, Internal Cutter Inc memo **[Other/1/62]**, **[WITN6984050]**
[290] 13 August 1975, Letter from Bayer UK to Cutter Inc re DHSS requirements **[Reg/1/3]**, **BAYP0000001_097**

[WITN6984051].[291]

186. Each plasma donation used to produce Koate at that time was tested in accordance with regulations of the US FDA **[WITN6984052]**.[292] Bulk product also underwent testing **[WITN6984053]**.[293]

187. Following submission of the product licence application, DHSS informed Bayer UK that the Minister for Health was "personally vetting all submissions on Factor VIII because there is a lot of publicity and emotional feeling about this at the moment". It was also stated that the price of the product would be important and would probably affect the success of the application DHSS was of the view that the product "look[ed] good" because each plasma donation was tested for hepatitis and there had been no reported cases of hepatitis since its introduction in the US **[BAYP0000022_097]**.[294]

188. Koate was considered by the Biologicals Subcommittee of the CSM in January 1976, and on 2 February 1976, DHSS informed Bayer UK that grant of the product licence for Koate (PL/0010/0061) had been advised subject to provision of certain information requested under section 44 of the Medicines Act 1968, namely:

> *"1. Satisfactory information is provided on:*
> *a) The number of donations in each pool;*
> *[….]*
> *4. On-going information is provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre.*
> *5. The applicant shall agree to the imposition of the batch release procedure, to be applied at the licensing authority's discretion."* **[BAYP0000001_110]** [295]

189. Cutter Inc provided information dated 23 February 1976 to Bayer UK by way of a letter dated25 February 1976. It was stated that Cutter Inc did not collect information about the rejection of plasma donors, but that plasma was collected in accordance with the US Code of Federal Regulations (the relevant legislation pertaining to collection of plasma, and the manufacture of plasma products in the US is set out in **Annex B**). All plasmapheresis donors had to be acceptable according to the criteria described in the Regulations and all centres from which source material was obtained had to be licensed by the US FDA. The FDA

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[291] 25 August 1975, Internal Cutter Inc memo re Koate registration [**Other/1/56**], [**WITN6984051**]
[292] 16 December 1975, Telex from Cutter Inc to Bayer UK [**Other/1/69**], [**WITN6984052**]
[293] 23 December 1975, Telex from Cutter Inc to Bayer UK [**Other/1/70**], [**WITN6984053**]
[294] 24 December 1975, Bayer UK Internal memo, 'Koate - telephone conversation with DHSS' [**Other/2/71**], **BAYP0000022_097**
[295] 2 February 1976, Letter from DHSS to Bayer UK 'Anti-Haemophilic Factor (Human) Koate - PL/0010/0061' [**Reg/1/15**], **BAYP0000001_110**

therefore sought to ensure that all donors and units of human source plasma were handled according to the Regulations which stipulated that only HBsAg screened units of source plasma from healthy donors could be used in the manufacture of licensed biological products such as Koate. Cutter Inc also stated that it would object to the batch release procedure because it considered that *"any additional routine testing would be redundant and would result in unnecessary waste of this valuable drug".* Cutter Inc did however state that if required it would provide complete summaries of all testing performed on Koate prior to release on a lot-by-lot basis **[WITN6984054]**,[296] **BAYP0000001_113**.[297]

190. On 27 February 1976, Bayer UK informed the DHSS by letter that each plasma pool of 2500 litres of plasma was comprised of approximately equal donations from at least 1000 individual donors. A given lot of Koate was produced from 3-5 separate plasma pools combined in solution to form the final product. It was also stated that Cutter Inc had not yet confirmed they would provide ongoing information about the rejection of donors or donations centre by centre nor had they yet agreed to the imposition of the batch release procedure **[IPSN0000312_109]**.[298]

191. On 18 August 1976, Bayer UK withdrew the pending licence application (PL/0010/0061) for Koate as *"the importation and marketing of Koate was to be solely in the hands of Speywood Laboratories*". Bayer confirmed that it had no objection to the data submitted by Bayer UK in connection with application PL/0010/0061 being considered in the assessment of the imminent application for a product licence from Speywood **[WITN6984055]**.[299]

Koate PL 3070/0004

192. On 27 August 1976, PL 3070/0004 for Koate was granted **[BAYP0000020_051]**.[300] Prior to grant, the product licence application had been assigned to Tuta Laboratories (UK) Ltd ("Tuta") with Speywood as the distributor **[WITN2988001]**.[301] The product licence was conditional upon compliance by Cutter Inc with the protocol for batch release agreed with DHSS **[WITN6984056]**.[302] Speywood subsequently distributed Koate in the UK for four years **[BAYP0000021_062]**.[303]

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[296] 25 February 1976, Letter from Cutter Inc to Bayer UK re 'Product Licence Application for Koate in the UK' [**Other/2/82**], [**WITN6984054**]
[297] 23 February 1976, Memo from Cutter Inc to Cutter UK Reg/1/17, **BAYP0000001_113**
[298] 27 February 1976, Letter from Bayer UK to DHSS [**Reg/1/16**], **IPSN0000312_109**
[299] 18 August 1976, Letter from Bayer UK to DHSS [**Reg/1/27**], [**WITN6984055**]
[300] 27 August 1976, Telex from Speywood Laboratories [**Other/2/117**], **BAYP0000020_051**
[301] Wilkinson, paragraph 16, **WITN2988001**
[302] 27 August 1976, Telex from Speywood to Cutter Inc [**Other/2/117**], [**WITN6984056**]
[303] 31 October 1980, Cutter Inc memo [**Other/3/178**], **BAYP0000021_062**

193. Bayer UK was not involved in the supply of Koate under PL 3070/0004 and has very little information in relation to such supply from the end of August 1976 to November 1979.

Koate PL 1605/0004

194. During the latter half of 1979, a decision was taken to terminate Speywood's distribution of Koate and an application was made to transfer the product licence to Cutter Laboratories Limited ("Cutter Ltd") **[WITN6984057]**,[304] **[WITN2988001]**.[305]

195. On 10 June 1980, DHSS granted product licence PL 1605/0004 to Cutter Ltd for Koate for the treatment of haemophilia A **[BAYP0000001_142]**.[306] The protocol for UK batch release of Koate supplied under licence PL 1605/0004 included the tests to be performed by Cutter Inc. Prior to release, samples from each batch had to undergo examination by NIBSC and a certificate had to be issued authorising that batch for sale or supply **[WITN6984058]**.[307]

196. On 19 October 1982, Cutter Ltd informed DHSS that, on 31 October 1982, it would be acquired by Miles Laboratories Ltd. Henceforth the company represented itself as the Cutter division of Miles Laboratories Ltd ("Cutter UK"). Cutter UK informed DHSS that Cutter UK should therefore hold a licence for Koate as soon as possible **[WITN6984059]**.[308] On the same day, Cutter UK applied for a product licence for Koate and confirmed that the particulars of the product conformed in all respects to Koate PL 1605/0004. Cutter UK stated that it would become the appointed distributor of Koate PL 1605/0004 from 1 November 1982, until such time as it was granted a product licence as *"an interim arrangement in the absence of statutory provisions for the transfer of licences"* **[WITN6984060]**.[309] From 1 November 1982, to the date of the grant of a re-issued product licence, Cutter UK retained full regulatory responsibility for Koate with Cutter UK acting as the UK distributor **[WITN6984061]**, [310] **[WITN2988001]**.[311]

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[304] 1980, Cutter UK, Year End Review and Report, page 5 [**Other/3/148**], [**WITN6984057**]
[305] As explained in Wilkinson, **WITN2988001**, it appears that following the termination, Speywood nevertheless managed to source Koate through wholesalers and imported it into the UK and supplied it until about March 1981 under the name Humanate, having removed the Koate labels and relabelled it as Humanate (Wilkinson, paragraph 16, **WITN2988001**)
[306] 10 June 1980, Product licence for Koate PL 1 605/0004 granted to Cutter Inc [**Reg/1/40**], **BAYP0000001_142**
[307] 22 September 1982/5 August 1982, NIBSC UK Batch Release Certificate and Protocol for release of Lot No. NC 8413 [**Reg/1/47**], [**WITN6984058**]
[308] 19 October 1982, Letter from Cutter UK to DHSS [**Reg/1/51**], [**WITN6984059**]
[309] 19 October 1982, Letter from Cutter Inc to DHSS [**Reg/1/50**], [**WITN6984060**]
[310] 25 October 1982, Letter from Cutter UK to DHSS [**Reg/1/54**], [**WITN6984061**]
[311] Wilkinson, paragraph 9, **WITN2988001**

197. Cutter Inc's manufacturing facilities were inspected by DHSS in or around November 1982 **[WITN6984062]**.[312]

Koate PL 0055/0065

198. In or around March 1983, Cutter UK submitted to DHSS a revised submission in support of its application for a product licence for Koate **[WITN6984063]**.[313] The application included (*inter alia):* confirmation that all units of plasma used for the preparation of Koate were tested and found negative for HBsAg **[WITN6984064]**;[314] details of source material, manufacture, testing and stability, and confirmation that the plasma was collected from donors who were healthy **[WITN6984065]**;[315] and FDA guidelines applicable to plasmapheresis including the methods of determining suitability of each plasma donor and the requirement that each unit of source plasma should be non-reactive to a test for HBsAg **[BAYP0000002_167]**.[316]

199. During this period, the possibility that the agent responsible for AIDS might be transmitted through blood and blood products was under consideration by the regulators. On 17 May 1983, Cutter UK provided DHSS with copies of documents issued by Cutter Inc concerning the procedures for collection of plasma at its centres in the US, including the physical examination of donors, notices displayed at plasma collection centres and literature relating to AIDS **[WITN6984066]**.[317]

200. On 26 May 1983, DHSS sought information, under section 44 of the Medicines Act 1968 related to: the precautions taken to exclude donors who might transmit AIDS; any reports of patients who had received Koate exhibiting AIDS or a similar illness; and any reports of donors who had provided blood for the manufacture of Koate and subsequently developed AIDS or an AIDS like illness **[BAYP0000002_182]**.[318]

201. Cutter UK responded to this request on 3 June 1983, based on information provided by Dr J. N. Ashworth PhD, Division Vice President, Scientific Affairs of Cutter Inc, that all donors were screened to an extent consistent with present medical-scientific knowledge and that Cutter Inc's investigations indicated that

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[312] 13 December 1982, Letter from Cutter UK to DHSS [**Reg/1/59**], [**WITN6984062**]
[313] 18 March 1983, Letter from DHSS to Cutter UK regarding PL submission [**Reg/2/75**], [**WITN6984063**]
[314] 9 March 1983, Cutter Inc memo to Cutter UK enclosing UK product licence application, section 3.2.1(a) [**Reg/2/65**], [**WITN6984064**]
[315] 9 March 1983, Attachment 3 to the UK product licence application PL 1605/0004 [**Reg/2/67**], [**WITN6984065**]
[316] 9 March 1983, Attachment 4 to the UK product licence application PL 1605/0004, (section 3.1.2) [**Reg/2/68**], **BAYP0000002_167** [First 13 pages only]
[317] 17 May 1983, Letter from Cutter UK to the DHSS [**Reg/2/78**], [**WITN6984066**]
[318] 26 May 1983, Letter from DHSS to Cutter UK [**Reg/2/80**], **BAYP0000002_182**

none of the cases of AIDS in haemophilia patients had received Koate. At that stage, Cutter Inc had not had to decide what would be done with a Koate lot that included plasma from a donor who was subsequently diagnosed with AIDS. Cutter UK advised DHSS that should this circumstance occur, the decision concerning the Koate lot would depend on many factors including, most importantly, receipt of advice from government health authorities based on the latest knowledge concerning AIDS **[BAYP0000002_183]**.[319]

202. Further queries were raised by the DHSS in a telex of 16 June 1983 concerning the location of plasma collection centres in relation to the high-risk areas for AIDS, donor screening, pooling of plasma, and compliance with the FDA Directive of 23 March 1983 **[BAYP0000002_185]**.[320] A telex reply with the information requested was sent on 17 June 1983. In particular, it was confirmed that:

202.1 Cutter Inc was able to identify the origin of plasma included in each batch of final product and the date on which it was collected;

202.2 there were no Cutter Inc owned or affiliated donor centres in New York, San Francisco, Los Angeles or Miami (areas considered at highest risk of AIDS transmission);

202.3 Cutter Inc implemented the FDA Directive on 1 March 1983, although general screening procedures that would have identified typically AIDS-like symptoms had been in place for many years; and

202.4 it was expected that plasma produced under the new FDA Directive would be available in the UK from August 1983 **[WITN6984067]**.[321]

203. Following a telephone request from DHSS, on 26 July 1983 Cutter UK sent to DHSS the December 1981 version of the CSOP , Cutter UK's Medical Director stated that:

> *"With regard to the three main clinical criteria for screening AIDS, ie. rapid weight loss, temperature swings and lymphadenopathy you will note that the previous document dealt with the first two but did not relate lymphadenopathy specifically to AIDS, since obviously it was not an issue at that time.*
>
> *In all other respects the 1981 document is identical with our current one."* **[BAYP0000002_192]**.[322]

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[319] 3 June 1983, Letter from Cutter UK to DHSS **[Reg/2/81]**, **BAYP0000002_183**
[320] 16 June 1983, Telex from DHSS to Cutter UK [**Reg/2/83**], **BAYP0000002_185**
[321] 17 June 1983, Telex from Cutter UK to DHSS [**Reg/2/84**], [**WITN6984067**]
[322] 26 July 1983, Letter from Cutter UK to DHSS regarding Cutter Inc previous procedure on plasmapheresis [**Reg/2/90**], **BAYP0000002_192** [Letter only]

204. The first batches of Koate authorised under PL 0055/0065 were authorised for release by NIBSC on 6 September 1983 **[WITN6984068]**.[323]

205. In January 1984, following a meeting at NIBSC a revised procedure for labelling and submission of samples to the NIBSC for testing and release on the UK market was suggested (it is not clear by whom). Three vials of each lot were to be sent to NIBSC by Cutter Inc for testing with current labels bearing correct UK codes. Once released, labelling, packaging and shipment of the entire lot was to be arranged and, when the consignment reached the UK, the NIBSC was to be sent one further vial in final packaging for their records **[WITN6984069]**.[324]

Koate HT

206. On 29 February 1984, Cutter Inc received a licence from the FDA to sell heat-treated Koate ("**Koate HT**") **[BAYP0000026_067]**.[325] The application had been made on 21 November 1983 as an amendment to the existing product licence for Koate to include an optional step to "dry" heat-treat lyophilized antihaemophilic factor in final containers **[WITN6984070]**.[326]

207. On 2 August 1984, Cutter UK notified DHSS of a clinical trial for Koate HT manufactured by Cutter Inc and imported into the UK by Cutter UK. The notice stated that:

> *"The purpose of the study is to investigate the incidence of Hepatitis in haemophiliacs following infusion of Koate HT"* **[WITN6984071]**.[327]

208. It was intended that the duration of the trial would be 9 months, following each patient's first exposure to Koate HT and it was stated that:

> *"If interim results show a high incidence of Hepatitis in the group under investigation, the trial will be stopped."* **[BAYP0000003_247]**[328]

209. Dr Peter Jones, Director of the Newcastle Haemophilia Centre, was named as the investigator. The scientific data in support of the clinical trial included a section on virus inactivation studies, which referred to inactivation of a number of specific viruses, and stated that:

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[323] 6 September 1983, NIBSC UK Batch Release Certificates - Koate (Factor VIII) - Batch No. NC 8497 A, NC 8498 A and NC 8502 A [**Reg/2/98 - 100**], [**WITN6984068**]
[324] 16 January 1984, Cutter Inc Telex re 'Koate Labels/NIBSC Testing' [**Other/8/534**], [**WITN6984069**]
[325] 29 February 1984, Cutter UK internal communication [**Other/8/547**], **BAYP0000026_067**
[326] 30 November 1983, Cutter UK internal note [**Other/7/474**], [**WITN6984070**]
[327] 2 August 1984, Letter from Cutter UK to DHSS [**Reg/3/152**], [**WITN6984071**]
[328] 2 August 1984, Form MLA 164 [**Reg/3/152**], **BAYP0000003_247**

"The results demonstrate that selected viruses are inactivated by the Koate HT process, and by inference, other viruses may also be inactivated."

210. The notice stated:

"The source material is pooled plasma obtained from at least 1000 healthy donors. It is collected by plasmapheresis at centres in the U.S.A licensed by the FDA and inspected by both the FDA and Cutter Laboratories to ensure compliance with the Code of Federal Regulations.

The plasma is collected according to the Cutter system of Plasmapheresis which incorporates all the current FDA requirements for Source Plasma (Human), including testing for Hepatitis B Surface Antigen. In addition, Cutter test samples from all new donors for Antibody to Hepatitis B Core Antigen. This test is also used at four monthly intervals for testing samples from repeat donors.
The plasma is immediately frozen after collection and stored in the frozen state until used in production."
[….]
"All quality control will be exercised by the manufacturer, Cutter Laboratories, USA, Miles Laboratories will maintain the necessary documentation to verify acceptable batch quality"
[….]
"All units of plasma are tested for Hepatitis B Surface Antigen prior to pooling using radioimmunoassay (AUSRIA).
The method used for testing for Antibody to Hepatitis B Core Antigen is an enzyme linked immunosorbent assay for total gammaglobulin to HBcAg (CORZYME).
All additives are tested for compliance with USP requirements and, in addition, for compliance with the USP test for absence of pyrogens." **[BAYP0000003_247]**[329]

211. On 30 August 1984, the Licensing Authority responded that it had no objection to the trial, granting a CTX from 1st September 1984 for three years. It was further stated that:

"The Licensing Authority would like you to note that adequate information should be submitted on the following by PL stage: -
i) evidence of the effect of heat-treatment on infectivity;
ii) justification for the inclusion and choice of heat-treatment;

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[329] 2 August 1984, MLA 164, internal page 4, 9 & 11 **[Reg/3/152, attachment]**, **BAYP0000003_247**

iii) suitable characterisation of the heat-treated product" **[BAYP0000003_250]**.[330]

212. Cutter UK requested this information from Cutter Inc by telex on 3 September 1984, and received the information on 10 September 1984. The evidence provided to satisfy point i was slides and the transcript of a presentation given by Dr Mozen to the XVI International Congress of the World Federation of Haemophilia, 24-28 August 1984 about heat inactivation of viruses **[WITN6984072]**.[331]

213. On 13 November 1984, Cutter UK submitted to DHSS an abridged application for a product licence for Koate HT, cross-referring to the Koate product licence **[BAYP0000003_268]**,[332] to be manufactured by Cutter Inc with Cutter UK responsible for packaging and labelling. The application was given number PL 0055/0107 **[WITN6984073]**.[333] Cutter UK stated that a variation of the Koate product licence would be in this instance "applicable" as it wished to be able to supply either product to meet the needs of particular clinicians **[BAYP0000003_268]**.[334]

214. The application stated that development of heat-treated Koate was directed towards reducing the risk of transmitting viral diseases, without loss of factor VIII activity and explained that Koate HT had initially been introduced in countries where the regulatory authorities required supply of a heat-treated product, namely the US (since 1984) and Germany (since mid-1983). Koate HT had also been supplied in Japan, Italy and Venezuela **[WITN6984040]**.[335]

215. The application form stated the selected method of heat-treatment, at 68℃ for 72 hours after lyophilisation (i.e., heating in the lyophilised form), had been found to inactivate a number of model viruses without loss of biological activity. The lyophilised powder could be stored for up to three months at room temperature (25℃) when required, such as in home treatment situations **[WITN6984040]**.[336]

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[330] 30 August 1984, Letter from DHSS to Cutter UK [**Reg/3/155**], **BAYP0000003_250**
[331] 10 September 1984, Memo from Cutter Inc to Cutter UK with attachment "Heat Inactivation of Viruses in Antihemophilic Factor Concentrates" by Dr. M. Mozen - presentation before XVI International Congress of the world federation of Haemophilia, 24-28 August 1984 [**Other/10/637**], [**WITN6984072**]
[332] 13 November 1984, Letter from Cutter UK to DHSS enclosing application for a product licence [**Reg/3/167a**], **BAYP0000003_268** [letter only, attachment not included]
[333] 20 November 1984, Cutter UK Telex re Koate HT - UK and product licence application labels [**Other/10/678**], [**WITN6984073**]
[334] 13 November 1984, Letter from Cutter UK to DHSS enclosing application for a product licence [**Reg/3/167**], **BAYP0000003_268** [letter only, attachment not included]
[335] 12 November 1984, Application for a product licence [**Reg/3/167a**], [**WITN6984040**]
[336] 12 November 1984, Application for a product licence [**Reg/3/167a**], [**WITN6984040**]

216. Part III of the application - "Experimental and Biological Studies" - described a study conducted in four chimpanzees to evaluate the effect of the heat treatment process applied to Koate HT on NANB hepatitis. It said:

"The study was designed to demonstrate inactivation of a known quantity of the Hutchinson strain of NANB hepatitis virus and an unknown quantity of endogenous NANB which could be present in dried Factor VIII concentrate.

Samples of the lyophilised Factor VIII concentrate were heated at 68ºC for 72 hours then reconstituted, spiked with Hutchinson strain NANB hepatitis virus, lyophilised and heated again at 68ºC for 72 hours.

One chimpanzee was inoculated with the product at a dose which would be equivalent to 2500CID (chimpanzee infected dose) if no inactivation had occurred.

One animal was inoculated with dry heat-treated Factor IX concentrate spiked as above for the Factor VIII preparation at a dose of 2500 CID.

One control animal received the non-heated Factor VIII concentrate containing this dose level.

A fourth animal received the Factor VIII concentrate which had been heated but not spiked with the NANB hepatitis virus.

There was no evidence of hepatitis over a period of 15 weeks in the chimpanzees inoculated with spiked and heated dried Factor VIII or Factor IX as indicated by transaminase levels or abnormal liver histopathology.

At week 15, these animals were rechallenged with the spiked non-heated preparation and positive liver histopathology was recorded 3 weeks later with elevated transaminase levels peaking at about 11 weeks.

These results demonstrate that these animals were susceptible to NANB hepatitis infection and that the heat-treatment inactivated the NANB spike.

In the chimpanzee used a[s] a positive control, the first evidence of hepatitis was observed in liver biopsy examination at 4 weeks post-inoculation. The peak in ALT levels was at 11 weeks comparable to that seen on rechallenging the other animals.

In the chimpanzee inoculated with heated, unspiked material there was no evidence of hepatitis over a period of 15 weeks. This animal was also rechallenged with unheated material to confirm susceptibility to the presence of endogenous NANB infectivity.

It was calculated that heating at 68°C for 72 hours inactivated a known amount of at least one strain of NANB hepatitis virus a well as an unknown quantity of endogenous NANB hepatitis virus.

The full report of this study is not yet available." **[BAYP0000003_264]**[337]

217. Part IV of the application - "Studies in Humans" - stated that pre-marketing clinical trials using Koate HT had not been performed as the properties of the product had been shown to be unaffected by the heat treatment and the regulatory situation in the US demanded immediate use of the product without awaiting the results of long term trials. However, during the period up to November 1984, 108,000 x 250 IU equivalents of Koate HT had been sold in the five countries listed in paragraph 214 and only one suspected adverse reaction had been reported; this had been a typical anaphylactoid type reaction. In addition, a post-marketing clinical study was at that time being conducted in the US; ten patients had initially been entered into the study one year previously and further patients were then also under observation. After one year of treatment there had been no evidence of NANB hepatitis in these patients **[BAYP0000003_265]**.[338]

218. On 17 January 1985, DHSS wrote to Cutter UK stating that in order to grant the product licence, it required agreement in writing that the data sheet for Koate HT would include a statement that the product had been heated at 68°C for 72 hours, and that this step has been introduced in order to reduce the risk of transmission of infectious agents **[MHRA0014172]**.[339] Cutter UK agreed to include the statement **[BAYP0000003_301]**.[340]

219. DHSS granted the product licence for Koate HT (PL 0055/0107) on 18 February 1985 **[BAYP0000008_064]**.[341] Each batch of the product was assayed independently by NIBSC and a certificate of release was required before the product could be sold consistent with requirements for non-heat-treated Koate **[WITN6984074]**.[342]

220. In March 1985, Cutter Inc made Cutter UK aware of a "Lancet article concerning absence of antibody to HTLV III in haemophiliacs receiving heated Factor VIII" and suggested that "this, along with Cutter's viral inactivation studies should calm some of the worries about AIDS" **[BAYP0000024_250]** &

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[337] 13 November 1984, Application for a product licence, Part III [**Reg/3/165**], **BAYP0000003_264**
[338] November 1984, Product licence application, Part IV [**Reg/4/166**], **BAYP0000003_265**
[339] 17 January 1985, Letter from DHSS to Cutter UK [**Reg/3/192**], **MHRA0014172**
[340] 23 January 1985, Letter from Cutter UK to DHSS [**Reg/3/194**], **BAYP0000003_301**
[341] 18 February 1985, Product licence for Koate HT PL 0055/0107 [**Reg/3/199**], **BAYP0000008_064**
[342] 26 March 1985, Letter from Cutter Inc to Northern Regional Health Authority [**Other/11/823**], [**WITN6984074**]

[BAYP0000024_097].[343] However, there is no correspondence on this article between Cutter UK and DHSS present in the documents available to me.

221. On 31 May 1985, Cutter UK applied to DHSS for a change in the source plasma specification of the Koate HT product licence as follows:

> *"SOURCE PLASMA (HUMAN)*
> *Source plasma is collected according to the Cutter System of plasmapheresis which incorporates all the FDA requirements for Source Plasma (Human) including testing of samples from all donors for antibodies to HTLV III.*
> *Reason*
> *The procedure for screening of donors has been updated in accordance with FDA requirements" (the added wording is underlined)* **[WITN6984075]**.[344]

222. At the request of DHSS **[BAYP0000004_311]**,[345] Cutter UK provided full details of the test method for antibodies to HTLV-III, including the test sensitivity **[WITN6984076]**.[346] The variation was granted on 31 July 1985 **[BAYP0000008_069]**.[347]

223. By this time, Cutter Inc was using the so-called megastandard, MEGA 1, for the factor VIII assay at batch release **[BAYP0000004_294]**.[348] An application for a variation to the Koate HT product licence to incorporate this change was made on 27 May 1985 and granted on 31 July 1985. The amendment read:

> *"Analytical Procedures: Factor VIII Assay*
> *Concentrate standard to be used is the US standard - Antihaemophilic Factor, MEGA 1. (potency 10.2iu/ml) which has been calibrated against the WHO 3rd International Standard for Factor VIII C.*
> *The use of the MEGA standard has been adopted in the U.S.A. at the request of the FDA. The National Institute of Biological Standards & Control was involved in the validation of this standard and accept its use in the assay"* **[BAYP0000006_100]**.[349,350]

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[343] 5 March 1985, Cutter Inc /Cutter UK Internal Memorandum "Trip Report - UK" [**Other/11/796**], **BAYP0000024_250** [memo] & **BAYP0000024_097** [attachment]
[344] 31 May 1985, Notification of change in product licence from Cutter UK to DHSS [**Reg/4/238**], [**WITN6984075**]
[345] 21 June 1985, Letter from DHSS to Cutter UK [**Reg/4/244**], **BAYP0000004_311**
[346] 5 July 1985, Letter from Cutter UK to DHSS [**Reg/4/250**], [enclosures not present] [**WITN6984076**]
[347] 31 July 1985, Approval of variation application [**Reg/6/498, attachment 10**], **BAYP0000008_069**
[348] 22 May 1985, Letter from Cutter UK to NIBSC [**Reg/4/231**], **BAYP0000004_294**
[349] 31 July 1985, Approval of variation application [**Reg/6/498, attachment 11], BAYP0000006_100**
[350] The licence presently stated *"Concentrate standard used for the assay is the in-house standard 06480 (potency 1.45 iu/ml) which has been calibrated against the WHO 3rd International Standard for Factor VIII C."* [**Reg/6/498, attachment 11**], **BAYP0000006_100**

224. In July 1985 NIBSC required the release protocol for Koate HT to be amended so that the heat treatment method employed was briefly described, as *"dry heat treated at 68°C for 72 hours"* **[WITN6984077]**.[351] In addition, the batch release protocol had to be revised to include a signed statement that individual donations had been screened for antibody to HTLV-III. This is reflected, for example, on the batch release protocol for lots sent in December 1985 **[WITN6984078]**.[352]

225. It seems that in late October 1985, DHSS requested a statement regarding HTLV-III antibody testing of plasma appear on packaging of coagulation products and that Cutter UK requested stickers from Cutter Inc be placed on stock for the UK, which had already been tested pending revision to the UK labelling **[BAYP0000007_126]**.[353]

226. On 20 February 1986, Cutter UK wrote to DHSS with the results of the McDougal study in which Koate was spiked with HTLV-III/LAV prior to lyophilisation and heat-treatment at 68°C. No virus was detectable after heating for 24 hours. Cutter UK noted that Koate HT was dry heat-treated at 68°Cfor 72 hours **[BAYP0000004_344]**.[354]

227. On 18 April 1986, Cutter UK wrote to NIBSC to confirm that only batches of Cutter Inc product that had been prepared from 100% screened plasma donations would be shipped from the US for sale in the UK. In addition, all batch release protocols would include a statement confirming that each individual donation had been tested for antibody to HTLV-III and found to be non-reactive **[BAYP0000004_351]**.[355] An example of the revised protocol for UK release of Koate can be seen at **[WITN6984079]**.[356]

228. On 10 July 1986, Cutter UK wrote to Cutter Inc stating that "the UK authorities assume that all physicians will be monitoring their patients and that all companies will be following-up patients included in their clinical trials. They do not expect us to conduct formal studies but we should be able to keep them informed of the proportion of patients receiving our products who have not seroconverted and provide details of any who do." **[BAYP0000008_282]**.[357]

229. On 11 July 1986, Cutter UK wrote to Cutter Inc "we have to agree to provide

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[351] 30 July 1985, Telex from Cutter Inc to Cutter UK [**Other/12/948**], [**WITN6984077**]
[352] 10 March 1986, Letter from Cutter UK to Cutter Inc [**Other/13/1124**], [**WITN6984078**]
[353] 23 October 1985, Telex from Cutter UK to Cutter Inc [**Other/12/1004**], **BAYP0000007_126**
[354] 20 February 1986, Letter from Cutter UK to DHSS [**Reg/4/276**], **BAYP0000004_344**
[355] 18 April 1986, Letter from Cutter UK to NIBSC [**Reg/4/283**], **BAYP0000004_351**
[356] 2 February 1987, Cutter UK Protocol for UK release [**Reg/4/336 attachment**], [**WITN6984079**]
[357] 10 July 1986, Letter from Cutter UK to Cutter Inc [**Other/13/1260**], **BAYP0000008_282**

them with the data from ongoing studies" [**WITN6984080**].[358] Cutter Inc replied, "what is meant by ongoing studies? We are satisfied that the method currently used combined with the liquid product should remove/inactivate the HTLV-III virus. If we change our method, we will test what effect this will have on HTLV-III virus, but if no modifications are made, we do not plan further studies" [**BAYP0000008_289**].[359] Cutter UK responded "ongoing studies are what we have agreed to do. That is, to continue to look at virus inactivation as the state of the art progresses" [**BAYP0000008_293**].[360]

230. In October 1986, in view of a shortage of factor VIII concentrate in the UK, the Licensing Authority agreed to a temporary importation of US labelled Koate HT, provided that a sticker bearing the name and address of Cutter UK was applied to the cartons [**WITN6984081**].[361] The US imported product could only be sold under the terms of the UK product licence, subject to NIBSC release as usual and five samples were required for release testing [**WITN6984082**].[362] On 15 October 1986, Cutter UK wrote to NIBSC enclosing samples for batch release. The US protocol was submitted with an added statement concerning screening of donations for antibodies to HTLV-III [**WITN6984083**].[363]

231. On 20 October 1987, NIBSC issued a batch release certificate for batch 50S062 of Koate HT. It can be seen from the protocol for UK release that by this stage, the second statement that had to be signed by the quality assurance release coordinator had changed to *"[e]ach unit of plasma has been tested for antibody to HIV by ELISA-ENI Virgo and for Hepatitis B Surface Antigen by Radioimmunassay-ENI Riausure II and found nonreactive"* [**WITN6984084**].[364] It previously read *"[e]ach unit of plasma has been tested for antibody to HTLV III by an FDA approved method and found non-reactive*" [**WITN6984085**].[365] The first statement that had to be signed by the quality assurance release coordinator remained the same as previous versions: *"[p]roduct prepared from fractionated pooled plasma obtained from donors tested for Hepatis B Surface Antigen, HTLV III Antibody, ALT, and found negative"* [**WITN6984084**],[366] [**WITN6984085**].[367]

232. On 16 February 1988, Cutter UK wrote to DHSS with an application to add

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[358] 11 July 1986, Telex from Cutter UK to Cutter Inc [**Other/13/1264**], [**WITN6984080**]
[359] 11 July 1986, Telex from Cutler Inc to Cutter UK [**Other/13/1267**], **BAYP0000008_289**
[360] 14 July 1986, Telex from Cutter UK [**Other/13/1271**], **BAYP0000008_293**
[361] 9 October 1986, Letter from Cutter UK to Cutter Inc [**Other/14/1362**], [**WITN6984081**] (The document contains a typo of HS in place of HT which is clarified in document [**Other/14/1384**] [**WITN6984082**])
[362] 28 October 1986, Fax from Cutter UK to Cutter Inc [**Other/14/1384**], [**WITN6984082**]
[363] 15 October 1986, Letter from Cutter UK to NIBSC [**Reg/4/315**], [**WITN6984083**]
[364] 20 October 1987, NIBSC release certificate for Koate HT batch 50S062 [**Reg/4/358**], [**WITN6984084**]
[365] 25 June 1987, Protocol for UK release 50S039A [**Reg/4/356, attachment**], [**WITN6984085**]
[366] 20 October 1987, NIBSC release certificate for Koate HT batch 50S062 [**Reg/4/358**], [**WITN6984084**]
[367] 25 June 1987, Protocol for UK release 50S039A [**Reg/4/356, attachment**], [**WITN6984085**]

Bayer UK to the product licence as a distributor. Cutter UK explained that, from 1 April 1988, it intended to cease trading under the name of Miles Laboratories Limited and in future Koate HT would be distributed by Bayer UK although the product licence would remain in the name of Miles Laboratories Limited **[MHRA0014233_153]**.[368] Cutter UK wrote to DHSS again on 1 June 1988, stating that from that date all registration activities concerning all licences, certificates and pending applications of Cutter UK in the UK would be handled by Bayer UK. In addition, medical support including the required reporting of adverse drug reactions was to be provided by the medical department of Bayer UK **[WITN6984086]**.[369]

233. On 28 March 1988, following an inspection at the Clayton manufacturing site on 16-19 February 1988, DHSS wrote to Cutter UK with deficiencies found and requesting proposed actions to be reported. There were no "critical" findings, two "major" findings, and six "others" findings **[BAYP0000011_046]**.[370] On 4 July 1988, Bayer UK responded to the findings **[WITN6984087]**.[371]

234. On 22 June 1988, NIBSC informed Bayer that it intended to carry out additional tests on the plasma pools used for manufacture of batches of Koate HT sold in the UK. NIBSC explained that samples from plasma pools used for preparation of immunoglobulin were already sent to NIBSC and it now requested the same for Koate HT, as a matter of urgency **[BAYP0000005_068]**.[372] Bayer agreed that samples from the plasma pool used for preparation of Koate-HT would be sent to NIBSC when batches were sent for release testing, with immediate effect **[WITN6984088]**.[373] An internal document of 8 July 1988, describes the sampling of the plasma pools as a condition of the product licence **[WITN6984089]**.[374]

235. It can be seen from the Protocol for UK release of Koate HT "signature date" 18 July 1988, that testing for HIV antibody in each individual pool of plasma that contributed to a final lot of Koate HT had been instigated by that date and added as a requirement of release. The section of the release protocol reads *"[t]he pooled plasma used in the manufacture of this final container has been tested for HIV antibody and found non-reactive"*, followed by the identification number of each pool lot, the test result, the test date, the final container (batch) number and the dated signature of the quality assurance release coordinator

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[368] 16 February 1988, Letter from Cutter UK to DHSS [**Reg/5/362**], **MHRA0014233_153**
[369] 1 June 1988, Letter from Cutter UK to DHSS [**Reg/5/385**], [**WITN6984086**]
[370] 28 March 1988, Letter from DHSS to Cutter UK [**Reg/5/369/2**], **BAYP0000011_046**
[371] 4 July 1988, Letter from Bayer UK to DHSS [**Reg/5/400**], [**WITN6984087**]
[372] 22 June 1988, Letter from NIBSC to Bayer UK [**Reg/5/393**], **BAYP0000005_068**
[373] 28 June 1988, Letter from Bayer UK to NIBSC [**Reg/5/397**], [**WITN6984088**]
[374] 8 July 1988, Procedure for the NIBSC Batch Release of Cutter Licensed Products [**Other/16/1695**], [**WITN6984089**]

[WITN6984090].[375]

236. On 26 and 27 July 1989, there was contact between NIBSC Bayer UK to say NIBSC would not release lot 55U011A of Koate HT because upon initial testing of the samples, a weakly positive (equivocal) result for HBsAg was obtained. The plasma pool was negative. Re-testing of both plasma pool and product gave similar results. A letter from Bayer UK informing Cutter Inc of this states: *"Since the weakly positive result could be neutralised with specific antibodies to HBsAg, they feel that, on balance, the lot should not be released. They have not observed such results with our products before. In due course we will be notified in writing by the Department of Health"* **[BAYP0000012_163]**.[376] Six plasma pools were included in lot 55U011A and a sample of each had been sent to NIBSC along with final containers. Tests by Cutter Inc on the plasma pools and the final container had been non-reactive **[BAYP0000012_161]**.[377] Cutter Inc supplied Bayer UK with information for NIBSC on lot 55U011A consisting of *"the SDO for the Plasma pool samples and final container, BPR showing what went into the lot, the test results on the pool and the UK release for the lot"* **[BAYP0000012_163]**.[378] On 7 September 1989, Bayer UK wrote to NIBSC to confirm that batch 55U011A of Koate HT would not be sold or supplied in the UK **[BAYP0000005_141]**.[379]

237. On 2 November 1989, Bayer applied to the MCA,[380] as it now was, to renew the Koate HT product licence (PL 0055/0107), which was due to expire on 17 February 1990 **[BAYP0000005_143]**.[381] The available documents do not show when the renewal was approved, but it is apparent that there were delays at the MCA on account of workload. Bayer was informed that pursuant to section 24(6) of Medicines Act 1968, the expiring licence remained in force until such time as the renewal application had been determined, as a renewal application had been duly made **[WITN6984091]**.[382]

238. On 30 November 1989, Bayer made an application to vary the product licence for Koate HT to change the name of the importer of the product from Miles Limited to Bayer UK Limited **[WITN6984092]**.[383] The licensing authority

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[375] 14 July 1988, Protocol for UK release of lot No. 55T029 [**Reg/5/409 attachment**], [**WITN6984090**]
[376] 27 July 1989, Telefax from Bayer UK to Cutter Inc [**Other/17/1879**], **BAYP0000012_163**
[377] 26 July 1989, Memorandum from Cutter Inc to Bayer UK [**Other/17/1877**], **BAYP0000012_161**
[378] 26 July 1989, Fax from Cutter Inc to Bayer UK [**Other/17/1878**], **BAYP0000012_163**
[379] 7 September 1989, Letter from Bayer UK to NIBSC [**Reg/5/453**], **BAYP0000005_141**
[380] Successor of the Medicines Division of the DHSS (Annex A, paragraph 6)
[381] 2 November 1989, Letter from Bayer UK to MCA [**Reg/5/455**], **BAYP0000005_143**
[382] 7 November 1989, Letter from MCA to Bayer UK [**Reg/5/459**], [**WITN6984091**]
[383] 30 November 1989, Letter from Bayer UK to MCA [**Reg/5/466**], [**WITN6984092**]

approved the variation on 12 April 1991 [**WITN6984093**].[384]

239. On 18 April 1990, the CSM wrote to Cutter UK. The letter stated that in light of the limitations of testing for HBsAg and antibodies to HIV in finished products, and the greater sensitivity of the test on the plasma pool, it required henceforth all manufacturers of pooled plasma products to submit samples of all plasma pools to NIBSC, in addition to other samples and protocols required for batch release [**WITN6984094**].[385] Cutter UK replied that it already did so, for all products for which it held a product licence, and it would continue to do so [**WITN6984095**].[386]

240. On 21 June 1990, CSM requested confirmation that all donors who contribute to pools of plasma used in Cutter UK's products were tested for antibodies to HIV-2 and that protocols for the tests should be submitted to NIBSC [**BAYP0000005_172**].[387] Cutter UK replied on 19 July 1990, stating that it was unable to give the confirmation sought because FDA had taken the view that there was no public health need at that time to screen donors of blood or source plasma for antibodies to HIV-2, and all Cutter UK's products were manufactured in the USA by Cutter Inc. A copy of a letter from FDA dated 21 June 1990 explaining FDA's position was enclosed (although this is not present in the files available to me). Cutter UK also informed CSM that Cutter Inc (as well as others) had studied the susceptibility of HIV-2 to inactivation by a number of procedures and found it was inactivated rapidly, similar to HIV-1. Three additional supporting scientific papers were enclosed [**MHRA0034569_017**],[388], [**MHRA0034569_018**],[389], [**MHRA0034569_019**],[390], [**BAYP0000005_177**].[391]

241. On 10 May 1991, Bayer UK informed the MCA that Koate HT was no longer imported into, sold or supplied in the UK [**BAYP0000005_189**].[392] MCA officially cancelled the product licence on 30 October 1992 [**BAYP0000006_109**].[393]

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[384] 12 April 1991, Letter from MCA to Bayer UK, enclosing application approvals relating to Koate HT [**Reg/6/498, attachment 2],** [**WITN6984093**]
[385] 18 April 1990, Letter from CSM to Cutter UK [**Reg/5/472**], [**WITN6984094**]
[386] 3 May 1990, Letter from Cutter UK to CSM [**Reg/5/473**], [**WITN6984095**]
[387] 21 June 1990, Letter from CSM to Cutter UK [**Reg/5/474**], **BAYP0000005_172**
[388] Schimpf, K *et al.* Absence of Anti-Human Immunodeficiency Virus Types 1 and 2 Seroconversion after Treatment of Haemophilia A or Von Willebrand's Disease with Pasteurised Factor VIII Concentrate. N. Engl J Med 1989; 321: 1148, **MHRA0034569_017**
[389] Busch, M.P *et al.* Monitoring Blood Donors for HIV-2 Infection by Testing Anti-HIV-1 Reactive Sera. Transfusion 1990; 30: 184-187, **MHRA0034569_018**
[390] Piszkiewicz, D. Inactivation of HIV-2 by Solvent/Detergent Treatment. Letter to the Editor, Transfusion 1990; 30: 192, **MHRA0034569_019**
[391] 19 July 1990, Letter from Cutter UK to CSM [**Reg/5/478**], **BAYP0000005_177**
[392] 10 May 1991, Letter from Bayer UK to MCA [**Reg/5/487**], **BAYP0000005_189**
[393] 30 October 1992, Letter from MCA to Bayer UK [**Reg/6/499**], **BAYP0000006_109**

Koate HS

242. On 9 August 1985, Cutter Inc sought authorisation from the FDA to market Koate HS, a factor VIII concentrate heated in solution at 60°C for 10 hours [**BAYP0000014_012/BAYP0000014_013**].[394] The FDA approved Koate HS on 16 April 1986 [**BAYP0000014_039**].[395]

243. An application for Koate HS product licence was made to DHSS on 26 September 1986 [**WITN6407004**].[396] The contents of the US application were the basis for the application, which application included viral inactivation data and a volunteer study conducted by Carol Kasper of the Los Angeles Orthopaedic Hospital [**BAYP0000014_024**], [**BAYP0000014_027**] & [**BAYP0000014_028**].[397] The viral inactivation data cited the Levy *et al* and McDougal *et al* studies [**PRSE0000008**],[398] [**PRSE0001941**].[399] The volunteer study and in vitro study data showed that the wet heat treatment process did not alter the properties of Factor VIII and, therefore, no efficacy change was anticipated [**BAYP0000014_028**].[400]

244. However, Cutter UK thought it likely that additional clinical safety data to address the transmission of NANB Hepatitis would now be required and, therefore, asked Bayer AG whether it would support the conduct of a Koate HS study in the UK [**BAYP0000015_010**],[401] [**WITN6984096**].[402] Clinicians were approached in the UK to act as investigators in such a study [**BAYP0000015_290**], [**BAYP0000015_294**], [**BAYP0000015_031**], [**BAYP0000015_051**] and [**BAYP0000015_052**].[403] Professor Bloom agreed to do so [**BAYP0000015_036**][404] and an application for a CTX was made to the

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[394] 9 August 1986, Antihemophilic Factor (Human) Heat-Treated (Wet, PEG), Koate-HS: Submission to amend the Antihemophilic Factor (Human) Product Licence Application [**HS Reg/1/1**], **BAYP0000014_012** [Attachment III only] & **BAYP0000014_013** [Attachment IV only]
[395] 28 April 1986, Memo from Cutter Inc to Cutter UK [**HS Reg/1/3**], **BAYP0000014_039**
[396] 26 September 1986, Cutter UK letter to DHSS [**HS Reg/2/17**], **WITN6407004**
[397] August 1986, Abridged Product Licence Application for Koate-HS Dried Factor VIII Fraction (heated in solution) [**HS Reg/1/6 - 8**], **BAYP0000014_024**, **BAYP0000014_027 & BAYP0000014_028**
[398] Levy *et al.* Inactivation by wet and dry heat of AIDS-associated retroviruses during factor VIII purification form plasma. Lancet. 1985; 1: 1456-7 [**Other/12/921**], **PRSE0000008**
[399] McDougal *et al.* Thermal inactivation of the Acquired Immunodeficiency Syndrome Virus, Human T Lymphotropic Virus-III/Lymphadenopathy-associated Virus, with Special Reference to Antihemophilic Factor. Journal of Clinical Investigations. 1985; 76: 875-877 [**Other/12/951**], **PRSE0001941**
[400] August 1986, Abridged Product Licence Application for Koate-HS Dried Factor VIII Fraction (heated in solution) [**HS Reg/1/8**], **BAYP0000014_028**
[401] 8 January 1986, Memo from Cutter UK to Cutter Inc [**HS Other/1/6**], **BAYP0000015_010**
[402] 20 June 1986, Cutter UK letter to Dr J. P. Fallise [**HS Other/1/18**], [**WITN6984096**]
[403] Between 21 July 1986 and 2 September 1986, Cutter UK correspondence with doctors [**HS Other/1/29**], **BAYP0000015_290**; [**HS Other/1/33**], **BAYP0000015_294**; [**HS Other/1/40**], **BAYP0000015_031**; [**HS Other/1/59**], **BAYP0000015_051** and [**HS Other/1/60**], **BAYP0000015_052**
[404] 15 August 1986, Cutter UK letter to Dr J. P. Fallise [**HS Other/1/44**], **BAYP0000015_036**

DHSS in August 1986 [**BAYP0000017_006/BAYP0000017_007**].[405] DHSS required additional time to consider the application [**WITN6984097**][406] and then requested certain assurances which were given regarding the manufacture of the product [**BAYP0000004_388**].[407] The CTX was finally approved in February 1987 [**BAYP0000004_412**].[408]

245. In parallel, samples of Koate HS were sent to the NIBSC for testing [**BAYP0000014_038**].[409] Koate HS was prepared from pooled units of plasma individually tested and found non-reactive for HBsAg and antibody to HTLV-III, using FDA-approved tests. In addition, the product was tested for elevated ALT levels which might suggest the presence of NANB hepatitis [**BAYP0000014_024**].[410] However, it was noted that testing methods then available did not guarantee that the plasma pool would not contain infectious viruses and that hepatitis viruses might be present in the preparation [**BAYP0000017_003**].[411]

246. On 26 September 1986, Cutter UK submitted to DHSS an application for the Koate HS product licence [**WITN6407004**].[412] By 1 October 1987 the Licensing Authority had not yet assessed the application [**WITN6984098**].[413] In the event the application could not be considered by the CSM until July 1988 [**BAYP0000017_039**],[414] by which time the assessors at the DHSS had made it clear that they required additional information as it was thought that the Koate HS described in the application had additional stabilisers as compared with the products used in the published studies submitted [**BAYP0000017_038**].[415] There was a concern that these could stabilise HIV and hepatitis viruses as well and make them less susceptible to heat treatment.

247. In June 1988, Bayer UK was advised by Cutter Inc that the production process in the US was not producing the yield hoped for and sufficient product, if Koate HS was launched in the UK, might not be available [**WITN6984099**].[416] It seemed that Bayer Group was now focused increasingly on clinical trials with

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[405] 22 August 1986, Form MLA 164 for Koate HS: Notice under the Exemption from Licences (Clinical trials) Order 1981 [**HS Reg/2/12**], **BAYP0000017_006 & BAYP0000017_007**
[406] 18 September 1986, Letter from DHSS to Cutter UK [**HS Reg/2/14**], [**WITN6984097**]
[407] 23 October 1986, Letter from DHSS to Cutter UK [**HS Reg/2/19**], **BAYP0000004_388**
[408] 9 February 1987, Letter from the DHSS to Cutter UK [**HS Reg/2/20**], **BAYP0000004_412**
[409] 15 January 1986, Letter from Cutter UK to NIBSC [**HS Reg/1/2**], **BAYP0000014_038**
[410] August 1986, Abridged Product Licence Application for Koate-HS Dried Factor VIII Fraction (heated in solution) [**HS Reg/1/6**], **BAYP0000014_024**
[411] August 1986, Koate HS: P.L. Application; Clinical Expert Report' authored by R. Rousell [**HS Reg/2/11**], **BAYP0000017_003**
[412] 26 September 1986, Cutter UK letter to DHSS [**HS Reg/2/17**], **WITN6407004**
[413] 1 October 1987, Letter from the DHSS to Cutter UK [**HS Reg/2/26**], [**WITN6984098**]
[414] 23 June 1988, Notes of a telephone conversation with DHSS [**HS Reg/2/33**], **BAYP0000017_039**
[415] 21 June 1988, Notes of meeting at DHSS Medicines Division [**HS Reg/2/32**], **BAYP0000017_038**
[416] 8 July 1988, Bayer UK Meeting minutes [**HS Other/1/109**], [**WITN6984099**]

its recombinant Factor VIII product rather than Koate HS. On 31 August 1988, approval was sought for an amendment to the existing Koate HS trial approval so that patients initially receiving Koate HS would then receive the recombinant product **[BAYP0000017_043]**.[417] The DHSS approved this on 29 September 1988 **[WITN6984100]**.[418] In the meantime, Bayer Group was also considering the possible registration of Koate HP rather than Koate HS **[WITN6984101]**.[419]

248. Discussion with the regulatory authorities concerning the Koate HS application continued. In October 1988, CSM notified Bayer UK of five conditions that must be met before it would advise the grant of a product licence for Koate HS **[BAYP0000005_217]**.[420] Importantly, CSM sought more information on the transmission of infectious agents. Bayer UK responded in June 1989 **[WITN6984102]**,[421] but was told that the relevant issues would not be considered by CSM until their January 1990 meeting **[BAYP0000016_051]**.[422]

249. Immediately prior to the CSM meeting scheduled for January 1990, Bayer UK was advised that CSM would not advise grant of a product licence for Koate HS because they were concerned about the absence of data specifically relating to product production and demonstration that the pasteurisation process used ensured adequate virucidal activity. They requested further studies. The authorities indicated that they were prepared to discuss the precise design of such studies, which it was recognised would also be relevant to any application for Koate HP **[BAYP0000016_056]**.[423] The formal rejection letter was received in March 1990 **[BAYP0000017_100]**.[424] Bayer UK notified its intention to make further representations to the CSM **[WITN6984103]**.[425] In May 1990, the MCA inspected Cutter Inc's Clayton plant in the US and reported no critical findings, two major findings and eight other findings **[BAYP0000035_040]**.[426] In August 1990 Bayer notified its intention to withdraw the application for Koate HS **[BAYP0000017_105]**.[427] The CTX for the trial involving use of Koate HS was allowed to lapse **[WITN6984104]**.[428]

250. On 13 November 1989, Bayer UK reported to MCA that a cluster of adverse

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[417] 31 August 1988, Letter from Bayer UK to the DHSS [**HS Reg/2/37**], **BAYP0000017_043 [no attachment]**
[418] 29 September 1988, Letter from DHSS to Bayer UK [**HS Reg/2/40**], [**WITN6984100**]
[419] 17 August 1988, Cutter Inc letter to Bayer UK [**HS Other/1/115**], [**WITN6984101**]
[420] 6 October 1988, Letter from CSM to Bayer UK [**Reg/5/427**], **BAYP0000005_217**
[421] 8 June 1989, Letter from Bayer UK to the CSM [**HS Reg/2/54**], [**WITN6984102**]
[422] 9 November 1989, Letter from Bayer UK to Cutter Inc [**HS Other/2/152**], **BAYP0000016_051**
[423] 23 January 1990, Bayer UK memo [**HS Other/2/156**], **BAYP0000016_056**
[424] 6 March 1990, Letter from the CSM to Bayer UK [**HS Reg/2/68**], **BAYP0000017_100**
[425] 22 March 1990, Letter from Bayer UK to the CSM [**HS Reg/2/71**], [**WITN6984103**]
[426] 4 May 1990, Memo from Cutter Inc to Bayer UK [**Other/18/1942**], **BAYP0000035_040**
[427] 16 August 1990, Letter from Bayer UK to the MCA [**HS Reg/2/73**], **BAYP0000017_105**
[428] 1 October 1992, Letter from Bayer UK to the MCA [**HS Reg/2/77**], [**WITN6984104**]

events, namely seven cases of hepatitis, had been reported from Japan, where Koate HS was a marketed product. As a result of the adverse events Cutter Inc. had voluntarily recalled five batches of product, although it had not proved possible to implicate any one product, or any one lot, as the source of infection. These events had led to an FDA inspection of Cutter's Berkeley manufacturing site and a summary of the FDA observations and Cutter's responses were sent to the MCA **[BAYP0000017_075/BAYP0000017_076]**.[429]

Koate HP

251. On 3 March 1989, Cutter Inc obtained authorisation to market Koate HP from the FDA. Koate HP which utilised a virucidal solvent/detergent process (TNPB and polysorbate 80) **[WITN6984105]**.[430] The process was licensed from the New York Blood Center. The aim was to produce a product of high purity (using a gel filtration procedure) with a similar safety profile, but without the decrease in potency often associated with methods that utilised heat-treatment. Chemical methods of virus inactivation were known to disrupt lipid-containing enveloped viruses. Effectiveness against model viruses had been established during the development of the process **[BAYP0000105]**.[431] The product was manufactured using pooled units of plasma that were non-reactive for HBsAg and negative for antibody to HIV, using FDA-approved tests **[WITN6984105]**,[432] although the product information noted that current testing methods were not totally effective in identifying viral infectivity and, therefore, the presence of hepatitis viruses should be assumed **[WITN6984106]**.[433] It was emphasised that individuals who had not received multiple infusions of blood or blood products were very likely to develop some viral infections, especially NANB hepatitis. Each unit used in the manufacture was also checked to have an ALT level less than twice the upper limit of normal **[WITN6984105]**.[434]

252. On 25 August 1988, Cutter Inc sent the US dossier and batch production records for Koate HP to the UK for consideration **[WITN6984107]**.[435] Bayer UK recognised that the UK authorities would likely require additional data relating

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[429] 13 November 1989, Letter from Bayer UK to the MCA [**HS Reg/2/59**], **BAYP0000017_075 & BAYP0000017_076**

[430] 2 August 1990, Correspondence from Cutter Inc to Bayer UK, internal page 4 and 8 [**HP Other/1/49/4,8**], [**WITN6984105**]

[431] May 1990, CTX application for Koate-HP Antihaemophilic Factor (Human) [**HP Reg/1/2/11**], **BAYP0000105**

[432] 2 August 1990, Correspondence from Cutter Inc to Bayer UK, page 8 [**HP Other/1/49/8**], [**WITN6984105**]

[433] 17 October 1989, Photocopy of a pack of Koate HP [**HP Other/1/20**], [**WITN6984106**]

[434] 2 August 1990, Correspondence from Cutter Inc to Bayer UK, internal page 8 [**HP Other/1/49**], [**WITN6984105**]

[435] 25 August 1988, Correspondence from Cutter Inc to Bayer UK [**HP Other/1/10**], [**WITN6984107**]

to transmission of infectious agents [**WITN6984108**].[436] The available inactivation data came from spiking experiments using three model viruses. Bayer UK also thought that additional data beyond a 24-patient volunteer study might be needed to establish the functional activity of Factor VIII after the viral inactivation step. In October 1989, Bayer UK provided Cutter Inc with detailed comments on the dossier and requested more data [**WITN6984109**],[437] [**WITN6984110**].[438] Cutter Inc stated that a phase 4 trial was underway in the US that might provide useful data [**WITN6984111**].[439] Cutter Inc provided additional information [**WITN6984112**][440] but noted that the solvent/detergent process was well-established and, if new clinical data were required by the UK authorities, they might need to be generated in the UK. Clinicians in the US were said to be increasingly resistant to testing new factor VIII concentrates and were waiting for the recombinant factor products to become available [**WITN6984113**].[441] As a result, in June 1990, Bayer UK sought approval from the MCA for a clinical trial of Koate HP in patients with moderate or severe haemophilia, with Dr G Savidge from St Thomas' Hospital in London as the lead investigator [**BAYP0000106**],[442] [**BAYP0000105**].[443] The MCA notified Bayer UK on 15 June 1990, that the trial exemption would take effect unless the company heard from the Agency within 35 days [**WITN6984114**].[444]

253. Later in June 1990, Bayer UK had discussions with Dr John Sloggen at the MCA, who identified some conditions that would attach to the approval of the clinical trial. At the time, he also indicated additional points that would have to be addressed in relation to the application for the product licence. In particular, he believed that a broader range of model viruses would have to be addressed in relation to viral inactivation [**WITN6984115**].[445]

254. On 9 July 1990, the MCA confirmed that no objection was raised to the clinical trial for Koate HP taking place, subject to certain conditions relating to the albumin and heparin used [**BAYP0000112**].[446] The objective of the study was to assess the efficacy of Koate HP and its safety. The product information noted that the presence of hepatitis viruses could not be excluded and the hazards of

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[436] 11 November 1988, Bayer UK internal memo [**HP Other/1/11**], [**WITN6984108**]
[437] 13 October 1989, Correspondence from Bayer UK to Cutter Inc [**HP Other/1/19**], [**WITN6984109**]
[438] 25 October 1989, Correspondence from Bayer UK to Cutter Inc [**HP Other/1/22**], [**WITN6984110**]
[439] 6 February 1989, Correspondence from Cutter Inc to Bayer UK [**HP Other/1/12**], [**WITN6984111**]
[440] 19 December 1989, Correspondence from Cutter Inc to Bayer UK [**HP Other/1/24**], [**WITN6984112**]
[441] 15 March 1990, Correspondence from Cutter Inc to Bayer UK [**HP Other/1/28**], [**WITN6984113**]
[442] 5 June 1990, Correspondence from Bayer UK to MCA [**HP Reg/1/3**], **BAYP0000106**
[443] May 1990, CTX application for Koate-HP Antihaemophilic Factor (Human) [**HP Reg/1/2**], **BAYP0000105**
[444] 15 June 1990, Correspondence from MCA to Bayer UK [**HP Reg/1/5**], [**WITN6984114**]
[445] 18 June 1990, Telephone note of a call between Bayer UK and the MCA [**HP Reg/1/6**], [**WITN6984115**]
[446] 9 July 1990, Correspondence from MCA to Bayer UK [**HP Reg/1/9**], **BAYP0000112**

using the product, especially in persons who had few previous transfusions of blood or blood products, needed to be weighed against the consequences of not using the product **[WITN6984105]**.[447] The patient information also stated that hepatitis C might be transmitted, but that the risks were similar for all products manufactured from human blood **[WITN6984105]**.[448]

255. Bayer UK sought to recruit 20 patients for the Koate HP study before the end of October 1990, and had further discussions with Dr Savidge **[WITN6984116]**.[449] In August 1990, Bayer UK notified the MCA that it wished to add Dr M Winter of the Isle of Thanet District Hospital as an additional investigator **[WITN6984117]**.[450] This was approved **[WITN6984118]**.[451] Bayer UK sent to the MCA *" a copy of the draft protocol for the study to be conducted by Cutter Biological to validate viral inactivation in Koate HP under worst case scenario conditions"* and the MCA in turn provided comments on the design proposals in January 1991 **[BAYP0000115_002]**,[452] **[WITN6984119]**.[453] The expected date of submission of the product licence application was August 1991 **[BAYP0000059_002]**.[454] However, in April 1991, at a Cutter strategic planning workshop it was suggested that even if Koate HP were to be approved, it would not be launched in the UK as it was expected that BPL would be at full capacity by 1994. Bayer UK was invited to consider an application for Kogenate **[BAYP0000062]**.[455]

256. Interim results of the UK clinical trial became available in August 1991, **[BAYP0000071_001/BAYP0000071_002]**[456] but there were said to be delays in getting the final report from Dr Savidge that would be needed for the product licence application **[WITN6984120]**, **[WITN6984121]**.[457,458] Bayer UK began working on the dossier for that application using the US dossier and re-presenting it in accordance with EC requirements **[WITN6984122]**.[459] However, in November 1992, Bayer UK informed Cutter Inc that meeting the new requirements for Koate HP was problematic and stated "*submission Koate HP*

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[447] 2 August 1990, Correspondence from Cutter Inc to Bayer UK [**HP Other/1/49/11**], [**WITN6984105**]
[448] 2 August 1990, Correspondence from Cutter Inc to Bayer UK [**HP Other/1/49/33**], [**WITN6984105**]
[449] 13 July 1990, Bayer UK meeting note with Dr Savidge [**HP Additional/1/3**], [**WITN6984116**]
[450] 9 August 1990, Correspondence from Bayer UK to MCA [**HP Reg/1/11**], [**WITN6984117**]
[451] 13 August 1990, Correspondence from MCA to Bayer UK [**HP Reg/1/12**], [**WITN6984118**]
[452] 14 January 1991, Correspondence from Bayer UK to MCA [**HP Reg/1/13**], **BAYP0000115_002**
[453] 24 January 1991, Correspondence from Bayer UK to Cutter Inc [**HP Other/1/65**], [**WITN6984119**]
[454] 11 March 1991, Cutter Inc internal note [**HP Other/1/69**], **BAYP0000059_002**
[455] 18 April 1991, Cutter Products Strategic Planning Workshop: 17 April 1991 [**HP Other/1/72**], **BAYP0000062**
[456] 1 August 1991, Bayer UK internal memo [**HP Other/1/81**], **BAYP0000071_001 & BAYP0000071_002**
[457] 27 February 1992, Correspondence from Bayer UK to Dr Savidge [**HP Other/2/93**], [**WITN6984120**]
[458] 25 March 1992, Bayer UK internal memo [**HP Other/2/94**], [**WITN6984121**]
[459] 10 December 1991, Correspondence from Bayer UK to Cutter Inc [**HP Additional/1/8**], [**WITN6984122**]

in UK to be re-evaluated" **[WITN6984123]**.[460]

257. In April 1993, Bayer UK said it was still keen to obtain a product licence for Koate HP and to market it before Kogenate became available **[WITN6984124]**.[461] However, in May 1993, the MCA wrote to all companies seeking further information on reports of hepatitis A transmission with licensed blood products and asked whether companies had any plans to introduce additional processes to inactivate non-lipid enveloped viruses **[WITN6984125]**.[462] At this time, it seems that European regulatory authorities had indicated they were considering the need for two different viral inactivation steps **[WITN6984126]**.[463] Initially, Bayer AG appears to have considered adding a second inactivation step for Koate HP **[WITN6984127]**.[464]

258. In the event, no application for a product licence for Koate HP was made. There is no correspondence on the available files concerning the final decision not to proceed with the application in the UK, but it seems that the imminent introduction of Kogenate had rendered further development of products like Koate HP clinically and commercially unattractive.

Kogenate

259. In May 1994, Bayer plc obtained a product licence (PL 0010/0194-95) for Kogenate, a sterile lyophilised preparation of the active ingredient, recombinant antihaemophilic factor (rFVIII), created from hamster cells using recombinant DNA technology. Kogenate was intended for the life-long treatment of haemophilia A.

Konyne PL 1605/0007

260. In April 1975, it was suggested that factor IX was being used in the UK to treat patients with "Christmas disease" who no longer respond to factor VIII. Meeting minutes state *"[t]he aetiology of this action is unknown, but it is in fact used for this indication."* **[WITN6984128]**[465]

261. On 3 July 1980, Cutter Inc submitted an application for a product licence for Konyne® - Factor IX Complex (Human) to DHSS, on behalf of Cutter UK. The product was licensed in the US on 31 December 1963. The application stated that Konyne, Factor IX Complex was *"a sterile lyophilized powder for*

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[460] 30 November 1992, Cutter UK internal memorandum [**HP Additional/1/19**], [**WITN6984123**]
[461] 5 April 1993, Bayer UK internal memorandum [**HP Other/2/107**], [**WITN6984124**]
[462] 26 May 1993, Correspondence from MCA to Bayer UK [**HP Reg/1/24**], [**WITN6984125**]
[463] 10 November 1992, Memo from Cutter Inc to Bayer UK [**HP Additional/1/16**], [**WITN6984126**]
[464] 26 May 1994, Correspondence from Bayer UK to Bayer AG [**HP Other/2/114**], [**WITN6984127**]
[465] 7 April 1975, Bayer UK meeting minutes [**Other/1/47**], [**WITN6984128**]

reconstitution with sterile water for administration" and that. *"Konyne is indicated whenever one or more of the specific coagulation factors must be elevated in order to correct or prevent a dangerous bleeding episode."* The product was to be manufactured by Cutter Inc, which was responsible for quality control and was to be imported into the UK by Cutter UK **[BAYP0000004_285]**.[466]

262. On 5 September 1980, DHSS acknowledged receipt of the application submitted three months earlier **[WITN6984129]**.[467] However, as the format of the application was not in compliance with DHSS guidelines, it was found to be unacceptable and was subsequently withdrawn. An internal note states *"for commercial reasons a re-submission of the data in the correct format was not pursued"* **[BAYP0000004_335]**.[468]

Konyne HT PL/0055/0108

263. In the US, Cutter Inc was granted a product licence for Konyne, Factor IX complex (Human) by the FDA on the 18 February 1983 **[BAYP0000028_039]**.[469] Examples of the package insert can be found in the documents provided to the Inquiry **[WITN6984130]**,[470,] **[BAYP0000025_032]**.[471]

264. A Cutter Inc report of a trip to the UK on 4 to 6 March 1985 states "a number of accounts have begun to purchase our Konyne H.T. on a named patient basis, recognizing that the same rationale that justifies using a heat-treated factor VIII applies also to factor IX" **[BAYP0000024_114]**.[472] It appears that on 22 March 1985, Cutter UK notified DHSS that it proposed to import Konyne HT manufactured by Cutter Inc and imported from the US on a named-patient basis **[BAYP0000004_269]**.[473]

265. On 8 May 1985, Cutter UK applied to DHSS for a product licence for Konyne HT **[WITN6984131]**.[474,] The heat-treatment process employed in production was the same as that approved in the Koate HT product licence **[BAYP0000003_315]**.[475] The clinical use of Konyne was in the proposed

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[466] 3 July 1980, Application for product licence for Konyne [**Reg/1/41/4**], **BAYP0000004_285**
[467] 5 September 1980, Letter from the DHSS to Cutter Inc [**Reg/1/42**], [**WITN6984129**]
[468] November 1985, Cutter UK draft notes of response to CSM [**Reg/4/269/3**], **BAYP0000004_335**
[469] 18 February 1983, Cutter Inc Product Licence [**Other/6/341**], **BAYP0000028_039**
[470] May 1983, Package Insert for Factor IX Complex (Human) Konyne [**Other/6/372**], [**WITN6984130**]
[471] October 1984, Package Insert for Factor IX Complex (Human) Konyne [**Other/10/642**], **BAYP0000025_032**
[472] 13 March 1985, Cutter Inc internal memorandum [**Other/11/806**], **BAYP0000024_114**
[473] 22 March 1985, Letter from Cutter UK to DHSS [**Reg/4/212**], **BAYP0000004_269**
[474] 8 May 1985, Letter from Cutter UK to DHSS [**Reg/4/225**], [**WITN6984131**]
[475] March 1985, Abridged product licence application for Konyne HT [**Reg/3/203**], **BAYP0000003_315**

indication of *"whenever one or more of the specific coagulation factors must be elevated in order to correct or prevent a dangerous bleeding episode".* An internal note stated that as the clinical use of Konyne was already well established, and the heat-treated product had been shown to be equivalent in terms of *in vivo* biological activity and half-life to the non-heated product, no specific clinical trials were conducted using Konyne HT **[WITN6984131]**.[476]

266. Konyne HT continued to be used on a named-patient basis while the licence application was being assessed **[WITN6984132]**.[477]

267. On 13 August 1985, Cutter UK wrote to DHSS in the context of the chimpanzee study reported in part III of the product licence application to *"confirm that, following rechallenge with the spiked non-heated preparation at 15 weeks, evidence of NANB hepatitis was observed in the Factor IX inoculated animals as indicated by elevated transaminase levels"* and provided more recently issued graphical representations of these results **[BAYP0000004_320]**.[478]

268. From 17 October 1985, only Konyne HT made wholly from HTLV-III screened plasma was supplied by Cutter Inc **[BAYP0000009_011]**.[479]

269. On 21 October 1985, CSM wrote to Cutter UK stating that on grounds relating to safety, quality and efficacy they may be unable to advise grant of a product licence for Konyne HT. CSM provisionally concluded, *inter alia,* that:

> *"2. Inadequate information had been provided on the fractionation and control procedures.*
> *3. Information should be provided on the standards used in finished product testing.*
> *4. Inadequate evidence had been provided of virus inactivation.*
> *5. Insufficient evidence had been provided of the clinical safety and efficacy of product or of the product on which it is based"* **[BAYP0000004_326]**.[480]

270. On 20 November 1985, Cutter UK informed Cutter Inc of a discussion with the DHSS about the CSM's comments. It was said that there would be no problem with batch release as the NIBSC had tested the samples Cutter UK sent and that there were *"no problems".* Regarding point 4, inadequate evidence of virus

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[476] 8 May 1985, Letter from Cutter UK to DHSS enclosing abridged product licence application for Konyne HT **[Reg/4/225]**, **[WITN6984131]**
[477] 31 May 1985, Letter from Cutter UK to the Newcastle Health Authority **[Other/11/903]**, **[WITN6984132]**
[478] 13 August 1985, Letter from Cutter UK to DHSS **[Reg/4/257]**, **BAYP0000004_320**
[479] 8 October 1986, Internal Cutter Inc telex **[Other/14/1357]**, **BAYP0000009_011**
[480] 21 October 1985, Letter from CSM to Cutter UK **[Reg/4/261]**, **BAYP0000004_326**

inactivation, the note states:

> *"It was the results of the viral inactivation studies which caused concern. We need to enlarge on the data presented. What was the relevance of the studies performed? Was there sufficient inactivation in these studies to provide evidence of safety? Why were those particular organisms selected for these studies? In other words, some viruses were completely inactivated and other were still detectable after heating. We need to comment on these results. (Apparently, Dr. Schild may have some ideas about what could be done. I will let you know what he has to say). However, we should emphasis the fact that the plasma pool is screened for HTLV III antibodies and any batch intended for the U.K. Market would have to be prepared from screened donations. Also, we should detail the other precautions used in screening donors. We should also emphasis the fact that the product is heat-treated and that the heat-treatment method is recognised as being effective in reducing the risk of transmitting infectious viruses. The viral inactivation studies would then provide supportive data but we will still need to prepare a good commentary."* **[BAYP0000007_153]**[481]

271. It appears that Cutter UK drafted a reply to the CSM. However, it is not apparent from the documents available if the reply was finalised or sent. The draft states:

> *"It should be noted that the initial viral inactivation studies performed by Cutter in 1984 included some work on Konyne-HT as well as Koate-HT and no seroconversion to antibodies to HTLV III/LAV and no clinical signs or symptoms of non-A, non-B hepatitis have been reported in any patient receiving either product".* **[BAYP0000004_335]**[482]

272. Cutter UK's position in response to the CSM's fifth provisional conclusion that "insufficient evidence had been provided of the clinical safety and efficacy of product or of the product on which it is based" was:

> *"[…] As reported in Attachment 4 of this representation, no virus was detectable in the final heated preparation after pre-lyophilisation inoculation with a viral titre of ID-50 > 10 HTLV III/LAV.*
>
> *The transmission of viral hepatitis has always been of concern in clinical use of antihemophilic factor VIII or IX, and the evidence to date suggests that the heating process employed in production of Konyne HT reduces this risk.*

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[481] 20 November 1985, Internal Cutter UK note of Konyne-HT: CSM meeting [**Other/12/1026**], **BAYP0000007_153**

[482] November 1985, Cutter UK' draft notes of response to CSM [**Reg/4/269/3**], **BAYP0000004_335**

As reported in our product licence application, a study in chimpanzees demonstrated that the heating process inactivated a known amount, 2,500 infectious doses, of the Hutchinson strain of non-A, non-B hepatitis virus as well as an unknown quantity of endogenous non-A, non-B hepatitis.

The results showed that the hepatitis observed in control animals in this study was not due to hepatitis A or B virus or cytomegalovirus, but due to the infectious dose of non-A, non-B hepatitis virus with which they were inoculated either with spiked non-heated Konyne or as a separate inoculum.

No evidence of non-A, non-B hepatitis or hepatitis B infection was observed in animals administered heated Konyne with or without an inoculum of non-A, non-B hepatitis virus.

Clinical studies designed to investigate the possibility of transmission of non-A, non-B hepatitis have to be performed in patients who have not previously received blood products, that is, virgin haemophiliacs with haemophilia B. Quite apart from the ethics of conducting trials in these patients, the number of available patients is very small.

Cutter is currently monitoring the use of Konyne HT in such patients but, so far, only two patients have become available for inclusion in the study and the study is not yet complete.

Although, as yet, we have no absolute evidence that heat-treated Konyne does not transmit non-A, non-B hepatitis in haemophiliacs, we have had no reports of non-A, non-B hepatitis in haemophiliacs receiving our dry heat-treated factor VIII preparation (Koate HT) which has been in clinical use for several years. As the same heating process is used for both products and since factor VII usage is much higher than factor IX, it would be expected that the possibility of a patients [sic] developing non-A, non-B hepatitis through administration of Konyne-HT would be very unlikely.

In conclusion, although all possible steps have been and are being taken by Cutter to reduce the risk of transmission of infectious viruses, the technology presently available does not allow us to claim with certainty that the product is completely free of infectious virus. The risk to the patient must be considered carefully in each individual case and balanced against the risk of depriving the patient of treatment with the product." [**BAYP0000004_335**][483]

273. On 1 November 1985, CSM requested the plans for screening of donors against infectious agents, including HTLV-III, from Cutter UK and stated that should a

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[483] November 1985, Cutter UK draft notes of response to CSM [**Reg/4/269/9-10**], **BAYP0000004_335**

product licence be granted, the batch release procedure should apply to include the provision of bulk and in-process samples [**BAYP0000004_328**].[484]

274. On 20 January 1986, a telex message from Cutter UK to Cutter Inc states "reports of the early clinical studies of Konyne which were included in the PLA submission in 1982 are inadequate. They were rejected by the CSM. Do we have any better reports? If not, we will have to rely on published articles. I cannot use inhibitor data as we did not ask for this indication" [**BAYP0000008_060**].[485]

275. An internal note between colleagues at Cutter UK dated the following day states:

> *"The following information on Konyne-HT is urgently required for our submission to CSM. We cannot make arrangements for the hearing until the data are assembled and the commentaries written up for inclusion in our representation.*
>
> *1. A commentary on the results of the studies included in the P.L. application entitled "Virus Inactivation Kinetics in Dry Heat-Treated Factor IX Complex (Human)" and "Inactivation Kinetics of Sindbis Virus and Feline Leukaemia Virus in Dry Heat-Treated Factor IX Complex (Human)".*
>
> *2. An overall discussion of these results and other studies which were carried out to demonstrate that the heating process is effective in preventing transmission of infectious viruses.*
>
> *What can we conclude from these studies apart from the fact that HTLV III/LAV is inactivated?*
>
> *3. Any clinical data which have recently become available particularly with reference to NANB hepatitis. Are they monitoring clinical use in any country?*
>
> *4. Do we claim that our dry heat-treatment process is as good as any wet heat-treatment process in reducing the risk of transmitting NANB hepatitis? If so, what reasons do we give for making that claim? If not, what reasons do we give for employing dry heat-treatment?"* [**BAYP0000008_062**][486]

276. On 27 January 1986, Cutter UK informed Cutter Inc in a note headed "NIBSC TESTING: KONYNE-HT" that: "as reported earlier, Dr. Schild wants in-process and bulk samples for testing. Dr. Thomas has said that he does not want them

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[484] 1 November 1985, Letter from CSM to Cutter UK [**Reg/4/263**], **BAYP0000004_328**
[485] 20 January 1986, Cutter UK telex to Cutter Inc [**Other/13/1087**], **BAYP0000008_060**
[486] 21 January 1986, Internal Cutter UK note [**Other/13/1089**], **BAYP0000008_062**

cluttering up his laboratory but Dr. Schild seems to think that the virologists should look at them. The DHSS has asked me what we think about the request to supply these samples. I have told them we would oppose it and they seem to agree that the new Director of the NIBSC is making unnecessary demands. We need to provide the CSM with good reasons for not sending them and the assessors will support us" **[BAYP0000008_072]**.[487] Cutter Inc replied to Cutter UK that:

> *"such samples are not suitable for testing. They are not stable. They are not valid for such testing. They are processed in an aseptic manner but are not sterile. We do not supply such samples to any health authority"* **[BAYP0000008_087]**.[488]

277. A further message from Cutter UK to Cutter Inc entitled "*HTLV III antibody test of final product*" stated:

> *"[…] testing of final product is a CSM requirement. The scientists concerned with HTLV III antibody testing put no reliability on it. This is why the NIBSC is asking for samples of plasma pool"* **[BAYP0000008_242]**[489]

278. On 12 February 1986, Cutter Inc sent to Cutter UK for submission to CSM/DHSS "clinical data to support the use of Konyne-HT in patients who have an inhibitor to Factor VIII. The results show comparability of the efficacy of heat-treated with the non heat-treated Konyne in treatment of hemorrhagic episodes in inhibitor patients". The enclosure is not present in the documents available **[WITN6984133]**.[490]

279. On 14 May 1986, Cutter UK wrote to Professor Temperley at St James Hospital Dublin requesting that he provide evidence from clinical use of the product in Ireland in order to support obtaining the product licence for Konyne HT in the UK **[BAYP0000008_188]**.[491] This was because after discussion with CSM it was agreed that Cutter UK would provide some long-term evidence of safety in clinical use with special reference to the transmission of infectious viruses. However, after further discussion with CSM on the problems of generating the safety data, Cutter UK decided to ask a clinician who had used the product to write a report and speak on behalf of Cutter UK at the hearing with CSM **[BAYP0000010_170]**.[492] In an earlier note it was stated that *"this is probably the only way the Committee on Safety of Medicines can be persuaded to*

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[487] 27 January 1986, Telex from Cutter UK to Cutter Inc [**Other/13/1092**], **BAYP0000008_072**
[488] 6 February 1986, Telex from Cutter Inc to Cutter UK [**Other/13/1103**], **BAYP0000008_087**
[489] 25 June 1986, Note from Cutter UK to Cutter Inc [**Other/13/1228**], **BAYP0000008_242**
[490] 12 February 1986, Letter from Cutter Inc to Cutter UK [**Other/13/1107**], [**WITN6984133**]
[491] 14 May 1986, Letter from Cutter UK to Professor Temperley [**Other/13/1182**], **BAYP0000008_188**
[492] 29 September 1987, Fax from Cutter UK to Cutter Inc [**Other/15/1561**], **BAYP0000010_170**

recommend grant of the licence" [**BAYP0000008_296**].[493]

280. In October 1987, the product licence had still not been granted. Following an apparent request from Cutter UK for further safety data, Cutter Inc replied that the only absolute data held was the *in vitro* work performed by McDougal *et al* (see paragraph 159 above). Options suggested to satisfy CSM requirements were:

280.1 to prepare at any time a detailed account from Cutter Inc's adverse reaction files indicating the total use of Konyne HT over any given period, coupled with the number and nature of spontaneously reported adverse reactions during that period, or;

280.2 to set up a prospective study similar to that proposed for Koate HS in which patients seldom-or-never previously treated with blood or blood products would be followed up over a six-to-twelve month period after receiving Konyne HT [**BAYP0000010_175**].[494]

281. In September 1988, following "the regular annual chasing that occurs when a Section 21(1) Notice has been received and not followed up by the company" [**BAYP0000011_228**],[495] Bayer UK considered that "an imminent and adequate reply to the CSM cannot be made, and thus withdrawal of the application would be appropriate" [**WITN6984134**].[496] Therefore, and following a further request from the CSM to inform it of the company's intentions regarding the application [**WITN6984135**],[497] Bayer withdrew the application on 7 November 1988, referencing the CSM's reasons for being unlikely to grant a product licence [**WITN6984136**].[498]

282. It is apparent from the documents available that Konyne HT was still being imported and supplied in the UK on a named-patient basis in June 1990 [**BAYP0000035_044**].[499] As detailed in **Annex A**, such import had to be approved by MCA. On 2 July 1990, an internal note stated that an application made by Bayer UK to import a stock of Konyne HT for named-patient use had not yet been granted because the Medical Assessor required information on the screening of donors and the heat treatment procedure [**BAYP0000035_049**].[500] An internal memo stated that the following information

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[493] 15 July 1986, UK Trip Report 4 July 1986 [**Other/13/1273**], **BAYP0000008_296**
[494] 13 October 1987, Fax from Cutter Inc to Cutter UK [**Other/15/1563**], **BAYP0000010_175**
[495] 9 September 1988, Telephone note of a call between CSM and Bayer UK [**Other/16/1741**], **BAYP0000011_228**
[496] 4 November 1988, Bayer UK internal memo [**Other/16/1760**], [**WITN6984134**]
[497] 4 November 1988, Letter from CSM to Cutter UK [**Other/16/1761, attachment**], [**WITN6984135**]
[498] 7 November 1988, Letter from Bayer UK to CSM [**Reg/5/430**], [**WITN6984136**]
[499] 21 June 1990, Bayer UK internal memo [**Other/18/1945**], **BAYP0000035_044**
[500] 2 July 1990, Bayer UK internal memo [**Other/18/1949**], **BAYP0000035_049**

should be sufficient for the assessor's needs:

> *"(i) All plasma donations are tested, using FDA approved kits, and must be found non-reactive for hepatitis B surface antigen (HBsAg) and antibody to HIV-1. Recently the CSM has requested that all donations are also screened with regard to HIV-2 but Cutter have not yet responded to this. The Konyne material will not have been screened with regard to HIV-2. However, at this point, it should not cause any problems with regard to named-patient supply. Each unit of plasma used in the manufacture of Konyne HT will also have been tested and found to have an ALT level less than twice the upper limit of normal for the test. (ii) The preparation of the Factor IX bulk solution is followed by centrifugation, sterile filtration, filling and freeze-drying. The lyophilised material is then heat-treated at 68 ± 2°C for 72-77 hours to inactivate contaminant viruses"* **[BAYP0000035_050]**.[501]

Concluding Comments

283. In summary, the risks of transmission of hepatitis through factor concentrates were recognised from the time of first supply. Efforts were made to exclude infected donors from plasma pools through donor screening and deferral. Testing for HBsAg began in the 1970s. When NANB hepatitis was recognised as a problem after screening for hepatitis B became possible, efforts to eradicate hepatitis from factor concentrates were hampered by the fact that the causative virus (hepatitis C) was not isolated until the end of the 1980s. The sensitivity of donor screening measures, hepatitis B testing and testing for surrogate markers was such that these efforts did not eradicate the risk of hepatitis in factor concentrates. Warnings of the possibility of hepatitis were at all times provided by Bayer in the labelling with its relevant blood products. There were substantial challenges in developing effective methods of viral inactivation of factor concentrates that would preserve factor activity and avoid denaturation of the factor proteins, with concern over the risks of thrombogenicity and development of inhibitors. The development of effective viral inactivation methods was also hampered by problems with validation; when the predominant concern was NANB hepatitis, the available tools were indirect chimpanzee studies and clinical testing in previously untreated patients, with the associated ethical difficulties.

284. When the new disease, subsequently known as AIDS and caused by HIV, was first recognised, neither the cause of the identified immune deficiency nor the natural history of the condition were initially properly understood. It was subsequently demonstrated that by the time the condition was first recognised,

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[501] 3 July 1990, Bayer UK internal memo [**Other/18/1950**], **BAYP0000035_050**

many people with haemophilia were already infected. Efforts to develop hepatitis safe factor concentrates through heat treatment methods by Cutter Inc and other fractionators, which were not successful in eradicating the risk of hepatitis, did prove effective in inactivating HIV.

285. I hope that this summary of the documents provided to the Inquiry is of assistance. If the Inquiry has any questions on the content, I am available to provide any further assistance that I can.

286. I, together with colleagues from Bayer, have closely followed the work of the Infected Blood Inquiry. We have been moved by the accounts of those who have been infected and affected by the tragedy and we recognise the enormous courage shown by each of them. On behalf of Bayer, I would like to say that we are truly sorry that this tragic situation occurred and that therapies that were developed by us, and that were prescribed by doctors to save and improve lives, in fact ended up causing so much suffering to so many.

Statement of Truth

I **BELIEVE** that the facts stated in this Witness Statement are true.

Signed: GRO-C

Dated: 21 December 2021

INFECTED BLOOD INQUIRY

BRENDON GRAY WITNESS STATEMENT

ANNEX A

ANNEX A - SUMMARY OF REGULATORY FRAMEWORK FOR MEDICINES APPLICABLE IN THE UK FROM 1970 - 1993

1. The Medicines Act 1968 ("the Medicines Act") came into force in 1971 and, subject to amendment at various times, provided the legislative framework for the manufacture and supply of medicinal products in the UK during the period covered by this statement.

2. When the UK became a member of the European Community on 1 January 1973, Directive 65/65/EEC, which provided the framework for the licensing of proprietary medicinal products in the European Community, became applicable in the UK. The provisions of Directive 65/65/EEC, and later Directives on proprietary medicines (Directive 75/319/EEC and 89/341/EEC), were implemented, at material times, through amendments to the Medicines Act and subsidiary legislation.

2.1 "Medicinal product" was defined by Directive 65/65/EEC as "*any substance or combination of substances presented for treating or preventing disease in human beings or animals*" or "*any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions*".[1] "*Substance was defined as including "any matter irrespective of origin, which may be: human, e.g. human blood and human blood products*' […]".[2]

2.2 Directive 65/65/EEC was amended by Directive 75/319/EEC, which came into force in May 1975. This provided that Directive 65/65/EEC should not apply to "[…] *proprietary medicinal products based on human blood or blood constituents […]*[3]", effectively excluding medicinal products derived from human blood or plasma from the scope of Council Directive 65/65/EEC. This allowed EU Member States to retain national control of the regulation of medicinal products derived from human blood or human plasma. In the UK, blood products continued to be subject to regulation under the Medicines Act.

2.3 On 12 January 1988, the European Council proposed a Council Directive to extend the scope of Directive 65/65/EEC by laying down additional provisions for medicinal products derived from human blood.[4] Following amendments by the European Parliament and the European Commission, this proposal was

[1] Article 1(2) of Directive 65/65/EEC
[2] Article 1(3) of Directive 65/65/EEC
[3] Article 34 of Directive 75/319/EEC
[4] Proposal for a Council Directive extending the scope of Directive 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down additional provisions for medicinal products derived from human blood; COM(87) 697 final; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:51987PC0697(03)&from=EN

adopted and introduced by Directive 89/381/EEC, applicable from 1 January 1992. This amended Directive 75/319/EEC and provided that Directive 65/65/EEC and Directive 75/319/EEC should apply to '*medicinal products derived from human blood or human plasma*'[5]. Directive 89/381/EEC did not, however, apply to *"whole blood, to plasma or to blood cells of human origin"*.[6]

2.4 However, it was not until 1991 that guidance was published, based on agreement between the EEC Member States, as to what was required to establish viral safety of biological product and which required review by the relevant regulatory authority of all licensed products derived from human blood or human plasma.[7] The effect was that the dossiers of previously authorised products had to be re-reviewed by the relevant regulatory agency to ensure compliance with the guidance.

3. In accordance with the requirements of the Medicines Act, medicinal products launched after 1 September 1971, could be marketed in the UK only in accordance with a Product Licence[8] (subsequently called a marketing authorisation), granted after assessment of safety, quality and efficacy by the Secretaries of State for Health and Agriculture and (during the period 1971 to 1999) the Secretary of State for Scotland ("the Licensing Authority").[9] Human and veterinary medicinal products which had been on the UK market on 1 September 1971 were eligible for a "Licence of Right",[10] but were required to undergo subsequent regulatory review of their safety, quality and efficacy.[11] Licences were also required for wholesale dealing in medicinal products and for manufacture and importation. The Licensing Authority had power to suspend, revoke or vary the provisions of any licence on the grounds that the medicinal product in question could no longer be regarded as a product which could be safely administered for the purposes indicated in the licence.[12]

4. In addition to the system of licences, the Medicines Act established controls over clinical trials and advertising of medicinal products and requirements for post-marketing safety surveillance.

5. Regulation of medicinal products (including blood products) in the UK was, from 1971, the responsibility of the Medicines Division of the Department of Health ("DHSS") and, from 1989, the Medicines Control Agency ("MCA"), an executive agency of the Department of Health (both referred to in this statement as, the

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[5] Article1(1) of Directive 89/381/EEC
[6] Article 1(2) of Council Directive 89/381/EEC
[7] Validation of Virus Removal and Inactivation Procedures (III/8115/89) / CPMP/BWP/268/95; and Medicinal Products derived from Human Blood and Plasma (III/8379/89)
[8] Section 7(2) of the Medicines Act 1968
[9] Section 19(1) of the Medicines Act 1968
[10] Section 25 of the Medicines Act 1968
[11] Section 25 of the Medicines Act 1968
[12] Section 28 of the Medicines Act 1968

"Regulatory Authority"). In 2003, the MCA merged with the Medical Devices Agency to form the Medicines and Healthcare products Regulatory Agency ("MHRA").

6. The grant, suspension, revocation and variation of licences was the responsibility of the Licensing Authority, advised by the Committee on Safety of Medicines ("CSM")[13] and its subcommittees, including the Subcommittee on Biologicals and the Subcommittee on Efficacy and Adverse Reactions ("SEAR"), with respect to the safety, quality and efficacy of medicinal products. The CSM was also tasked with promoting the collection and investigation of information relating to adverse reactions.[14]

7. The documents and material to be submitted in support of an application for a Product Licence were set out in regulations.[15]

8. Regulations setting out the requirements for product labels and data sheets including information for prescribers in relation to appropriate use of each licensed medicinal product, were made under the Medicines Act with the purpose of, *inter alia,* securing that any appropriate warning and other relevant information or instructions were provided[16]. The content of such product labels and data sheets formed part of the Product Licence for a medicinal product and all revisions were subject to approval by the Regulatory Authority, on the basis of an assessment of whether the contents properly reflected the state of scientific and technical knowledge at that time, before being put into circulation.

9. The importer of a medicinal product required a manufacturers (import) licence.[17] In granting an application for such a licence, the Licensing Authority was required to take into account the methods, standards and conditions of manufacture of the product. The Licensing Authority could require the applicant to provide from the overseas manufacturer of the medicinal product: (i) an undertaking that its premises and operations might be inspected by the Licensing Authority; (ii) an undertaking that it would comply with any conditions of the Licensing Authority; and (iii) a declaration that any requirements imposed under the law of the country in which the product was manufactured had been complied with.[18]

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[13] established under the Medicines (Committee on Safety of Medicines) Order 1970 pursuant to section 4 of the Medicines Act 1968

[14] Medicines (Committee on Safety of Medicines) Order 1970, SI 1970/1257

[15] Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Regulations 1971 SI 1971/973

[16] The Medicines (Labelling) Regulations 1976 pursuant to Sections 85(2)(b) and 86(1) Medicines Act 1968

[17] Section 7(3) of the Medicines Act 1968

[18] Section 19(3) of the Medicines Act 1968

Batch Release

10. A licence to market a biological medicine, such as Factor VII or Factor IX concentrates, in the European Community included a requirement that samples of each batch or lot of the product should be submitted to one of the EC's Official Medicines Control Laboratories ("OMCLs") before being released onto the market. Batch release, in this context, refers to the independent testing of such products and examination of test data supplied by the manufacturer, by OMCL scientists in order to confirm the quality and safety of such products. At all material times the National Institute for Biological Standards and Control ("NIBSC") carried out batch release on behalf of the DHSS for the UK market.[19]

11. The NISBC was established in 1972 with responsibilities including the development of standards and reference materials, product control testing and the conduct of applied research. As a result of the Biological Standards Act 1975, from that time until 2009, the NIBSC was controlled by the National Biological Standards Board ("NBSB"), a non-departmental government body. In 2009 the functions of the NBSB were transferred to the Health Protection Agency and, in 2013, the NIBSC merged with the MHRA.

Unlicensed Supply on a Named Patient Basis

12. In certain circumstances a medicinal product could be supplied for use by a patient in the absence of a Product Licence. One such circumstance was supply on a so-called "named-patient" basis in accordance with section 9 Medicines Act, whereby an unlicensed medicinal product could be specially prepared or specially imported to the order of a doctor or dentist for administration to a particular patient under his care.

13. In November 1978, the Medicines (Exemption from Licences) (Importation) Order 1978, imposed further conditions for the import of unlicensed products for the purposes of supply on a named patient basis.[20] These conditions were that:

13.1 The importer of the product should notify the Licensing Authority within 21 days of the first occasion upon which each particular description of such product was received for the purposes of sale or supply;

13.2 The Licensing Authority had not directed on the grounds of safety that this exemption should not apply or should cease to apply; no advertisement or representation of such products was issued or made;

13.3 The sale or supply of such products was in response to a bona fide unsolicited

[19] NBSB Annual Report and Accounts 2001/2; https://www.nibsc.org/PDF/NBSB_annual_report_200102.pdf

[20] The Medicines (Exemption from Licences) (Importation) Order, SI 1978-146

order; written records would be kept, maintained and made available to the Licensing Authority on request; and that such products would be stored in such a way to reduce to a minimum the risks of deterioration or contamination.

14. The 1978 Order was replaced from June 1984, by the Medicines (Exemption from Licences) (Importation) Order 1984. The 1984 Order amended the requirement that the importer should inform the Licensing Authority within 21 days of receipt of an unlicensed product for the purposes of supply on a named patient basis, to provide that the importer should give the Licensing Authority prior notice, in writing of the intention to import such product (giving details of manufacturer and constituents), and the quantity to be imported. The importer was also required to provide an undertaking that the quantity of the medicinal product to be imported did not exceed 25 single administrations or 25 courses of treatment not exceeding three months and that he would inform the Licensing Authority of any matter coming to his attention which might reasonably cause the Licensing Authority to believe that the product could no longer be regarded either as a product which could safely be administered to human beings or as a product which was of satisfactory quality for such administration. The relevant product could not be imported if the Licensing Authority provided a notice in writing within 28 days of acknowledging receipt of the importer's intention to import, that the provisions of the Order should not apply, including because the Licensing Authority had reasonable cause to believe that the product could not be regarded as a product which could safely be administered to human beings or as a product which was of satisfactory quality for such administration[21].

Clinical Trials

15. From the entry into force of the Medicines Act, a person could sell or supply or procure the sale, supply, manufacture or assembly of an unlicensed medicinal product for the purposes of a clinical trial only pursuant to a Clinical Trial Certificate issued by the Licensing Authority, certifying that the Licensing Authority had consented to the clinical trial in question and that certificate was at that time in force and the trial was to be carried out in accordance with that certificate.[22]

16. However, from March 1981, regulations[23] provided that the restrictions on sale, supply, manufacture and assembly of unlicensed medicinal products for the purposes of a clinical trial, as set out in paragraph 15, would not apply if the following conditions were met:

16.1 A notice has been submitted to the Licensing Authority by the supplier, setting out an intention to sell or supply or procure the sale, supply, manufacture or assembly of a medicinal product for the purposes of a clinical trial and providing

[21] The Medicines (Exemption from Licences) (Importation) Order, SI 1984-673
[22] Section 31 of the Medicines Act 1968
[23] Medicines Exemption from Licences (Clinical Trials) Order 1981

certain information in relation to the product; and the Licensing Authority has not, within 35 days of receipt of such notice from the supplier, sent a notice stating that such regulations shall not apply to the proposed clinical trial in relation to the medicinal product.

16.2 The supplier has provided an undertaking to the Licensing Authority that it will inform them of: any adverse reactions or effects associated with administration of the medicinal product; any other matter which might reasonably cause the Licensing Authority to think that the medicinal product could no longer be safely administered for the purposes of a clinical trial or as a product of satisfactory quality for those purposes; any change in the medicinal product or the clinical trial (as set out in schedule 2 to the regulations; and any refusal by an ethics committee in the UK to approve the clinical trial.

17. Exemptions conferred by the 1981 Order were valid for 3 years, unless terminated by the Licensing Authority.

Adverse Events

18. The Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (the "Standard Provisions Regulations ") set out, at Schedule 1, are the standard provisions that were incorporated into product licences, including the duty to report information that cast doubt on the assessment of safety, quality or efficacy of the medicinal product and the obligation to record reports of adverse events and provide copies to the Licensing Authority upon request. In addition, paragraph 4 of Schedule 1 permitted the Licensing Authority to issue "Standard Directions" regarding the reporting of suspected adverse events. The focus was upon reports arising in the UK which had been made or confirmed by a doctor. The first Standard Directions, published in the early 1970s (a copy of which was subsequently attached to Medicines Act Information Letter ("MAIL") 18), stated that:

"the licensing authority directs the holder of [any product licence] to furnish to the authority, for the information of the CSM... copies of all reports, as defined below and originating in the UK, of which he is aware of adverse effects on human beings suspected of association with the use of any medicinal product to which any such licence relates. The holder of the licence is required to furnish such reports as soon as possible after receipt or, where appropriate, immediately after substantiation by the patient's doctor".

This requirement applied to

"any report made or confirmed by a medical or dental practitioner, a pharmacist, a coroner or a procurator fiscal and which relates to an adverse effect which has occurred at doses in normal use and falls within one or more of the following:

(a) a reaction with a fatal outcome,

(b) a reaction of sufficient severity to interfere with normal activities,

(c) any unusual reaction, not referred to in standard publication or in literature issued by the manufacturer or licence holder, or

(d) any reaction which may be an example of possible drug-interaction".

The licence holder was also required "to furnish without delay information from abroad of which he becomes aware about suspected adverse reactions to medicinal products of the kind to which the licence relates, that is containing the same active ingredients, which suggests that an associated serious hazard may exist. Separate reports of every individual suspected adverse effect are not required".

19. The Standard Directions were amended in December 1977 (MAIL18) to state: "Licence holders should ensure that in all cases such reports are furnished no later than one month after receipt". The revised Directions also stated that if, by that time, the doctor had not provided any information, the Licensing Authority should be informed, and if the doctor subsequently provided information, a further notification should be submitted to the Licensing Authority.

20. In October 1984, new Standard Directions were published, by way of MAIL 41, which came into force on 1 November 1984 and revoked previous versions of the Directions. It stated that reports of suspected reactions should contain the following basic information: patient name (or identifying code), the reporting doctor's name and address, name(s) of the drug(s), and details of the reaction. The guidance advised that reactions should be confirmed in writing by the patient's doctor or dentist, a coroner or procurator fiscal. "It may be necessary to seek substantiation before reporting a reaction. However, companies should not wait for the outcome of the reaction before reporting and should not draw distinctions between "conceivable" and "suspect" reactions to justify failing to report some reactions." Companies did not need to send reports of particular cases of reactions published in the standard scientific literature.

20.1 The Directions included the following requirements:

- Reports of Reactions originating in the UK

  Reports on products subsequent to marketing

  i. New Products

  "All products containing new chemical entities (or novel formulations of existing substances) are the subject of special reporting arrangements.

Companies will be told of the need to follow the special reporting arrangements when the product licence is granted,....."

Special reporting arrangements required reporting of all adverse reactions to the Licensing Authority and the inclusion of a black triangle in the datasheet. The special reporting would usually last for a period of 4 years from the date of grant (or, if there was a delay, the date of first marketing).

"All spontaneous reports from doctors, whether serious or otherwise, should be submitted to the licensing authority immediately. .....(NB For the purposes of this guidance "serious" means fatal, life threatening, disabling or incapacitating. Examples of serious reactions are anaphylaxis, blood dyscrasias, congenital abnormalities, endocrine disturbances, fertility effects, haemorrhage from any site, jaundice (however mild), ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women)."

ii. Other Drugs

"Serious reactions which arise spontaneously or from clinical studies after marketing should be reported immediately... Spontaneous reports of minor reactions need not be reported."

Serious reactions meant that "the reaction is fatal, life threatening, disabling or incapacitating.".

Products under trial

i Products subject to clinical trial certificates (CTC)

"Companies are required to inform the licensing authority of any information which casts doubts on the continued validity of the data submitted with the application for a CTC in relation to the safety of the product in its proposed indications. Serious reactions should be submitted immediately; all other reports should be provided in summary form at the conclusion of the trial. All investigators should be informed of serious, unpredictable reactions occurring in the trials....."

ii Products subject to clinical trial exemption (CTX)

"Companies are required to inform the licensing authority forthwith of any adverse reactions or effects associated with the administration of the medicinal product. Speed in reporting is particularly important with serious reactions. All investigators should be informed of serious, unpredictable reactions occurring in the trials".

- Reports originating abroad

  Reports on all products subsequent to marketing.

  "Reactions which are both serious and unpredictable ("unpredictable" means not previously referred to in the data sheet or scientific literature) should be reported immediately. Reports of other reactions are not required. (It is obviously important that companies should ensure a prompt exchange of information on adverse reactions between the parent company and subsidiaries if this requirement is to be implemented effectively").

  Products under trial

  i Products subject to CTCs

  "All serious and unpredictable reactions should be reported immediately. Other reactions should be submitted in summary form either at the conclusion of the UK trials or in any product licence application".

  ii Products subject to CTX

  "Companies are required to inform the licensing authority forthwith of any adverse reaction, whether serious or not, associated with the administration of the product. Speed in reporting is particularly important with serious reactions".

20.2 The Directions included a summary table of the obligations for the reporting of single reports of domestic UK adverse reactions:

	All serious reactions or effects	**Minor reactions**
Licensed Products: Spontaneous reports (New drugs)	Report on yellow forms immediately	Report on yellow forms immediately
Licensed Products: Spontaneous reports (Other drugs)	Report on yellow forms immediately	Not required
Clinical studies after marketing (New drugs)	Report on yellow forms immediately	Report in summary at conclusion of trial or study
Clinical studies after marketing (Other drugs)	Report on yellow forms immediately	Report in summary at conclusion of trial or study

Products under clinical trials	Immediately on Company Reporting Form	Summary form at the end of trial

And for reactions originating abroad:

	Serious *and unpredictable* reactions	**Minor or predictable reactions**
Products licensed in the UK	Report on yellow forms immediately	Not required
Unlicensed products under clinical trials in the UK	Report on yellow forms immediately	Report in summary at conclusion of UK trial or at the time of a product licence application

21. In March 1987, new guidance on the reporting of adverse drug reactions was provided in MAIL 49 [24] and introduced new forms to be used for reporting ADRs.

21.1 The guidance provided:

(A) Reporting requirements for licensed products

…

"Adverse "events" not suspected of being drug related by the doctor attending the patient should not be reported. This guidance is concerned with the reporting requirements of adverse reactions or effects which are suspected to be drug related. ...

…It may be necessary to submit an initial, incomplete report, which will be augmented with more extensive data when available. ...

Companies are expected to validate fully and follow-up all serious reactions reported by them to the Licensing Authority…".

- Reactions occurring in the UK

For spontaneous reports, all adverse reactions or effects associated with new

[24] This guidance was based on an initial report on *International Reporting of Adverse Drug Reactions* by the CIOMS' first Working Group on pharmacovigilance, *Working Group on International Reporting of Adverse Drug Reactions*

drugs had to be reported, but only serious reactions or effects associated with "other drugs". The guidance stated that "Serious reactions or effects" were "those suspected adverse reactions that are fatal, life threatening, disabling, incapacitating or which results in, or prolong, hospitalisation. Serious reactions should be reported immediately i.e. as soon as they are brought to the company's attention" (no specific time limit was given).

For reports from clinical trials conducted within the terms of the product licence (such as Phase IV clinical trials and post marketing surveillance studies), all serious reactions or effects had to be reported immediately with minor reactions reported in summary at the conclusion of each study.

Companies were also required to provide the details of reports obtained from published literature on company reporting forms as for individual spontaneous reports. These reports had to be followed-up by the company as for any other type of report. No specific time lines were given, and the Directions were unclear regarding whether 'literature' referred to the UK only.

- Reactions occurring aboard

"Only reports of suspected adverse drug reactions which are both "serious and unpredictable" arising abroad (either spontaneous or from a clinical trial carried out under the terms of the licence) should be submitted to the Licensing Authority. ... Minor or predictable reactions or coincidental events need not be reported." "Unpredictable" meant "events not previously referred to in the warnings, precautions or contra-indication section of the data sheet, SPC or product licence" .

The licence holder "should advise the Licensing Authority if the implications of the collective data base for a reaction change e.g. if a reaction notified in a data sheet ceases to be rare due to the collection of such reactions occurring abroad. The UK licence holder should inform the Licensing Authority of suspected adverse reactions occurring aboard, which are brought to the company's attention, even if they are not the licence holder in those countries".

21.2 The Directions included a summary table of the obligations for the reporting of single reports of domestic UK adverse reactions:

	All serious reactions or effects	**Minor reactions**
Licensed Products: Spontaneous reports (New drugs)	Report immediately on Company Reporting Form	Report immediately on Company Reporting Form

Licensed Products: Spontaneous reports (Other drugs)	Report immediately on Company Reporting Form	Not required
Clinical studies after marketing within the terms of product license	Report immediately on Company Reporting Form	Report in summary at conclusion of trial or study
Products under clinical trials	Report immediately on Company Reporting Form	Report in summary at conclusion of trial or study

And for single reports of reactions occurring aboard:

	All serious reactions	**Serious *and unpredictable* reactions**	**Minor reactions**
Products licensed in the UK	Not applicable	Report immediately on CIOMS[25] Form	Not required
Products under clinical trials in the UK	Report immediately on CIOMS Form or Company Reporting Form	Not applicable	Report in summary at conclusion of the UK trials, or at the time of the product licence application

(B) Reporting requirements for products under CTX or CTC or CTMP trials

"Companies are required to report forthwith "serious adverse reactions or effects associated with the administration of the medicinal product" whether occurring in the UK or abroad….."

22. MAIL 58 issued in March 1989, prescribed that "product licence holders are expected to maintain current familiarity with the indexed literature relating to the safety of the products which they market, and they are responsible for notifying adverse reactions in both UK and foreign literature", in the same way as for other adverse reaction reports.

[25] Council for International Organisations of Medical Sciences. in 1986, CIOMS set up its first Working Group on pharmacovigilance, a *Working Group on International Reporting of Adverse Drug Reactions* to explore means of coordinating and standardizing international adverse drug reporting by pharmaceutical manufacturers to regulatory authorities. The Working Group devised a method for the reporting by manufacturers of suspected adverse drug reactions which included standardized definitions, procedures and format. The report contains the CIOMS reporting Form 1, which for the first time set the minimum standard for reporting.

Promotion of Medicinal Products

Legislation

23. The Medicines Act included provisions regulating the advertising of medicinal products at all time relevant to this statement.

23.1 "Advertisement was defined broadly at section 92(1) of the Medicines Act as:

> "....every form of advertising, whether in a publication, or by the display of any notice, or by means of any catalogue, price list, letter (whether circular or addressed to a particular person) or other document, or by words inscribed on any article, or by the exhibition of a photograph or a cinematograph film, or by way of sound recording, sound broadcasting or television, or in any other way..."

23.2 The issue of false or misleading advertisements and representations by commercially interested parties, including advertisements consisting of unauthorised recommendations (i.e. recommendations for use of a medicinal product for indications other than those specified in the product licence for such product) was prohibited[26].

23.3 Any advertisement or representation directed towards medical practitioners was required to be accompanied by a datasheet and the content of the advertisement had to be consistent with such datasheet[27].

23.4 Advertisements and representations in relation to unlicensed medicinal products imported for the purposes of supply on a named patient basis in accordance with section 9 Medicines Act were specifically prohibited as a result of the Medicines (Exemption from Licences) (Importation) Order 1978 and the Medicines (Exemption from Licences) (Importation) Order 1984

24. The Medicines (Advertising) Regulations 1994 which implemented Directive 92/28/EEC in the UK, came into force in August 1994.

24.1 The 1994 regulations defined "advertising" as follows:

> "For the purposes of these Regulations, "advertisement" has the meaning assigned to it by section 92 of the Act, except that, in relation to a relevant medicinal product—

[26] Section 93 of the Medicines Act 1968
[27] Section 96 of the Medicines Act 1968

(a) provided that it makes no product claim, reference material, a factual, informative statement or announcement, a trade catalogue or a price list shall not be taken to be an advertisement, and

(b) an advertisement includes a representation,

and for the purposes of this paragraph, "representation" has the meaning assigned to it by section 92 of the Act, except that it does not include the making of a factual, informative statement or announcement which includes no product claim".

24.2 The 1994 regulations included more detailed provisions regarding the advertising of medicinal products including explicit prohibition of advertising of unlicensed products and advertising of prescription only medicines to members of the public.

The Association of the British Pharmaceutical Industry (ABPI) Code of Practice

25. The ABPI Code of Practice, established in 1958, is a voluntary set of principles, providing standards to be followed in the promotion of prescription only medicines. More recently, the Code has also included provisions relevant to certain non-promotional activities. Compliance with the Code is a condition of membership of the ABPI but, additionally, pharmaceutical companies who are not ABPI members may also commit to follow its provisions. At times relevant to this statement, the ABPI Code of Practice was administered by the Code of Practice Committee, established by the ABPI Board of Management with an independent legally qualified chair from outside the industry. Any person who believed that the promotion of a medical product had fallen below the standards required under the Code could write to the Code of Practice Committee in relation to such matter.

26. The Code of Practice has been revised and updated at regular intervals since 1958. Relevant editions of the Code and provisions applicable to the matters addressed in this statement are set out below.

27. The fifth edition of the Code was issued in December 1978.

27.1 The 1978 Code defined "promotion" at clause 1.1 as:

"...those informational and marketing activities, undertaken by the product license holder or with his authority, the purpose of which is to induce the prescribing, supply or administration of his medicinal products. It includes for example, the activities of representatives; various aspects of sales promotion such as journal and direct mail advertising; the use of films and other audio-visual material and exhibitions; and the provision of samples, gifts or hospitality.

The term "promotion" does not extend to:

(i) Replies made in response to particular doctors or replies in response to a specific communication, whether of enquiry or comment, including letters published in a medical journal.

(ii) Announcement of pack changes, adverse reaction warnings or recall of products provided they contain no product claims.

(iii) Trade Advertisements as defined in the Medicines (Advertising of Medicinal Products) Regulations 1975 i.e. catalogues, price lists or other documents with a view to wholesale dealing but not containing any reference to product usage other than a therapeutic classification".

27.2 The provisions of the Code included the following:

- A requirement that "information about medical products should accurately reflect current knowledge or responsible opinion" (clause 3.2);
- That "information about medical products must be accurate, balanced and must not mislead either directly or by implication" (clause 3.3);
- That "information must be capable of substantiation, such substantiation being provided without delay at the request of members of the medical profession" (clause 3.4);
- "Any statement about side effects should be specific and based on data submitted with the licence application or notified to the licensing authority or on published data to which references are given…" (clause 4.3);
- "Subject to clause 17.2 [inexpensive items relevant to the practice of medicine or pharmacy] no gift or financial inducement shall be offered or given to members of the medical profession for the purposes of sales promotion" (clause 17.1);
- "Entertainment or other hospitality offered to members of the medical and allied professions for purposes of sales promotion should always be secondary to the main purpose of the meeting. It should not extend beyond members of the professions. The level of hospitality should be appropriate and not out of proportion to the occasion; its cost should not exceed that level which the recipients might normally adopt when paying for themselves " (clause 18);
- "Medicines which cannot legally be sold or supplied to the public otherwise than in accordance with a prescription or which are legally

limited to promotion for sale or supply only on prescription, must not be advertised to the general public" (Clause 20.2);

- "Information about medical products or matters related thereto, including scientific discoveries or advances in treatment, should not in general be made available to the general public either directly or through any lay medium" (clause 20.4);

28. The fifth edition of the Code was revised in April 1982 through the addition of supplementary text to clarify the interpretation of the various provisions. This supplementary text included:

- Clarification of "wholesale dealing" in the context of trade advertisements, excluded from the definition of promotion in clause 1.1:

  "By "wholesale dealing" is meant the sale of a product to a person who, during the course of his business or professional practice, buys it for the purpose of selling it or administering it or causing it to be administered to one or more human beings".

- Further information regarding hospitality at clause 18:

  "Medical and group meetings are desirable and are to be encouraged. Both the British Medical Association and the [ABPI] share the opinion that such meetings should only take place if the advertising content is supported by a clear educational content. If hospitality is offered at meetings attendance should be restricted to members of the medical and allied professions.

  It follows therefore that invitations to such medical and group meetings should not be extended to wives or husbands unless they themselves are practising members of the medical or allied professions.

  When organising a meeting at which hospitality will be offered, a factor to be taken into account is the impression which will be created in the minds of the recipients or those who hear about it. Hospitality which becomes little more than pure entertainment has limited value in terms of the provision of information and promotion; such hospitality can only be regarded therefore, as irrelevant and wasteful".

- Clarification of the requirement that information regarding medical products should not in general be provided to members of the general public at clause 20.4:

  "The intention is to ensure that arrangements made for a press conference or the extent of a press release are such as to confine the disclosure of information about medical products or matters relating thereto to persons who are capable of evaluating the information responsibly and not concerned to exaggerate or even sensationalise its significance".

29. The sixth edition of the Code was issued in January 1984.

- This introduced a new clause 3 , which provided:

  "A medical product must not be promoted prior to the grant of the product licence authorising its sale or supply",

- Clause 3 did not prohibit those activities excluded from the definition of promotion at clause 1.1.

- The content of clause 3 of the fifth edition of the Code was reflected in clause 4 of the sixth edition; clause 4 of the fifth edition was reflected in clause 5 of the sixth edition; clause 17 of the fifth edition was reflected in clause 19 of the sixth edition; clause 18 of the fifth edition was reflected in clause 20 of the sixth edition; and clause 20 of the fifth edition was reflected in clause 22 of the sixth edition.

30. The sixth edition of the Code was revised in January 1986.

31. The seventh edition of the Code was issued in January 1988.

INFECTED BLOOD INQUIRY

BRENDON GRAY WITNESS STATEMENT

ANNEX B

ANNEX B - SUMMARY OF REGULATIONS AND PROCEDURES RELEVANT TO THE OPERATION OF PLASMA COLLECTION CENTRES IN THE USA

1. The United State Food and Drug Administration (the "FDA"), through its Bureau of Biologics (the "BoB"), licensed and regulated the manufacture of biological medicinal products.[1] Cutter Inc was a licensed manufacturer and seller of biologics including factor concentrates.

2. The FDA's Code of Federal Regulations ("CFR's") codified the general and permanent rules for the manufacture of biologics[2]. The FDA Regulations became effective in 1972 and were finalized in the summer of 1973. Since 1975, all manufacturers of biologics, including factor concentrates, have been required to be licensed and regulated by the FDA.

3. By 1976, a manufacturer wishing to obtain a product licence for a biological product was required to submit an application containing a description of the facilities and equipment,[3] identify key personnel[4] (regulatory head, medical directors, etc.), detail of all manufacturing steps[5] (in Cutter's case, the proprietary fractionation process, through Product Licensing Applications or "PLA's"), a description of quality control procedures for plasma centres[6] (Cutter's System of Plasmapheresis or "CSOP's"), reports of all preclinical and clinical studies[7] to demonstrate that the product was safe and effective and a demonstration of the ability to consistently produce multiple lots of the product in conformance with the

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[1] § 601.2, 'application for establishment and product licenses, procedure of filing' (page 32052) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics , PDF page 6).
[2] See first § under 'reorganization and republication' (page 32048), of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II. (1973 biologics, PDF page 2)
[3] § 600.11 'Physical establishment, equipment animals, and care' (page 32049) and § 601.20 'Product licenses; issuance and conditions' (page 32053) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics , PDF pages 3 and 7).
[4] § 600.10 'Personnel' (page 32049) and § 601.20 'Product licenses; issuance and conditions' (page 32053) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics , PDF pages 3 and 7).
[5] § 601.2 Application for establishment and product licenses; procedure for filing (page 32052) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics , PDF page 6).
[6] § 640.65 'Plasmapheresis' (page 32094) (which sets out procedure specific requirements) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics , PDF page 48).
[7] § 601.2 Application for establishment and product licenses; procedure for filing (page 32052) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics , PDF page 6).

proscribed standards.[8]

4. A manufacturer's facilities[9] and records[10] were inspected by BoB personnel prior to licensure and annually thereafter.[11] The published general standards for the manufacture of biological products[12] were supplemented by specific additional standards[13] which prescribe requirements in areas such as manufacturing, quality control testing and labelling that are unique to individual products.

5. In the case of batch products such as factor concentrates, the manufacturer was required to submit a protocol providing results of the required tests on each lot and a sample of the lot for review and testing at the BoB. Satisfactory lots were then released by the BoB for sale and distribution by the manufacturer.[14]

6. The CFRs mandated large pools (from which immune globulins and factor concentrates were prepared) of at least 1000 different donors for the manufacture of immune globulins to ensure the inclusion of a broad spectrum of antibodies.[15]

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[8] § 610.1 'Tests prior to release required for each lot' (page 32065) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics , PDF page 10).

[9] § 600.22 'Duties of inspector', point (c) (page 32051) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II. (1973 biologics, PDF page 5)

[10] § 600.22 'Duties of inspector', point (g) (page 32052) and § 600.12 'Records' (page 32051) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II. (1973 biologics, PDF pages 5 - 6)

[11] § 600.21 'Time of inspection' (page 32051) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II. (1973 biologics, PDF page 5)

[12] Part 610 - General biological products standards (page 32056) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics, PDF page 10); page 26163 of the Federal Register, Vol 39, NO. 138- Wednesday, July 17, 1974 (1975antigen, PDF page 13); and, page 29710 of the Federal Register, Vol 40, NO. 136- Tuesday, July 15, 1975 (1975antigen, PDF page 5)

[13] Part 640 - Additional standards for human blood and blood products (page 32089) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II (1973 biologics, PDF page 43); page 26164 of the Federal Register, Vol 39, NO. 138- Wednesday, July 17, 1974 (1975antigen, PDF page 14); and page 29711 the Federal Register, Vol 40, NO. 136- Tuesday, July 15, 1975

[14] § 610.1 'Tests prior to release required for each lot' and § 610.2 'Requests for samples anti protocols; official release' (page 32056) of the Federal Register, Department of Health, Education and Welfare, FDA, Reorganization and republication, November 20, 1973. Volume 38, Number 223, Part II. (1973 biologics, PDF page 10)

[15] 1 April 1974, Code of Federal Regulations, Manufacture of Immune Serum Globulin (Human) #640.102(d) **[WITN6984022]**

INFECTED BLOOD INQUIRY

BRENDON GRAY WITNESS STATEMENT

ANNEX C

ANNEX C - SCHEDULE OF WARNINGS

Schedule showing the development of the text, over time, regarding risk of viral transmission in the package insert, label and data sheet of Koate and Koate HT.. Only where a change is made regarding risk of viral transmission is the relevant document included in the schedule. Where changes are embedded within existing text, the change is underlined.

October 1975 (application) **[Reg/1/4], BAYP0000001_098**	Koate - package insert	"Antihemophilic Factor (Human) Koate™ SEE SECTIONS ENTITLED "INDICATIONS" AND "WARNING" FOR DESCRIPTION OF HEPATITIS RISK" "THIS PRODUCT IS PREPARED FROM UNITS OF HUMAN PLASMA WHICH HAVE BEEN TESTED AND FOUND NON-REACTIVE FOR HEPATITIS ASSOCIATED (AUSTRALIA) ANTIGEN. UNFORTUNATELY THIS TEST DOES NOT WITH CERTAINTY PRECLUDE THE PRESENCE OF HEPATITIS VIRUS. SEE WARNING." INDICATIONS […] "CAUTION: BECAUSE OF THE POSSIBILITY THAT ANY LOT OF KOATE™ MIGHT CONTAIN THE CAUSATIVE AGENTS OF VIRAL HEPATITIS, ITS USE MUST BE CONSIDERED IN LIGHT OF THIS HAZARD, PARTICULARLY IN PERSONS WITH FEW PREVIOUS TRANSFUSIONS OF BLOOD AND PLASMA PRODUCTS. Kasper and Kipnis[4] have concluded that those who had little exposure to blood products had a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild hemophilia, they recommend single donor products. However, for patients

		with moderate or severe hemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients. WARNING Koāte™ concentrate is a purified dried fraction of pooled plasma obtained from many donors. *SINCE THE PRESENCE OR ABSENCE OF HEPATITIS VIRUS IN KOĀTE™ CONCENTRATE CANNOT BE PROVEN WITH ABSOLUTE CERTAINTY, THE PRESENCE OF SUCH A VIRUS SHOULD BE ASSUMED* and the hazard of administering Koāte™ concentrate should be weighed against the medical consequences of withholding it. Since there is this definite risk of hepatitis, we suggest that the physician give consideration to explaining to the patient (or the patient's family) the relative risks of giving or withholding this product. Then, should the patient develop hepatitis, as a result of the injection, it will not come as a surprise, and there is not nearly the likelihood of resentment, which will almost surely follow an unexplained and unexpected infection." "4. Kasper CK, Kipnis SA: Hepatitis and clotting-factor concentrates. JAMA 221:510, 1972." WARRANTY "[….] and that the risk of transmitting hepatitis be carefully weighed before the product is prescribed."

October 1975 (application) **[Reg/1/4], BAYP0000001_098**	Koate - label	"WARNING: Since the presence or absence of the virus of hepatitis in Koāte™ cannot be proven with absolute certainty, the presence of such virus should be assumed and the hazard of administering Koāte™ should be weighed against the medical consequences of withholding the use of Koāte™." "HEPATITIS DANGER SEE DIRECTION SHEET"
January 1981 **[Other/4/190], BAYP0000019_012**	Koate - data sheet	"[…] Koate concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous infusions of blood and plasma products. Kasper and Kipnis have concluded that those who have had little exposure to blood products have a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild haemophilia, they recommend single donor products. However, for patients with moderate or severe haemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe haemophilia that these products should not be denied to appropriate patients."
March 1981 **[Other/4/199], BAYP0000019_025**	Koate - package insert	"Antihemophilic Factor (Human) Koāte® […]

		"**THIS PRODUCT IS PREPARED FROM HUMAN VENOUS PLASMA. EACH INDIVIDUAL UNIT OF PLASMA AND EACH LOT OF FINAL PRODUCT HAS BEEN FOUND NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN USING A LICENSED THIRD-GENERATION ASSAY. HOWEVER, THIS TEST DOES NOT PRECLUDE THE PRESENCE OF HEPATITIS VIRUS. SEE WARNING**." **WARNING** Antihemophilic Factor (Human) Koāte™ concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koāte concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood and plasma products. Kasper and Kipnis[4] have concluded that those who have had little exposure to blood products have a high risk of developing hepatitis after introduction of clotting factor concentrates, such as this product. For those patients, especially those with mild hemophilia, they recommend single donor products. However, for patients with moderate or severe hemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe hemophilia that these products should not be denied to appropriate patients. "4. Kasper CK, Kipnis SA: Hepatitis and clotting-factor concentrates. *JAMA*. 221(5):510, 1972."

December 1981 **[Other/4/236], BAYP0000019_087**	Koate - package insert	**"THIS PRODUCT HAS BEEN PREPARED FROM LARGE POOLS OF HUMAN VENOUS PLASMA COLLECTED FROM MANY PAID DONORS. EACH INDIVIDUAL UNIT OF PLASMA AND EACH LOT OF FINAL PRODUCT HAS BEEN FOUND NONREACTIVE FOR HEPATITIS B SURFACE ANTIGEN (HBsAg) USING A U.S. FEDERALLY APPROVED TEST OF AT LEAST THIRD-GENERATION SENSITIVITY. UNFORTUNATELY, THIS TEST DOES NOT PRECLUDE THE PRESENCE OF HEPATITIS VIRUSES. SEE WARNING.** **NO KNOWN LABORATORY TEST METHOD CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT HEPATITIS."**
16 August 1983 (Product Licence) **[Reg/2/93], BAYP0000002_196**	Koate - data sheet	"Warning Koate concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. The presence of hepatitis viruses should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequence of withholding it, particularly in persons with few previous transfusions of blood or blood products." [same as data sheet of January 1981]

March 1984 **[Other/8/548], [WITN6407005]**	Koate - package insert	**WARNINGS** **Koāte® concentrate is a purified dried fraction of pooled plasma obtained from many paid donors. Although each unit of plasma has been found nonreactive for hepatitis B surface antigen (HBsAg) using a U.S. Federally approved test with third-generation sensitivity, the presence of hepatitis viruses in such pools should be assumed.** Kasper and Kipnis[5] have concluded that those who have had little exposure to blood products have a higher risk of developing hepatitis after introduction of clotting factor concentrates. For those patients, especially those with mild haemophilia, they recommend single donor products. For patients with moderate or severe haemophilia who have received numerous infusions of blood and plasma products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe haemophilia that these products should not be denied to appropriate patients. Isolated cases of Acquired Immune Deficiency Syndrome (AIDS) have been reported in haemophilics who have received blood and/or coagulation factor concentrates, including Factor VIII concentrates. It is not known if the disease is due to a transmitted specific agent, secondary to multiple antigenic exposures, or to some other mechanisms. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of AIDS and weigh the benefits of therapy accordingly."

		"5. Kasper CK, Kipnis SA: Hepatitis and clotting-factor concentrates. *JAMA*. 221(5):510, 1972."
2 April 1984 **[Reg/3/124], BAYP0000003_214**	Koate - label	"**This product has been prepared from large pools of human venous plasma collected from many paid donors. Each individual unit of plasma and each lot of final product has been found nonreactive for hepatitis B surface antigen (HBsAg) using a U.S. Federally approved test with third-generation sensitivity.** **WARNING: KOĀTE® CONCENTRATE IS A PURIFIED DRIED FRACTION OF POOLED PLASMA OBTAINED FROM MANY PAID DONORS. THE PRESENCE OF HEPATITIS VIRUSES SHOULD BE ASSUMED AND THE HAZARD OF ADMINISTERING KOĀTE® CONCENTRATE SHOULD BE WEIGHED AGAINST THE MEDICAL CONSEQUENCE OF WITHHOLDING IT, PARTICULARLY IN PERSONS WITH FEW PREVIOUS TRANSFUSIONS OF BLOOD OR BLOOD PRODUCTS**."
12 November 1984 (application) **[Reg/3/167a] [WITN6984040]**	Koate HT - label	"HEPATITIS DANGER - SEE INSERT LEAFLET This product has been prepared from large pools of human venous plasma collected from many paid donors. Each individual unit of plasma and each lot of final product has been found non-reactive for hepatitis B surface antigen (HB_sAg) using a U.S. Federally approved test with third generation sensitivity. <u>WARNING</u>: Koate-H.T. Concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be assumed and the hazard of administrating Koate-H.T. concentrate should be weighed against the medical consequence of withholding treatment."
February 1985	Koate HT - data sheet	"Koate-HT concentrate is a purified dried fraction of pooled plasma obtained from many donors. The presence of hepatitis viruses should be

[Other/11/848], **[WITN6984041]**		assumed and the hazard of administering Koate-HT should be weighed against the medical consequence of withholding it, particularly in persons who have had few previous transfusions of blood or blood products." […] "Koate-HT has been heated at 68°C for 72-77 hours and there is no evidence of any adverse effect upon the properties of the product. The heat treatment step has been introduced to reduce the risk of transmission of infectious agents. Studies have demonstrated that the heat-treatment process used in the production of Koate-HT inactivates potential infectious viruses, including a retrovirus, but it has not yet been established that agents of any transmittable disease would be inactivated."
June 1985 **[Other/12/908 - 911]**, **[WITN6984042]**	Koate HT - label	"**WARNING: KOĀTE®-HT CONCENTRATE IS A PURIFIED DRIED FRACTION OF POOLED PLASMA OBTAINED FROM MANY DONORS. THE PRESENCE OF HEPATITIS VIRUSES SHOULD BE ASSUMED AND THE HAZARD OF ADMINISTRATING KOĀTE®-HT CONCENTRATE SHOULD BE WEIGHED AGAINST THE MEDICAL CONSEQUENCE OF WITHHOLDING IT PARTICULARLY IN PERSONS WITH FEW PREVIOUS TRANSFUSIONS OF BLOOD OR BLOOD PRODUCTS**."
May 1986 **[Other/13/1180]**, **BAYP0000008_186**	Koate HT- label	"HEPATITIS DANGER SEE DIRECTION SHEET The risk of transmission of hepatitis is present". "WARNING: THIS PRODUCT IS PREPARED FROM LARGE POOLS OF HUMAN PLASMA WHICH MAY CONTAIN THE CAUSATIVE AGENTS OF NON-A, NON-B HEPATITIS, HEPATITIS B AND OTHER VIRAL DISEASES. EACH UNIT OF PLASMA HAS BEEN TESTED

		AND FOUND NONREACTIVE FOR HBsAg AND HTLV-III ANTIBODY BY FDA APPROVED TESTS. THE PRESENCE OF HEPATITIS VIRUSES SHOULD BE ASSUMED AND THE HAZARD OF ADMININSTERING THIS PRODUCT SHOULD BE WEIGHED AGAINST THE MEDICAL CONSEQUENCES OF WITHHOLDING TREATMENT. SEE PACKAGE INSERT WARNINGS."
July 1986 **[Other/13/1231], [WITN6407007]**	Koate HT-package insert	UK version amended to match US version of March 1986. "This product has been heated and there is no evidence of adverse effect upon the product. In a study designed to assess the effectiveness of the heat treatment, two hepatitis naive chimpanzees were inoculated with either heated Antihaemophilic Factor (Human), Koāte® or heated Factor IX Complex, Konȳne®, each preparation having been spiked with 2500 chimpanzee infectious doses (CID) non-A, non-B hepatitis Hutchinson strain.[6] An additional chimpanzee was used to verity that Koāte which did not have a spike of infective virus added to it still contained an endogenous level of infective non-A, non-B. In each case, the animals receiving heated failed to exhibit symptoms of non-A, non-B hepatitis during a 15 week observation period. However, when they were subsequently challenged with the same materials that had not been heated, all animals exhibited clear evidence of non-A, non-B hepatitis. From these results, it was concluded that heat treatment of Antihaemophilic Factor (Human), Koāte® inactivated a known quantity of at least one type of non-A, non-B hepatitis as well as an unknown amount of endogenous non-A, non-B hepatitis. Additional *in vitro* studies on the effect of the heat treatment process on virus inactivation were carried out with a number of viruses, including lymphadenopathy associated virus/human T lymphotrophic virus-III

(LAV/HTLV-III) and AIDS related virus (ARV) added to the Koãte prior to heating. The following table shows the amount of each model virus inactivated by the process.

Virus	Starting Amount (Logs)	Inactivated (Logs)
Lymphadenopathy Associated Virus/ HTLV-III*	4.3	4.3
AIDS Related Virus †	2.8	2.8
Mouse C Retrovirus †	4.0	4.0
Cytomegalovirus	2.0	2.0
Herpes Simplex Virus Type I	1.0	1.0
Vesicular Stomatitis Virus	3.5	3.5
Sindbis Virus	6.0	6.0
Feline Leukaemia Virus	3.1	3.1

*McDougal JS, Martin LS, Cort SP, *et al:* Thermal inactivation of the acquired immunodeficiency syndrome virus, human T lymphotropic virus-III/lymphadenopathy-associated virus, with special reference to antihemophilic factor. *J Clin Invest* 76:875-7, 1985.

† Levy J, Mitra G, Wong M, *et al:* Inactivation by wet and dry heat of AIDS-associated retroviruses during Factor VIII purification from plasma. *Lancet* 1 *(8443)*: 1456-77, 1985.

WARNINGS

Antihaemophilic Factor (Human), heat-treated, Koāte®-HT is prepared from pooled units of plasma which have been individually tested and found nonreactive for hepatitis B surface antigen and antibody to human T-lymphotropic virus type III (HTLV-III) by FDA approved tests. Other screening procedures are used to eliminate high risk plasma donors and a heat-treatment step in the manufacturing process is designed to reduce the risk of transmitting viral infection. However, testing methods presently available are not sensitive enough to detect all units of potentially infectious plasma, and treatment methods have not been shown to be totally effective in eliminating viral infectivity from this product.

Individuals who have not received multiple infusions of blood or plasma products are very likely to develop signs and/or symptoms of some viral infections, especially non-A, non-B hepatitis as shown by recent data.[7]

Fletcher, *et al*[7] have concluded that those who have had little exposure to blood products have a higher risk of developing hepatitis after introduction of clotting factor concentrates. For such patients, especially those with mild haemophilia, Kasper and Kipnis[8] recommend single donor products. For patients with moderate or severe haemophilia who have received numerous infusions of blood or blood products, they feel that the risk of hepatitis is small. They believe that the clotting factor concentrates have so greatly improved the management of severe haemophilia that these products should not be denied to appropriate patients. The physician and patient should consider that Factor VIII concentrates may be associated with the transmission of hepatitis and weigh the benefits of therapy accordingly.

		[…] [6] Feinstone SM *et al:* Non-A, non-B hepatitis in chimpanzees and marmosets. *J Int Dis* 144:588-97, 1981. [7] Fletcher ML, Trowell JM, Kraske J, *et al:* Non-A, non-B hepatitis after transfusion of Factor VIII in infrequently treated patients *Br Med J* 287:1754-7, 1983. [8] Kasper CK, Kipnis SA: Hepatitis and clotting-factor concentrates. *JAMA* 221(5):510, 1972.
January - February 1987 **[Other/15/1446], BAYP0000010_021**	Koate-HT- label	"HEPATITIS DANGER - SEE INSERT LEAFLET The risk of transmission of hepatitis is present". "WARNING: THIS PRODUCT IS PREPARED FROM LARGE POOLS OF HUMAN PLASMA WHICH MAY CONTAIN THE CAUSATIVE AGENTS OF NON-A, NON-B HEPATITIS, HEPATITIS B AND OTHER VIRAL DISEASES. EACH UNIT OF PLASMA HAS BEEN TESTED AND FOUND NON-REACTIVE FOR HBsAg AND HTLV-III ANTIBODY BY FDA APPROVED TESTS. EACH UNIT HAS ALSO BEEN TESTED FOR ALT LEVELS. THE PRESENCE OF HEPATITIS VIRUSES SHOULD BE ASSUMED AND THE HAZARD OF ADMININSTERING THIS PRODUCT SHOULD BE WEIGHED AGAINST THE MEDICAL CONSEQUENCES OF WITHHOLDING TREATMENT. SEE PACKAGE INSERT WARNINGS."
July 1987 **[Other/15/1540], BAYP0000010_141** [no attachments]	Koate HT - package insert	"Each unit used in the manufacture of this product has been found to have an ALT level less than two times the upper limit of normal for the test". "HTLV-III/LAV" has been changed to "HIV" wherever it appeared on the direction sheet [...]."
July 1987	Koate HT- label	"HEPATITIS DANGER - SEE INSERT LEAFLET The risk of transmission of hepatitis is present".

[Other/15/1540], **[WITN6984137]** [attachments]		"WARNING: THIS PRODUCT IS PREPARED FROM LARGE POOLS OF HUMAN PLASMA WHICH MAY CONTAIN THE CAUSATIVE AGENTS OF NON-A, NON-B HEPATITIS, HEPATITIS B AND OTHER VIRAL DISEASES. EACH UNIT OF PLASMA HAS BEEN TESTED AND FOUND NONREACTIVE FOR HBsAg AND HTLV-III ANTIBODY BY FDA APPROVED TESTS. ~~EACH UNIT HAS ALSO BEEN TESTED FOR ALT LEVELS.~~ THE PRESENCE OF HEPATITIS VIRUSES SHOULD BE ASSUMED AND THE HAZARD OF ADMININSTERING THIS PRODUCT SHOULD BE WEIGHED AGAINST THE MEDICAL CONSEQUENCES OF WITHHOLDING TREATMENT. SEE PACKAGE INSERT WARNINGS."
August 1987 (variation application) **[Reg/4/354]**, **BAYP0000004_453**	Koate HT- label	"Source plasma is collected according to the Cutter System of Plasmapheresis which incorporates all the FDA requirements for Source Plasma including testing of samples from all donors for antibodies to ~~HTLVIII~~ HIV. In addition Cutter test each donation for ALT levels. Only units found to have an ALT level less than twice the upper limit of normal for the test are used in the manufacture of KOATE HT."
August - September 1988 **[Other/16/1745]**, **BAYP0000011_232**	Koate HT- data sheet	"Koate HT is prepared from pooled units of plasma which have been individually tested and found non-reactive for hepatitis B surface antigen and antibody to human immunodeficiency virus 1 (HIV-1) by approved FDA tests. Each unit used in the manufacture of this product has been found to have an ALT level less than twice the upper limit of normal for the test. Koate HT has been heated at 68℃ for 72-77 hours and there is no evidence of any adverse effect upon the properties of the product. The heat treatment step has been introduced to

		reduce the risk of transmission of infectious agents. In-vitro studies have demonstrated that the heat-treatment process used in the production of Koate HT inactivates a number of viruses including HIV-1, but it has not yet been established that agents of any major transmittable disease would be eliminated".

INFECTED BLOOD INQUIRY

BRENDON GRAY WITNESS STATEMENT

ANNEX D

ANNEX D - TABLE OF BAYER / ASSOCIATED COMPANIES' BLOOD AND rDNA PRODUCTS

Product	Date of application for PL	Date of grant of PL	Date of lapse / cancellation / withdrawal / renewal	PL Number or application	PL holder or (as the case may be) applicant for PL	Manufacturer
Koate	October 1975	27 July 1976	[Unclear]	PL 3070/0004	Bayer UK Limited applied for the PL, but prior to the licence being granted, requested that the application be read as having been submitted by Tuta Laboratories Ltd (UK). As such, the PL was granted to Tuta (which later became Cutter, see below).	Cutter Laboratories Inc.
Koate	24 January 1980	10 June 1980	Circa 7 September 1983	PL 1605/0004	Cutter Laboratories Ltd.	Cutter Laboratories Inc.

Product	Date of application for PL	Date of grant of PL	Date of lapse / cancellation / withdrawal / renewal	PL Number or application	PL holder or (as the case may be) applicant for PL	Manufacturer
Koate	Circa 9 March 1983	16 August 1983	16 August 1988 (date of cancellation)	PL 0055/0065	Miles Laboratories Limited.	Miles Laboratories Inc. but from 2 May 1984 onwards, Miles Laboratories Limited was authorised to perform assembly activities (labelling and re-packaging activities) at Bridgend, Wales.
Koate-HT	13 November 1984	18 February 1985	1992	PL 0055/0107	Miles Laboratories Limited. From April 1988, Bayer UK Ltd distributed the product.	Miles Laboratories Inc. In the application for a product licence, Miles Laboratories

Product	Date of application for PL	Date of grant of PL	Date of lapse / cancellation / withdrawal / renewal	PL Number or application	PL holder or (as the case may be) applicant for PL	Manufacturer
						Limited was listed as one of the 'assemblers', who could also perform packaging and labelling activities.
Koate-HS	26 September 1986	-	16 August 1990 (the product licence application was formally withdrawn	Formerly PL 0055/0113 Latterly PL 0010/0163	Miles Laboratories Limited. Bayer UK Limited (after assuming responsibility for liaison with the authorities in relation to the application)	Miles Laboratories Inc.
Konyne	3 July 1980	-	-	PL 1605/0007	Cutter Laboratories Limited.	Cutter Laboratories, Inc.

Product	Date of application for PL	Date of grant of PL	Date of lapse / cancellation / withdrawal / renewal	PL Number or application	PL holder or (as the case may be) applicant for PL	Manufacturer
Konyne-HT	8 May 1985	-	7 November 1988 (the product licence application was formally withdrawn)	PL 0055/0108	Miles Laboratories Limited.	Miles Laboratories, Inc.
Gamimune (Immunoglobulin)	-	16 January 1984	An application to vary the PL was received by the DHSS on 30 May 1985.	PL 0055/0104	Miles Laboratories Limited.	Miles Laboratories, Inc.
Gamimune-N	-	29 August 1986	The merits of conducting post-marketing	PL 0055/0109	Miles Laboratories Limited	Miles Laboratories, Inc.

Product	Date of application for PL	Date of grant of PL	Date of lapse / cancellation / withdrawal / renewal	PL Number or application	PL holder or (as the case may be) applicant for PL	Manufacturer
			studies vs the collection of ongoing safety information was referenced in a telex dated 15 July 1986, it is not clear whether a PL was in place at this point, or not.			

Product	Date of application for PL	Date of grant of PL	Date of lapse / cancellation / withdrawal / renewal	PL Number or application	PL holder or (as the case may be) applicant for PL	Manufacturer
Plasbumin (-5, -20,-25)		1 June 1984	unknown	PL 0055/0071-73	Miles Laboratories Limited.	Miles Laboratories, Inc.
Kogenate (recombinant Factor VIII)	-	May 1994	-	PL 0010/0194 - 95	Bayer plc	Bayer AG

INFECTED BLOOD INQUIRY

BRENDON GRAY WITNESS STATEMENT

ANNEX E

ANNEX E - KEY OF REFERENCES TO SCHEDULES OF DOCUMENTS PROVIDED TO THE INQUIRY

[**Other**] - The Schedule of Other Correspondence and Documents Relating to Factor Concentrates provided to the Inquiry on 13 May 2019

[**Reg**] - The Schedule of Regulatory Correspondence and Documents Relating to Factor Concentrates provided to the Inquiry on 13 May 2019

[**HS Other**] - The Schedule of Other Correspondence and Documents Relating to Koate HS provided to the Inquiry on 13 May 2019

[**HS Reg**] - The Schedule of Regulatory Correspondence and Documents Relating to Koate HS provided to the Inquiry on 13 May 2019

[**HP Other**] - The Schedule of Other Correspondence and Documents Relating to Koate HP provided to the Inquiry on 13 June 2019

[**HP Reg**] - The Schedule of Regulatory Correspondence and Documents Relating to Koate HP provided to the Inquiry on 13 June 2019

[**Miles Inc**] - The Schedule of Voluntary Disclosure of Miles Inc. Documents provided to the Inquiry on 9 January 2020

[**HP Additional**] - The Schedule of Documents Regarding Koate HP provided to the Inquiry on 25 June 2021