Witness Name: Joseph Smith
Statement No.: WITN5281001
Exhibits: WITN5281002 - WITN5281095
Dated: 11 December 2021

INFECTED BLOOD INQUIRY

FIRST WRITTEN STATEMENT OF JOSEPH SMITH

I, Joseph Smith, will say as follows: -

Contents

Introduction and Preliminary Comments

I, JOSEPH SMITH, will say as follows: -

0.1. My full name is Sir Joseph William Grenville Smith. I was born on GRO-C 1930. My address is known to the Infected Blood Inquiry ("IBI"). My professional qualifications are set out below in Section 2: Professional Qualifications and Career.

0.2. I have been asked, by way of a Rule 9 Request from the IBI dated 22 January 2021, to provide a witness statement regarding my involvement in the issues covered by the IBI's Terms of Reference and, in particular, when I was the Director of the National Institute for Biological Standards and Control ("NIBSC") (1976 to August 1985), the Director of the Public Health Laboratory Service ("PHLS") (August 1985 to 1992), sat on the Committee on the Safety of Medicines (1978 to 1986) and was the Chairman of the CSM's Sub-Committee on Biological Products ("CSM(B)") (1981 to 1986).

A. Structure of this Statement and Exhibits

0.3. A Table of Contents has been included above, for ease of navigation. I have adopted the same section numbering as that used by the IBI in the Rule 9 Request.

0.4. Where a document has been drawn to my attention by the Inquiry in the Rule 9 Request and is already available on the Inquiry's Relativity Database, I have included the Inquiry's Relativity document ID number in the body of this Statement. All other documents that I refer to are exhibited (exhibits WITN5281002 to WITN5281095).

0.5. An unsigned draft of this Statement was submitted to the Inquiry on 25 June 2021 and, I understand, circulated to Core Participants in that form. Since that date, I have reflected further on the events that I have been asked to recall and I have added some further comments at paragraphs 3.21, 3.22, 3.25, 3.35, 3.49 and 3.50.

B. Opening Comments

0.6. I would like to begin my witness statement by making a few brief opening comments.

0.7. Now at the age of 90, my memory is not good and can be unreliable. The events under consideration occurred some 30 to 40 years ago. My hazy memory of them has been somewhat refreshed by reading relevant documents from that period and I shall try to answer the Rule 9 questions as best I can.

0.8. I would also like to take this opportunity to convey my sincere sympathy to all those who have been affected by the issues being explored by the IBI.

Section 1: Previous Evidence

1.1. The Inquiry has drawn my attention, at question 2, to the written and oral evidence I gave to the BSE Inquiry in 1998 [BSEI0000012, BSEI0000006 and BSEI0000013]. I am asked to confirm whether the content of my evidence is true and accurate. To the best of my knowledge and belief, it is.

1.2. The Inquiry has also drawn my attention, at question 3, to the written evidence I provided to the Archer Inquiry dated 27 August 2007 [ARCH0000442_005] and the oral evidence I gave to the Archer Inquiry on 29 August 2007 [ARCH0000009]. I am again asked to confirm whether the content of this evidence is true and accurate. To the best of my knowledge and belief, it is.

1.3. I am asked at question 3 whether I have provided any evidence to, or been involved in, any other inquiries, investigations, or criminal or civil litigation in relation to human immunodeficiency virus ("HIV") and/or hepatitis B virus ("HBV") and/or hepatitis C virus ("HCV") infections and/or variant Creutzfeldt-Jakob disease ("vCJD") in blood and blood products. I do not recall having done so.

Section 2: Professional Qualifications and Career

2.1. I am asked by the Inquiry, at questions 5 and 6, to provide details of my professional career, as well as my membership, or regular attendance at, any committees, groups, associations, working parties or societies, relevant to the IBI's Terms of Reference.

2.2. My professional qualifications are as follows: MD (Doctor of Medicine), FRCP (Fellow of the Royal College of Physicians), FRCPath. (Fellow of the Royal College of Pathologists), FFPHM (Fellow of the Faculty of Public Health Medicine), Dip. Bact (Diploma in Bacteriology).

2.3. I qualified as a doctor in 1953 in Cardiff and after early appointments specialised in medical bacteriology. I became a Lecturer at the London School of Hygiene and Tropical Medicine in 1960 and was a Senior Lecturer from 1962. I was Consultant in Clinical Bacteriology to the Radcliffe Infirmary, Oxford from 1965 to 1968 and I was also Head of Bacteriology at the Wellcome Research Laboratories for a short period in 1969. Then, after 2 years in General Practice, in 1972 I joined the PHLS as the Deputy Director of the Epidemiological Research Laboratory. In 1976, I became the Director of the NIBSC. I remained in this post until August 1985 when I became Director of the PHLS, from which I retired in 1992.

2.4. Over the course of my career, I sat on a number of committees and working groups which provided advice to the Department of Health and Social Security ("DHSS") (later, from 1988, the Department of Health ("DoH")) and the Medical Research Council, including:

a) The Committee on the Safety of Medicines ("CSM"). I was a member of the CSM from 1978 to 1986, sat on its Biological Sub-Committee ("CSM(B)") from 1980 to 1986 and served as Chairman of the CSM(B) from 1981 to 1986.

b) The Chief Medical Officer's Expert Advisory Group on AIDS ("EAGA"). From the documents now provided to me, it appears that I was a member of the EAGA from 1985 until 1992.

c) The EAGA Sub-Group on Monitoring and Surveillance. I chaired this Sub-Group, which was set up in 1987 for the particular purpose of producing recommendations, applicable throughout the UK, for improving the monitoring and surveillance of the epidemic of HIV 1 infection. The Sub-Group's first meeting took place on 28 April 1987 and our report was published in May 1988.[1]

d) The Joint Committee on Vaccination and Immunisation ("JCVI"). I was a member from 1976 to 1992.

e) The Medical Research Council. I was a member from 1989 to 1992 and Chairman of its Tropical Medicine Research Board from 1991 to 1992.

2.5. I cannot, at this remove, provide any more precise dates than those set out above for the periods I held these positions.

2.6. I have been asked by the IBI, at question 7, to provide an outline of the remit, functions and activities of the organisations, committees and groups referred to above, as well as my role in relation to each. I have already provided a brief description of the committees and working groups and my role in relation to them at paragraph 2.4 above. I have provided some more detail in relation to the CSM and the CSM(B) below, given their obvious importance to the Inquiry's Terms of Reference. I have also addressed below the remit, functions and activities of the NIBSC and the PHLS, and my role as Director of these organisations.

Remit, functions and activities of the NIBSC and my role as Director

2.7. When I was Director of the NIBSC, the National Biological Standards Board, under the Biological Standards Act 1975, was responsible on behalf of the Health Ministers of the United Kingdom for the provision of biological standards, reference preparations and reagents, and for functions related to the control of substances used in human medicine. The Board executed its functions through

[1] See further below at paragraphs 4.18 to 4.25.

management of the NIBSC, which provided the scientific facilities and expertise for discharging the Board's responsibilities. As Director, I was responsible for the management and scientific work of the Institute.

2.8. The scientific work of the NIBSC was (and to the best of my knowledge still is) concerned with the purity and potency of licensed biological products used in human medicine, which sometimes impacted upon the safety of those products. Biological products may be defined as those whose purity and potency cannot adequately be evaluated by physical and chemical means alone. They include antibiotics, antisera, bacterial and viral vaccines, blood products, enzymes, hormones and other substances. Their potency needs to be assayed by comparison with a biological standard. Assessment of their purity often requires examination not only of the final products, but also of source materials, which in many instances are living, as well as in-process samples.

2.9. The wide variety of different biological products necessitated a corresponding range of scientific disciplines at the NIBSC. During my time as Director, the Institute had five scientific Divisions: Antibiotics (which became Antibiotics and Chemistry); Bacterial Products; Blood Products; Hormones and Viral Products (which became Viral Products and Electron Microscopy). There were also supporting sections, including Immunology, Standards Processing, Statistics and Administration, the last of which included the Control Records Office, which maintained records of samples and protocols relating to all batches of manufactured biological products submitted to the NIBSC for examination under the "batch release" procedure (which is addressed further below at paragraph 2.11)[2]. The work of these departments can broadly be divided into three: standardisation, control and research.

2.10. Standardisation can be explained in the following way. Biological products cannot reliably be prescribed in the same way as other medicines. Unlike aspirin, for example, biological products cannot be prescribed by weight. The only way of prescribing biological products in a dose which is meaningful and

[2] From September 1981, the Control Records Office also became responsible on behalf of DHSS for the issue of release certificates under this procedure – see the NIBSC report for January 1981 to March 1983 [WITN5281002] at p. 82.

reasonably constant is to create a yardstick, a concept developed by Sir Percival Hartley, who described it in this way: *"As we use a yardstick for measuring length, we need a yardstick for measuring the potency of biological products."* This involves laying down a batch of the product which is carefully characterised and preserved by freeze drying. This would be a large batch of ampoules which serves as either the national or international standard for that product. The potency of the biological product one wishes to test would then be tested against the potency of the standard for that product. The NIBSC produced such standards.

2.11. The control work of the NIBSC included the evaluation of medicinal products both before and after licensing, and advice was given to the Licensing Authority and the Committee on the Safety of Medicines on applications for product licences and clinical trial certificates for biological products. The NIBSC also had a part to play in the batch release process, which was applied by the Licensing Authority of the DHSS to manufacturers of certain biological products and required them to submit to the NIBSC, on a batch-to-batch basis, protocols describing the results of in-process tests made during the manufacture, and, in the majority of cases, samples of all such batches. The samples could include, in addition to the finished product, bulk and in-process materials, the control of which is essential to ensure the quality and safety of biological medicinal products. A batch release order could require that marketing or supply of any batch shall not take place without the issue of a formal release certificate by the Board on behalf of the Licensing Authority. This type of order was known as a 'full stop order'. Such orders were usually judged to be necessary for new biological products, and sometimes remained in force permanently, as in the case of potentially hazardous products, such as live virus vaccines. In other cases, satisfactory control could be maintained by scrutiny of protocols only. Once satisfactory evidence had been provided that the manufacturer produced a product of consistently acceptable quality and related safety, a batch release order might have been partially relaxed or completely withdrawn.

2.12. The testing carried out by NIBSC on biological products used in human medicines included testing against the appropriate biological standard the

potency of submitted batches of biological products which were the subject of a UK product licence or clinical trials certificate application in the United Kingdom, but may also have included other tests relating to the purity and potency of the product, which I have addressed further below at paragraph 2.20 in the specific context of the control work done by the Blood Products Division.

2.13. The research work of the NIBSC was generally done in support of the standardisation and control work of the Institute and is unlikely, at least for the time I was Director of the NIBSC, to have been of direct relevance to the issues being explored by the Inquiry.

2.14. The effective discharge of the scientific functions of the NIBSC required much collaborative work, both with other organisations as well as individual scientists and clinicians. Close liaison with the Licensing Authority for medicinal products was maintained, as necessary, by means of meetings attended by representatives of the Medicines Division of the DHSS and senior staff of the Institute. The senior staff of the NIBSC also attended the meetings of the appropriate sub-committees of the Committee on Safety of Medicines and the Committee on the Review of Medicines. Collaboration with the World Health Organisation was an important aspect of the scientific work of the NIBSC and the Institute served as a World Health Organisation international laboratory for biological standards.

2.15. The Blood Products Division was established as a separate entity within the NIBSC on 1 October 1976, with the appointment of Dr Duncan Thomas as its Head and the transfer of scientific and technical staff from the former Division of Hormones and Blood Products, which until then had been responsible for the control of haematological materials. When I was Director, the Blood Products Division was responsible for controlling certain blood products, for preparing International and British standards, and for carrying out related research.

2.16. Most of the drugs which the Division controlled under the Medicines Act, or for which standards were provided, were used in the prophylaxis and treatment of haemorrhage (for example, albumin, Factor VIII, Factor IX) and thrombosis (for example, heparin); other substances, such a thromboplastins, were used in the diagnosis and treatment of these conditions.

2.17. When I first became Director of the NIBSC in 1976, the Division's control work under the Medicines Act was generally carried out on imported blood products. The section of the NIBSC report for the period July 1976 to June 1977 dealing with the Blood Products Division explained as follows:

> *"Most of the control work under the Medicines Act has until now been carried out on imported products, such as Factor VIII, heparin, albumin and streptokinase. For example, there are currently five firms with licences to sell imported Factor VIII concentrate for the treatment of haemophilia. Samples of every batch of this material sold in the United Kingdom are tested on a routine basis at NIBSC; 44 batches were tested in 1976-77. Factor VIII is extremely expensive, and the market value of the batches tested during the year amounted to approximately £1 million; assurance of its quality is therefore important both medically and to ensure "value of money". Work on Factor VIII is expected to increase as the British blood fractionation centres become licensed."* [WITN5281003, p. 41]

2.18. I can see from the NIBSC report for the period July 1977 to December 1980, however, that during this period the NIBSC began to receive protocols and samples of blood products from the fractionation laboratories run by the National Blood Transfusion Service ("NBTS") as well as from commercial manufacturers of blood products imported into the UK:

> *"The Division received protocols and samples of some 730 batches of blood products in the period under review. About half of these were of Factor VIII and 25% concerned albumin; the remainder included samples of heparin, Factor IX, streptokinase, urokinase, and other products.*
>
> *……..*
>
> *An important recent development in control work has been the examination by the Division of protocols and samples of blood products manufactured by the plasma fractionation laboratories of the National Blood Transfusion Service. It is now possible to compare the material (albumin, plasma protein fraction, Factor VIII and Factor IX) produced by these National Health Service laboratories at Elstree, Oxford and Edinburgh with commercial blood products, and a fruitful dialogue with the Blood Transfusion Service manufacturers has been established. These products of the Blood Transfusion Service have been found to be generally of excellent quality.*
>
> *The period under review has seen a continuing increase in the number of batches of Factor VIII controlled. Material is currently examined from five commercial firms and three Blood Transfusion laboratories."* [WITN5281004 p. 29]

2.19. The NIBSC report for April 1983 to March 1984 provided this explanation of the control work done by the Division on products received from British fractionation laboratories:

> *"In the control of therapeutic substances licensed under the Medicines Act, over 300 batches of various products were examined during the year. While most of the work of the Division in this area involves testing commercially-produced products, certain products produced by the National Health Service (NHS) fractionation laboratories are also examined at NIBSC. Although NHS fractionation laboratories are not technically under licensing control in England and Wales (unlike Scotland), samples and protocols of Factor VIII, Factor IX and albumin are sent to the Division from the Blood Products Laboratory (BPL), Elstree."* [WITN5281005 p. 19]

2.20. Apart from testing the purity and potency of samples of blood products examined by the NIBSC, tests for thrombogenicity (the tendency of a material to generate blood clotting and/or thrombus, when in contact with the blood) could be carried out, as well as tests for certain blood borne infections where these were available. For example, when I was Director, samples were tested for hepatitis B antigen, and later, when a test became available, for HTLV III. It appears from the NIBSC report for April 1984 to March 1985, that samples were being tested for HTLV III by this time:

> *"A total of 124 batches of manufacturers' products was submitted, a slight fall from last year, which was probably mainly due to the switch by manufacturers at the end of 1984 to Factor VIII preparations subjected to heat treatment (see below). The batches included 18 from the Blood Products Laboratory, Elstree, and 10 batches from the Protein Fractionation Centre, Edinburgh. Tests at NIBSC on these materials gave negative results for HTLV III and hepatitis B."* [WITN5281006 p. 20]

Remit, functions and activities of the CSM and CSM(B) and my roles on these committees

2.21. The CSM's primary role was to consider questions relating to medicines licensing. The CSM would regularly consider applications for product licences and clinical trial certificates made by drug manufacturers. These applications, including applications to vary existing product licences as well as applications for product licences for new products, were referred to the CSM by the Licensing Authority, strictly speaking the Secretary of State, but in practice the

Medicines Division of the DHSS. Applications for consideration by the CSM went in the first instance to the Secretariat of the CSM and would then be presented to the appropriate sub-committee. There was a main sub-committee dealing with most pharmaceutical products and a second sub-committee dealing with biological products (the CSM(B)).

2.22. As explained above at paragraph 2.8, biological products were products which could not be assessed by physical and chemical means alone, and required biological standards against which to measure their potency. This would include vaccines, certain antibiotics, hormones and blood products. The CSM(B) was composed of senior members with expertise appropriate to its work, that of assessing the safety of biological medicines and their risk-benefit balance. They were experienced in assessing the necessary biological, clinical and epidemiological evidence contained in the cases submitted for their consideration. Their expertise included clinical infectious diseases, clinical and experimental virology and bacteriology, haematology, endocrinology, epidemiology and the production of biological medicines. The Sub-Committee's evaluations also benefited from the assessments made by the medical and scientific staff of the Medicines Division of the DHSS as well as the views of the professional staff of the NIBSC. The advice of the administrative and legal staff of the Medicines Division could also be taken into account, particularly regarding the requirements of the Medicines Act, for example the need for confidentiality.

2.23. The conclusions and recommendations of the CSM(B) would accompany the application papers when they were considered by the CSM. The CSM would in turn make recommendations to the Licensing Authority.

2.24. To illustrate the considerations that applied to applications relating to blood products being assessed by the CSM(B) and the CSM, I have exhibited, by way of example, the minutes from some CSM(B) and CSM meetings at which such applications were considered:

a) The CSM meeting of 24 July 1980; consideration of the licensing position in relation to Humanate from Speywood Laboratories [WITN5281007]

b) The CSM meeting of 22 January 1981; hearing held in relation to Humanate from Speywood Laboratories [WITN5281008];

c) The CSM(B) meeting of 22 January 1982; consideration of licence applications relating to Factor VIII products from Nordisk UK Ltd and Biotest Folex Ltd [WITN5281009];

d) The CSM meeting of 25 February 1982; consideration of licence applications relating to Factor VIII products from Nordisk UK Ltd and Biotest Folex Ltd [WITN5281010];

e) The CSM(B) meeting of 9 March 1983; consideration of licence applications relation to Factor VIII products from Alpha Therapeutic, Speywood Laboratories Ltd and Alpha Therapeutic [WITN5281011];

f) The CSM meeting of 24 March 1983; consideration of licence applications relating to Factor VIII products from Speywood Laboratories and Alpha Therapeutic [WITN5281012];

g) The CSM(B) meeting of 4 January 1984; further consideration of a licence application relating to a Factor VIII product from Alpha Therapeutic [WITN5281013]

h) The CSM meeting of 26 to 27 January 1984; further consideration of an application for a licence for a Factor VIII product from Alpha Therapeutic [WITN5281014].

2.25. As can be seen from these minutes, even before the advent of AIDS, the CSM(B) and the CSM gave careful consideration to the source of plasma used to manufacture blood products. Often further information or data was required from the manufacturers. Controls, such as the requirement that the NIBSC batch release procedures be applied to the product, were frequently proposed as conditions for the grant of a product licence for a blood product.

2.26. As Chairman of the CSM(B), I led the Sub-Committee, chaired its meetings, liaised with the Medicines Division, the Chairman of the CSM and other relevant contacts and, when required, presented the CSM(B)'s conclusions and recommendations at the main CSM meetings. As a member of the CSM, I

contributed to discussions at meetings, gave my views on the matters we were asked to consider and contributed to its conclusions and recommendations.

Remit, functions and activities of the PHLS and my role as Director

2.27. The PHLS Board's responsibility, as described in The Public Health Laboratory Service Act 1960, was to *"provide a bacteriological service for the control of infectious diseases"*, for which it was accountable to the Health Ministers of England and Wales. The National Health Service Act 1977 (Schedule 3) incorporated the PHLS Board. The PHLS was funded from the central funds of the DHSS (later the DoH). The Public Health Laboratory Service Act 1979 gave the Secretary of State the power to include in the role of the PHLS additional activities which could be carried out in conjunction with a microbiological service.

2.28. In the time I served as its director, the PHLS organisation included the following:

a) 52 area and regional (peripheral) diagnostic PHLS laboratories spaced over England and Wales, each providing diagnostic services and support for outbreak investigation to local hospitals, public health authorities and environmental health departments. Each laboratory also provided surveillance data and sent microbiological samples for reference testing to the central PHLS units at Colindale, and also took part in national investigations into infectious diseases.

b) The Central Public Health Laboratory ("CPHL") at Colindale, London, which provided national reference laboratory services to both the PHLS and NHS laboratories.

c) The Communicable Disease Surveillance Centre ("CDSC"), also at Colindale but with a Welsh Unit located in Cardiff. The CDSC served as the epidemiological arm of the PHLS. It kept human infectious diseases under surveillance and, working with other PHLS units, provided expert epidemiological support for the study of infectious diseases including the investigation of outbreaks. Its surveillance function was based upon

regular returns of diagnostic data from the peripheral and central PHLS laboratories, supported by other information, including when necessary reports from clinicians and others.

d) The Centre of Applied Microbiology and Research ("CAMR"), Porton Down. As well as providing a few services supporting the PHLS' public health work, such as diagnostic tests for dangerous pathogen infections, CAMR was expected by the Secretary of State for Social Services to generate income from its research. To this end, in 1985 the Board made an agreement with Porton Products Limited for marketing the products and processes resulting from CAMR research.

e) The Headquarters office, at Colindale, London.

2.29. In the period 1985 to 1992, the PHLS was heavily involved with investigations into a range of human infections, including AIDS and HIV infection, Botulism, E-coli infections, Legionnaires' disease, Listeriosis, Meningitis and Salmonellosis. The PHLS also engaged in research, mostly applied research, with the aim of improving the diagnosis, prevention and control of infections and communicable diseases.

2.30. As the Director of the PHLS, it was my role to ensure that the Service discharged its functions in the field of infectious diseases efficiently and economically. Regular weekly meetings were held with the Heads of the Central PHLS laboratory, Colindale, CDSC, CAMR, and the Deputy Director of the Service. These meetings helped in planning priorities, scientific studies, finances and the coordination of PHLS work. Regular meetings of all PHLS Laboratory Directors were held every 3 months.

2.31. Management of the scientific work was supported by setting up appropriate sub-committees or working groups to tackle current scientific problems, such as Viral Gastroenteritis, Hepatitis, and AIDS. These were particularly valuable for planning and running collaborative or epidemiological studies involving a number of laboratories. The Director could disband such groups when appropriate or establish others for new or growing problems.

2.32. I tried to visit each of the 52 peripheral laboratories over a two-year period, and also met many staff at the Annual PHLS Scientific Meetings which were held at a suitable University campus each summer.

2.33. During my period in office, CAMR required much attention and took up a good deal of my time. The Board had set up the CAMR Committee, and a scientific sub-group was created to help in reviewing its work. Meetings with the Head of Porton Products were also held as necessary.

Section 3: Consideration of AIDS at the CSM and the CSM(B)

Knowledge of AIDS and its aetiology in 1981 to 1984

3.1. I am asked by the IBI, at question 8(a), for an explanation of the sources of my knowledge of AIDS and its aetiology in 1981 and 1982. My background was mainly in bacteriology, vaccination and, later, medical management, and I was therefore to a certain extent reliant, when AIDS cases began to emerge in the United States, upon the knowledge of those with more relevant specialisms. My knowledge in 1981 and 1982 was based in the main upon medical journals and discussions with professional colleagues and clinicians in relevant fields, such as blood transfusion, disease surveillance, virology and haemophilia. AIDS was of great interest in the medical and scientific community and discussion about its possible causes was frequent. The data and views published weekly in USA's Morbidity and Mortality Reports from the Communicable Disease Centre ("CDC") in Atlanta were particularly helpful in keeping up to date with data and scientific opinion on the epidemic - which had started and was spreading rapidly in the USA. I can see from the documents now provided to me that I was also in contact with the American Bureau of Biologics (the USA equivalent of the NIBSC) in the summer of 1982 and it seems likely that I received some information about emerging AIDS cases in the United States from this source as well [WITN5281015].

3.2. As I explained in my oral evidence to the Archer Inquiry on 29 August 2007 [ARCH0000009, at p. 116, lines 3-9], it is my recollection that when AIDS cases first started appearing in the United States in 1981 and 1982 it was suspected that a new virus was one of the likely possible causes. Whilst I recall that my own view by the end of 1982 was that this was almost certainly the correct explanation, as I also explained in my oral evidence to the Archer Inquiry [ARCH0000009, at p. 116, line 21 to p. 117, line 5], it only became clear that AIDS was due to a new virus at the end of 1983 when Montagnier in France isolated a candidate causal virus, and it was confirmed in early 1984 by Gallo in the United States.

3.3. I am asked by the IBI, at question 8(b), about the basis for my own view about the cause of AIDS by the end of 1982. I think that, slowly and steadily over time, it appeared to me more likely that AIDS was caused by a virus.

3.4. I am also asked, at question 8(c), whether I sought in my oral evidence to Archer to draw a distinction between my own subjective view as to the cause of AIDS by the end of 1982 and scientific exposition of the same through the discoveries of Montagnier and Gallo of a candidate causal virus at the end of 1983 and in early 1984. This was indeed the distinction I was drawing. I was highlighting to the Archer Inquiry, as I would highlight to this Inquiry, that before Montagnier's discovery, even in 1983, there was still a significant amount of speculation and debate about the possible cause or causes of AIDS, including a possible new virus, with or without a co-factor such as a silent existing latent infection, for example with Epstein Barr virus, herpes or varicella. Many thought that the repeated injection of a foreign protein in haemophilia patients could be causal or a contributory factor, a view still being expressed by the time of the scientific meeting held by the NIBSC in February 1984 (as to which, see below at paragraphs 3.12 to 3.15).

The role that (i) the NIBSC, (ii) the CSM, (iii) the CSM(B) and (iv) I personally had in advising government on the response to AIDS

3.5. I am asked by the IBI, at question 9, to explain the role that (i) the NIBSC, (ii) the CSM, (iii) the CSM(B) and (iv) I personally had in advising government on the response to AIDS.

The NIBSC

3.6. As far as I can recall, the role of the NIBSC in relation to advising government on the response to AIDS was relatively limited. There would have been a general role in advising the Licensing Authority (through the Medicines Division of the DHSS), the CSM and the CSM(B) in the context of evaluation of applications for product licences, variations in product licences or clinical trial certificates. This advice would be based in part upon any scientific work carried

out by the NIBSC in relation to the product in question, such as batch testing, which I have addressed above at paragraph 2.11. Individuals might also be asked to advise on particular issues on account of their expertise.

3.7. It would appear from the NIBSC report for April 1983 to March 1984 that during this period the NIBSC first began to receive protocols and samples of new heat-treated Factor VIII products:

> *"A total of about 140 batches of manufactured Factor VIII was submitted for testing, as well as related materials such as heat-treated batches and house standards.*
>
> *Assays on a new heat-treated preparation of Factor VIII submitted for licensing were satisfactory, and immunological studies showed no evidence of antigenic alteration; this has also been the case with a previously licensed heat-treated product. Other control samples tested were Factor IX (9 batches), antithrombin III (9 batches) and porcine Factor VIII."* [WITN5281005 p. 21]

3.8. The NIBSC report for April 1984 to March 1985 provided some insight into the control work being done by the NIBSC in relation to heat-treated Factor VIII products by the following year:

> *"Heat-Treated Factor VIII. A major development during the year was the introduction of heat-treatment in the production of Factor VIII concentrates, initially designed to eliminate non-A non-B hepatitis, but subsequently found capable of inactivating the heat-labile HTLV III virus. Samples of heat-treated products have been obtained from all five commercial companies whose products are licensed in the UK. The results of studies of several batches of material from each manufacturer showed that potency determination on the heated products was no more of a problem than tests on the unheated product. In addition, sensitive immunological measurements of VIII C:Ag and VIII R:Ag in heated material failed to detect any major differences from the unheated product, indicating that heating has not produced any detectable changes in the antigenic properties of Factor VIII."* [WITN5281006 pp. 20-21]

3.9. As noted above at paragraph 2.20, this NIBSC report indicated that blood product samples tested by the NIBSC were by this period (April 1984 to March 1985) being tested for both hepatitis B and HTLV III infections.

3.10. The NIBSC would have provided advice to the Licensing Authority, the CSM and the CSM(B) based upon the Institute's examination of protocols and samples of these heat-treated blood products.

3.11. It would not generally have been a part of the role of the NIBSC to advise government on policy matters, including regulatory action in relation to imported blood products, which would primarily have been a matter for the Medicines Division, with input from the CSM and perhaps the Medicines Commission. However, senior staff members at the NIBSC, including myself, sat on a number of committees and advisory groups whose work would have included consideration of the response to AIDS.[3] The most relevant of these would have been the CSM and the CSM(B) and the CMO's EAGA.

3.12. In addition, I can see from the documents now provided to me that a scientific meeting was held at the NIBSC on 9 February 1984 to discuss the possible infectious hazards following administration of blood products. The NIBSC report for April 1983 to March 1984 described the meeting in the following way:

> *"One area of concern during 1983-84 was the question of the transmission of infection by blood and blood products and, in particular, the potential hazard represented by acquired immunodeficiency syndrome (AIDS). In February 1984, a meeting held at NIBSC to discuss this problem was attended by plasma fractionators (both commercial and NHS), virologists, Blood Transfusion Centre directors and a representative from the Food and Drug Authority (FDA) of the USA. One of the main items in the discussion was consideration of the dilemma posed by finding that donors who had contributed to large plasma pools subsequently developed AIDS. The general feeling of the meeting was that, if the diagnosis of AIDS in a donor is definite, then products prepared from pools to which the donor had contributed should be withdrawn. There was also discussion about the value of heat-treating Factor VIII concentrates, which is being widely carried out in the United States. Even though there was no conclusive evidence that heat treatment reduced the infectivity of blood products in relation to non-A non-B hepatitis, or AIDS, there was considerable pressure on plasma fractionators, particularly in the US, to carry out various forms of heat-treatment. The meeting provided a very useful forum in which to review areas of current concern in the Blood Products field."* [WITN5281005 pp. 19-20]

3.13. This meeting was referred to again in the NIBSC report for the period April 1984 to March 1985:

> *"Last year, a meeting at NIBSC discussed the infectious hazards of blood products, with particular reference to AIDS and hepatitis. It is a measure of the speed with which developments in this field that, a year*

[3] I have set out the relevant committees and groups that I personally sat on above at paragraph 2.4.

> *later, much more information is available about the transmission of AIDS by transfusion of blood and blood products. Stringent safety requirements have been introduced into the Division with regard to the handling of samples of Factor VIII and Factor IX concentrates, although there is currently no documented evidence that a laboratory worker examining blood products has thereby been infected with the HTLV III virus. The precautions include using a designated area of the laboratory for assaying clotting concentrates, not withdrawing needles from bottles once a sample has been removed, and whenever possible avoiding the use of haemophilic plasma in substrate assays."* [WITN5281006, p. 20]

3.14. This meeting was a scientific one, held to facilitate the exchange of ideas between scientists, those involved in the production of blood products and those with a specialism or interest in the fields relevant to the transmission of infection by blood products. It was not, therefore, an event at which the NIBSC was providing advice to government on the response to AIDS. However, it is an example of the NIBSC working to promote better understanding of the risk posed by AIDS at the time.

3.15. Some documents relating to the meeting have been drawn to my attention. I can see that on 28 November 1983 I wrote to invite a number of speakers and attendees to the meeting, including Dr J Petricciani from the National Center for Drugs and Biologics within the Food and Drugs Administration ("FDA"), Dr Geoffrey C Schild and Dr Duncan Thomas from the NIBSC, Dr R S Tedder from the Middlesex Hospital and Dr T Snape from the Blood Products Laboratory, enclosing a proposed agenda [WITN5281016]. The final agenda for the day and list of participants are exhibited to this statement at [WITN5281017]. The draft minutes of the meeting [WITN5281018] give a good summary of the presentations given by the various speakers and the issues which were discussed following the presentations.

The CSM / CSM(B)

3.16. The remit of the CSM and the CSM(B), in relation to advice on the response to AIDS, related to licensed blood products and, for the most part, applications for product licences and variations to product licences.[4] In addition, there were

[4] The CSM(B) and CSM considered a number of individual product licence applications relating to heat-treated blood products, once these applications began to be received by the Licensing Authority, and provided advice to the Licensing Authority on these. This is addressed further below, at paragraphs 3.66 to 3.71 and 3.73.

occasions on which the CSM(B) and/or the CSM considered broader issues relating to the safety of blood products in the context of AIDS at their meetings, which led to advice, recommendations or "remarks" being conveyed to the Licensing Authority through the Medicines Division of the DHSS. The most obvious example of this is the consideration at the CSM(B) meeting of 13 July 1983, at my suggestion, of possible regulatory steps that might be taken in relation to AIDS in respect of licensed products and the consideration and endorsement of the meeting's conclusions and recommendations by the main CSM at its meeting on 21 and 22 July 1983. This is dealt with in detail below at paragraphs 3.54 to 3.57. Other examples include:

a) The CSM(B) and the CSM considering, in November 1984, an article published in the MMWR suggesting that heat treatment of Factor VIII abolished detectable infectivity of AIDS virus added to the preparation, which led to the CSM advising the Licensing Authority to prompt the manufacturing companies concerned to make early applications for variations of product licences to use a dry heat treat process in the manufacture of their Factor VIII products.[5]

b) The CSM(B)[6] and the CSM considering, in November 1985, the question of screening for HTLV III and passing the following remark to the Licensing Authority:

"The Committee are anxious that individual donations for all blood products should be screened for HTLV III from the earliest possible date. Manufacturers should be requested to confirm that donations are being screened and to provide information about the nature of the screening tests used." [CSM minutes of 21 Nov 1985 WITN5281020]

c) The CSM(B) and the CSM considering, in March 1986, concerns raised about the safety of heat-treated Factor VIII as regards the transmission of HTLV III, and providing advice;[7] and

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[5] As I explained in my evidence to the Archer Inquiry [ARCH0000009, p. 121, lines 12-16]; I have addressed this further below, at paragraphs 3.62 to 3.65.
[6] See the minutes of the CSM(B) meeting of 6 November 1985 [WITN5281019] at pp. 2-3.
[7] Addressed further below, at paragraphs 3.75 – 3.81.

d) The CSM(B) and the CSM considering the safety of immunoglobulin preparations in relation to the transmission of HTLV III in 1985 and 1986 and albumin preparations in relation to the transmission of HTLV III in 1986, and making recommendations to the Licensing Authority.[8]

Me personally

3.17. I did not, in my own personal capacity, have any role in advising government on the response to AIDS. To the extent that I had input into the provision of advice, this was in my capacity as Director of the NIBSC, Chairman of the CSM(B), a member of the CSM or other relevant committees or working groups, or Director of the PHLS.

Involvement in discussions about the regulatory response to AIDS before the meeting of the CSM(B) on 13 July 1983

3.18. I can see from the documents now provided to me that on 28 March 1983 I wrote to Dr Keith Fowler, a medical civil servant in the Medicines Division of the DHSS, about the problem of AIDS in relation to licensed blood products [WITN5281021]. My letter was copied to Dr John Holgate, also a medical civil servant in the Medicines Division at the DHSS and the DHSS Medical Assessor. I made the following suggestions:

> *"I think it would be advisable to consider, at a meeting of the CSM(B), the problem of AIDS in relation to licensed blood products. At such a meeting it would be extremely helpful to secure the advice of Professor Arthur Bloom, who acts as Chairman of the Haemophilia Unit Directors' group. I gather than there would be no difficulty in asking him along to a meeting (except that of his availability) since he would be advising on a general problem and would not act as a member of the sub-committee. Additionally, it would be helpful to have the latest information on the surveillance of this condition in the UK. This is being undertaken by the CDSC at Colindale. Possibly Tom Pollock could be asked to provide the up-to-date picture, but if he is unwilling or unable to do this it would then be useful if Dr Spence Galbraith, Director of the CDSC, would be asked to attend.*
>
> *Attached are letters recently released by FDA, on or about the 17th March 1983. You will see that the US are taking steps to avoid the*

[8] Addressed further below at paragraphs 3.87 – 3.100.

> *use of blood from high risk groups in the preparation of certain blood products.*
>
> *Would you find it possible to prepare a brief paper on which the discussion might be based? The letter from the Office of Biologics to the licensed manufacturers of plasma derivatives could also be circulated, together possibly with a note that Spence Galbraith's unit might be prevailed upon to prepare."*

3.19. I have been provided with the minutes of a meeting held at the DHSS on 3 June 1983, convened to discuss the implications for the Department of recent media reports on AIDS and to examine possible courses of action [WITN5281022]. It appears from these minutes that I was in attendance at this meeting, although I do not recall the details of this particular meeting now. The documentary record suggests that an agenda and papers for this meeting were sent to attendees from the DHSS on 1 June 1983 [WITN5281023]. I do not think that I would have been provided with the papers for the meeting, although I may have been provided with the agenda. The agenda indicates that the meeting's focus was on the actions that the DHSS might take, including what action could be taken by the Medicines Division and Supply Division to minimise risks in light of new requirements introduced by the FDA.

3.20. The minutes of the meeting summarised the discussion relating to the control of imports in the following way:

> *"7. The meeting examined the question of restrictions on imports of Factor VIII manufactured from plasma which had been donated before the introduction of the new FDA requirements on 23 March. Miss Spencer explained that the effective application of legal restrictions would present significant practical difficulties and suggested that informal discussions with the companies concerned were more likely to lead to successful control.*
>
> *8. It was agreed that Medicines Division and Supplies Division should instigate such discussion.*
>
> *9. Dr Walford emphasised that excessive restrictions on the import of Factor VIII would hold severe consequences for UK haemophiliacs and recommended that the proposed discussions should be used to ascertain the effects of stricter controls on supply. Meanwhile Dr Walford would obtain from Haemophilia Centre Directors details of levels of import of individual brands of Factor VIII."* [WITN5281022 pages 1-2]

3.21. The meeting also considered (see the Minutes at paragraphs 12 – 15) the need to increase the supply of plasma to BPL for preparing Factor VIII in order to

reach UK self-sufficiency. It was agreed that Regions should be pressed urgently for action to achieve this. The Minutes record that Dr Oliver urged that, in order to ensure that capacity to handle a rapidly increasing plasma supply, the utilisation of all UK fractionation facilities should be examined and the feasibility of a further "speeding-up" of the BPL redevelopment programme examined.

3.22. Although, as I have said, it is difficult to recall this meeting now, I believe that it was this discussion that caused me to expect that self-sufficiency could possibly be reached within perhaps six months.

CSM(B) Meeting

3.23. I am asked at question 10 about my recollection of the CSM(B) meeting of 13 July 1983, at which questions relating to AIDS and licensed blood products were considered, and the documents that are available relating to this meeting.

3.24. I have been provided with a letter that I sent to Mr Hugh Morgan, of the Medicines Division of the DHSS, on 4 July 1983 [DHSC0003824_085]. This letter read as follows:

> *"At the meeting of the Biological Sub-Committee of the CSM on 13 July, 1983, and with the help of invited experts, consideration will be given to AIDS and licensed blood products. A proposed agenda is attached which includes suggested first speakers for each item, and I very much hope that those named will agree to introduce that topic. The paper also includes for each point a tentative conclusion to act as a target for discussion purposes.*
>
> *It is proposed that the AIDS discussion will take place in the morning and I understanding that lunch will be provided for both the visitors and members of the sub-committee. The business meeting of the sub-committee can then be taken in the afternoon. I very much hope that you will be able to attend this meeting and that sub-committee members will be available for the afternoon."*

3.25. I can see that the proposed agenda that I attached [WITN5281024] was sent on to a number of medical and non-medical officials at the DHSS by Mr Morgan under cover of a minute dated 6 July 1983 [WITN5281025]. These officials included Dr Walford, Dr Oliver, Dr Sibellas and Mr Sloggem, who I believe attended the AIDS discussion which took place in the morning part of the

CSM(B)'s meeting of 13 July 1983. They also included Ms Zoe Spencer, who I believe was part of the Medicines Division Staff and played a role with regards to the CSM and CSM-B meetings, as well as attending the DHSS meeting held on 3 June. Mr Morgan described the proposed agenda as a working paper, prepared by me. He also enclosed a paper by Dr Fowler entitled "Acquired Immune Deficiency Syndrome (AIDS): A New Hazard for Haemophiliacs?" [WITN5281026]. It was suggested that these documents would be the basis of the discussion at the meeting.

3.26. I am asked, at question 10(a), why the CSM(B) considered the question of AIDS and blood products at the meeting on 13 July 1983. It did so at my suggestion, made in my letter to Dr Fowler of 28 March 1983 and summarised above at paragraph 3.18. I would have made this suggestion because the AIDS question had by this time become a matter of great current interest and concern and I was worried about it. The first of four notes set out at the beginning of the proposed agenda explained the aim of the discussion in this way:

> *"(1) The aim of the discussion is to help the sub-committee to formulate advice to the CSM on whether any action is needed, and if so what action, in respect of AIDS and blood products licensed under the Medicines Act. These products include Factors VIII and IX, Immunoglobulin G, Albumin and hepatitis B vaccine."*

3.27. The IBI has asked me, at question 10(b), which papers had been considered by (i) me, and (ii) other members of the CSM(B) before the meeting. Given the passage of time, I am guided to a great extent by the contemporaneous documents. Whilst it is *possible* that there were other documents seen by me and provided to attendees ahead of the meeting[9], my letter to Mr Morgan of 4 July 1983 and Mr Morgan's minute of 6 July 1983 seem to suggest that the papers provided for the meeting were limited to the proposed agenda and Dr Fowler's paper.

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[9] For example, I suggested in my letter to Dr Fowler of 28 March 1983 that the letter from the Office of Biologics to the licensed manufacturers of plasma derivatives might be circulated in addition to the paper I asked Dr Fowler to prepare. I also raised the possibly that Dr Spencer Galbraith's unit (the CDSC) might be prevailed upon to prepare a short note.

3.28. I am asked, at question 10(c), what expertise (i) I, and (ii) other members of the CSM(B) had on AIDS and blood products at the time of the meeting. As I have already explained above at paragraph 3.1, my background was mainly in bacteriology, vaccination and, later, medical management. I did not, in July 1983, possess expertise in AIDS, although I had followed the publications about AIDS since cases began to be reported in the US and I paid particular attention to publications relating to AIDS and blood products, given my roles as Director of the NIBSC and the Chairman of the CSM(B). I am unable now to remember the expertise that each individual member of the CSM(B) had. Members' expertise included clinical infectious diseases, clinical and experimental virology and bacteriology, haematology, endocrinology, epidemiology and the production of biological medicines. In relation to the last of these areas, Dr Richard Lane from the BPL sat on the CSM(B) and had knowledge of the production of clotting factor concentrates. As I explained in my oral evidence to the Archer Inquiry, Professor Harold Lambert and Dr David Tyrell would also have had knowledge of haemophilia.

3.29. Whilst the Sub-Committee did not have expertise specifically in AIDS, the third of the four notes set out at the beginning of the proposed agenda for the meeting on 13 July 1983 explained as follows:

> *"(3) It is assumed that participants will be familiar with the problem and with at least a proportion of the many publications."*

3.30. At the meeting, the Sub-Committee was helped by the participation of invited senior doctors with relevant expertise, namely Professor Bloom (Professor of Haematology, who I considered to be an expert in haemophilia and its clinical care), Dr Craske and Dr Mortimer (Consultant Virologists with the PHLS; Dr Craske was the Chairman of the PHLS Hepatitis Virus Sub-Committee and had, I believe, done work on hepatitis in relation to the risk from blood and its products; and Dr Mortimer was Head of the PHLS Virus Reference Laboratory), Dr Galbraith (Director of the CDSC, PHLS, who had set up and ran the AIDS surveillance programme) and Dr Gunson (Director of the Regional Blood Transfusion Centre, Manchester and DHSS Adviser on Blood Transfusion). In answer to question 10(d), I was ultimately responsible for choosing which external experts to invite to the meeting, although it is likely that I would have

sought the views of other members of the Sub-Committee and of Medicines Division officials, and in particular Dr Fowler, in doing so. The meeting was also attended by DHSS representatives.

3.31. At question 10(e), I am asked a number of questions about the proposed agenda for the meeting. I will address these in turn:

i) Who was responsible for producing the proposed agenda. The proposed agenda, dated 28 June 1983, bears my initials. Although I have no recollection of it now, this, combined with Mr Morgan's description of the document as a working paper prepared by me in his minute of 6 July 1983, leads me to believe that I was the author of this document. I would however have sought input from others to assist with its preparation. I expect that I would have sought Dr Fowler's views, in light of the fact that I had tasked him with preparing a paper to form the basis for the discussion at the meeting. It is likely that I would also have sought the views of others with expertise in haemophilia and its treatment and of the manufacture processes for blood clotting factors.

ii) What the purpose of this document was. The document's purpose was explained in the fourth of the notes set out at the beginning of the proposed agenda:

> *"(4) This 'agenda' suggests headings for the discussion and a suggested first speaker is given. As a target for discussion, brief possible conclusions are indicated – doubtless these will be changed radically."*

iii) What the "brief possible conclusions" contained within it were based on and who had proposed them. As explained above at i), I would have sought input from others in preparing this proposed agenda. I cannot now remember how the possible conclusions came to be drafted in the way they were. I can see from the notes to the agenda, however, that the possible conclusions were tentative and I expected that they might change following discussion at the meeting.

3.32. Question 15 asks about Dr Fowler's paper, "Acquired Immune Deficiency Syndrome (AIDS): A New Hazard for Haemophiliacs?" [(DHSC0003824_088)]. I can confirm that this was the paper I referred to in my written evidence

[ARCH0000442_005, paragraph 6] and oral evidence [ARCH0000009, p.118, lines 1-5] to the Archer Inquiry. In answer to the specific questions posed by the Inquiry about this:

a) The origins, purpose and circulation of this document. I believe that Dr Fowler prepared this paper after I asked him, in my letter to him of 28 March 1983 (the content of which is set out in full above at paragraph 3.18), to prepare a paper on which discussion at the meeting might be based. His paper was, as I explained in my oral evidence to the Archer Inquiry [ARCH0000009, p.118, lines 1-5], the DHSS Medicines Division's evaluation of the AIDS problem. I cannot now recall what was sent to attendees ahead of the meeting of 13 July 1983. Generally, however, papers prepared for a CSM(B) meeting would be sent to attendees ahead of that meeting. As such, I expect that this document, along with the proposed agenda I prepared, would have been sent to attendees ahead of the CSM(B) meeting of 13 July 1983.

b) Whether this document was provided to the CSM(B) or the CSM as part of their consideration of AIDS and blood products. As explained above, I expect that this document was provided to the CSM(B) ahead of the meeting and would have formed a part of its consideration of AIDS and blood products accordingly. I cannot now remember whether this paper was provided to members of the CSM ahead of its consideration of the CSM(B)'s recommendations at its meeting held from 21 to 22 July 1983, although I note that the minutes of the CSM do not refer to it.

c) What, if any, influence this paper had on (i) the CSM(B), (ii) the CSM, and (iii) me personally, in respect of discussion on AIDS and blood products. The main focus of Dr Fowler's paper was on the background to the AIDS problem and presentation of the current available information on incidence and epidemiology, aetiology and related factors (most of the first three of the paper's four pages dealt with these issues). There was one paragraph dealing with the issue of imported concentrate on the last page of the paper. This focussed mainly on how the DHSS might ensure that concentrate imported from the US for use in the UK was not

prepared from plasma collected before the FDA Regulations came into force on 23 March 1983. Whilst I believe that Dr Fowler's paper was very helpful to the CSM(B), and to me personally, particularly in relation to the background to the AIDS problem and presentation of the current available information on incidence and epidemiology, aetiology and related factors, it would have been considered alongside all of the information and views available to the CSM(B) at its meeting on 13 July 1983, including the information presented by the guest experts. I do not believe this paper was determinative of any of the conclusions reached by the CSM(B), not least because the paper did not address in any detail the possible options for regulatory action that were set out in my proposed agenda and discussed at the meeting. I cannot assist with what influence, if any, Dr Fowler's paper had on the CSM since, as I have explained above at b), I cannot now recall whether Dr Fowler's paper was provided to members of the CSM.

3.33. The discussions and conclusions at the meeting of 13 July 1983 relating to AIDS and blood products are summarised in two documents, the minutes of the meeting [WITN5281027] and a paper prepared for the meeting of the CSM held from 21 July to 22 July 1983, which summarised the main points from the CSM(B) meeting [WITN5281028].

3.34. The minutes would have been prepared by the Secretariat, and approved by me before they were considered and approved by the Sub-Committee as a whole. Unfortunately, my memory of this meeting is now very poor. I can see from the minutes, however, that, having heard from the expert advisors in attendance at the meeting and considered the current information available on incidence and epidemiology, aetiology and related factors, the CSM(B) reached the following conclusions in relation to the cause of AIDS and the risk to patients receiving blood clotting-factor concentrates:

> *"5.1 The cause of AIDS in unknown, but an infectious aetiology seems likely. A previously unrecognised or new agent may be responsible, but repeated exposure to, or reactivation of, known agents, (eg CMV, EBV) may be involved. Heightened susceptibility may be an important factor, e.g. immunological deficiencies induced by unusual sexual practices or exposure to*

blood products. Based on the clinical evidence, transmissibility of the supposed agent(s) appears to be low, requiring intimate contact or introduction into the tissues.

5.2 Patients who repeatedly receive blood clotting-factor concentrates appear to be at risk, but the evidence so far available suggests that this risk is small. The risk appears to be greatest in the case of products derived from the blood of homosexuals and IV drug abusers resident in areas of high incidence (eg, New York and California), and in those who repeatedly receive concentrates in high dosage. Balanced against the risks of AIDS (and of other infections transmitted by blood products) are the benefits of their use; in the case of haemophilia they are life-saving." [WITN5281027]

3.35. The CSM(B) examined strategies for limiting or eliminating risks from blood products, together with possible practical measures including the attainment of self-sufficiency within the UK. It reached the following conclusions in relation to possible regulatory action:

"5.3 The possibility was considered of withdrawing clotting factor concentrates from the market and replacing them with cryo-precipitate. It was concluded that this is not feasible in the UK on grounds of supply."

5.4 The possibility was considered of withdrawing US preparations from the UK. It was concluded that this is not at present feasible on grounds of supply. Moreover, the perceived level of risk does not at present justify serious consideration of such a solution. Efforts are however being made to secure UK independence of foreign suppliers of clotting factor concentrates. This should reduce markedly, although not eliminate, the risks to recipients of these products, and the Sub-committee strongly supports this aim. The Sub-committee was also informed that the UK Haemophilia Centre Directors have adopted a policy for use of US Factor VIII in order to minimise risks as far as possible.

5.5 It is advisable that all clotting-factor concentrates derived from US plasma sources and intended for use in the UK be prepared only from material manufactured from plasma collected after new regulations were introduced by the FDA on March 23rd 1983. These regulations were introduced specifically to minimise the likelihood of collecting blood from affected donors. This step is recommended notwithstanding the possibility that its practical value may be relatively small. It cannot, however, be taken until supplies of post-March 23rd material can be assured. It is recommended that close contact is maintained between the Licensing Authority and Supplies Division with the aim of introducing this step immediately it become feasible." [WITN5281027]

3.36. The possibility of products being treated to reduce risk was discussed at the meeting. Dr Fowler had addressed this in his paper prepared for the meeting, "Acquired Immune Deficiency Syndrome (AIDS): A New Hazard for Haemophiliacs?":

> *"The other possibility for control is by treatment of the product. Most, if not all, of the manufacturers have been working on means of reducing the transmission of hepatitis by concentrate. So far, the most promising method seems to be heat treatment. This reduces the total yield of Factor VIII considerably, but is believed to reduce, but not eliminate, transmission of non A non B hepatitis. The effect on transmission of hepatitis B is not as great, but this is less of a problem because tests exist for screening blood for this type of hepatitis. It is now suggested that what works for hepatitis might work for the presumed AIDS agent. The FDA have certainly accepted this possibility, but it must remain a very speculative hypothesis for the time being."* [WITN5281026 pg. 4]

3.37. At the meeting, this possibility was discussed and was welcomed and viewed as a "promising future development". The minutes summarised the discussion at paragraphs 5.6 and 5.7 in the following way:

> *"At present no such products are available in the UK but it is known that manufacturers are working upon their development. When licence applications are received it is important to examine not only possible improvement in the safety margin but also the clinical effectiveness of material treated by heat or by other means. Thus, for example, treated material could possibly induce reactions in recipients which could render them more susceptible to infectious agents.*
>
> *The Sub-Committee learnt that manufacturers were producing advertising material for use in the UK which appeared to make unjustified claims concerning the safety of heat-treated Factor VIII. It is advised that this should be stopped. It is feared that unlicensed material could be used on a named-patient basis, despite the fact that its safety and effectiveness had not been established or considered by the Licensing Authority."* [WITN5281027]

3.38. Also addressed at the meeting was the safety of the hepatitis B vaccine and immunoglobulins and albumins (see the minutes of the meeting at paragraphs 5.8 and 5.9) [WITN5281027].

3.39. The conclusion in relation to the hepatitis B vaccine was that there was no evidence of risk from the material licensed in the UK and that the licence should remain unchanged, i.e., for use in high-risk groups only. It was recommended, however, that the position should be kept under close observation and that the manufacturer should be asked to provide ongoing data relating to the safety of

the product in respect of AIDS. Surveillance of recipients of the hepatitis B vaccine had been recommended and was planned by the PHLS and the CSM(B) supported this. It was noted that the vaccine licensed in the UK was subjected to three separate inactivation processes and it was recommended that any new vaccines derived from human blood should be licensed only if subjected to similar stringent treatment.

3.40. As for immunoglobulins and albumins, it was concluded that there was no evidence of risk from these products, and no action was thought to be justified. It was recommended, however, that the position be kept under close observation.

3.41. The CSM(B) recommended that the DHSS made sure that adequate arrangements were maintained to ensure coordination of activities between the many groups professionally involved in the AIDS question. The Sub-Committee also identified the *"need for research work on AIDS in the UK, especially in relation to the possible new introduction of this disease into the virgin soil of the United Kingdom"*, and was glad to learn that a number of groups, including the Medical Research Council, were planning or had started work.

3.42. The wording of the paper for the CSM containing a summary of the main points from the CSM(B) meeting of 13 July 1983 was substantially the same as that contained within the minutes of the meeting.

3.43. I am asked, at questions 10(f) and 10(g), about the conclusions summarised at paragraphs 5.3 and 5.4 of the minutes of the CSM(B) meeting, set out above at paragraph 3.33. In particular, I am asked who proposed and opposed these suggestions and why the meeting concluded that the possibilities being considered were not feasible on the grounds of supply. More broadly, I am asked, at question 10(i), to provide any further information I am able to on the reasons for any of the recorded conclusions.

3.44. At the meeting of 13 July 1983, careful consideration was given, in particular, to the problem of AIDS and Factor VIII. Although very little scientific evidence was then available, the Sub-Committee tried carefully to estimate the risk-benefit balance of continuing the use of imported US Factor VIII in the treatment of the 2,500 (approximately) haemophilia patients in Britain, at a time when

home-produced Factor VIII could provide rather less than 50% of the number of doses required. A shortage of Factor VIII doses would have had serious consequences for the health of haemophilia patients and would include deaths if only half of the Factor VIII needed for their treatment were available.

3.45. Although I can now recall little of the detailed consideration we gave to the problem, given the passage of time, I believe that the following aspects are likely to have been included in the discussion:

a) Limited and uncertain understanding of the possible causes of AIDS and its transmissibility existed at the time. An example of the some of the arguments being made may be seen in a Lancet editorial of April 2nd 1983 [page 745], which included the following:

> *"...the recognition of disease in a few haemophiliacs does not necessarily reflect the tip of an iceberg. Of course we can expect to see side effects of transfusion therapy with plasma collected from many thousands of donors but if the explanation of AIDS were that easy, even allowing for a transmissible agent introduced in the late 1970's and with a long incubation period, the syndrome would surely have affected far greater numbers of either American or West German recipients who have received far more factor VIII transfusions of United States origin than have haemophiliacs in other developed countries. The links suggested by the American workers must be regarded as not proven. Whilst careful surveillance must continue the reported cases do not constitute a strong case for a change in treatment policy."*

b) The limited evidence available in July 1983 suggested that there was risk to patients given imported clotting factor concentrates but that it was then small, especially in comparison with the risks from not using Factor VIII. Despite the wide use of US Factor VIII in the developed world, and that haemophilia patients receive repeated doses of Factor VIII, at that time the relatively small number of 15 cases had been reported among haemophilia patients world-wide. Of these 11 were in the USA where AIDS was a rapidly growing problem. One affected haemophilia patient had been confirmed in the UK (this patient was under the clinical care of Professor Bloom, who was an expert adviser attending the meeting). One additional possible UK case was currently under investigation.

c) The dose of Factor VIII used in patients in this country was *"the lowest in the developed countries"* [Berridge[10], p 41], so that the level of risk here could be lower than in other countries, both in terms of the dose of a possible infectious agent to which UK recipients might be exposed, and in relation to any contributory immunological effects from the injection of Factor VIII. Although doctors everywhere would have been on the alert for any possible AIDS cases, only 4 haemophilia patients with AIDS had been identified outside the USA, despite the very wide use of US Factor VIII in developed European countries, often at high doses.

d) Evidence on the incubation period (IP) was then limited, and it was not established until serological testing allowed follow-up of a sufficient number of patients to identify the interval between infection and onset of clinical AIDS. The IP question was of course of much interest at that time. Probably the most considered view then available was CDC Atlanta's estimate [MMWR March 4, 1983 WITN5281029] which suggested an IP of several months to 2 years.

e) The frequency with which AIDS would develop in an infected individual was not known - many believed that perhaps 10% went on to develop AIDS [Berridge p46].[11] Some of those studying AIDS thought that the development of antibody as a consequence of infection would be protective against AIDS.

f) Such considerations contributed to the meeting's conclusion that the risk from use of imported Factor VIII was real but comparatively small. However, the level of risk from a communicable disease can change, up or down, and sometimes rapidly. AIDS was being studied by many groups, including the PHLS CDSC. Significant evidence of a change in risk level might be identified by any such groups. The meeting advised that observation of all such work needed to be maintained by CDSC and

[10] AIDS in the UK: The Making of Policy, 1981-1994, OUP 1996 by Virginia Berridge
[11] Most virus infections give rise to a high proportion of sub-clinical infections which nevertheless stimulate immunity.

that relevant groups within DHSS should be kept fully aware of all CDSC's surveillance findings.

g) As is apparent from the minutes of the meeting and as I explained in my written evidence to the Archer Inquiry [ARCH0000442_005] at paragraph 11, we considered the possibility of withdrawing clotting factor concentrates from the market and replacing them with cryo-precipitate (from frozen plasma) which was prepared from small donor pools or single donors and might therefore pose a lower risk than Factor VIII concentrate. However, it was made clear, I think by those with particular knowledge of haemophilia, that it would not have been possible to supply and administer sufficient quantities of cryo-precipitate to treat more than a small proportion of patients.

h) In all the circumstances, the Sub-Committee considered that the evidence then available about the level of risk to recipients of clotting factor concentrates did not justify taking a step that would directly result in a drastic reduction of supply of concentrates, when no alternative product was available in sufficient quantities to make up the shortfall; a step that the subcommittee agreed would have serious consequences for patients, including fatalities.

3.46. My impression on re-reading paragraph 5.4 of the minutes (set out in full above at paragraph 3.35) now is that the Sub-Committee took some comfort from being told that efforts were being made to secure UK independence of foreign suppliers of clotting factor concentrates. This was an aim strongly supported by the Sub-Committee. It also appears to me from paragraph 5.4 of the minutes that the Sub-Committee was reassured to some extent by being informed that the UK Haemophilia Centre Directors had adopted a policy for the use of US Factor VIII in order to minimise risks as far as possible.

3.47. As can be seen from paragraph 5.5 of the minutes of the meeting (set out in full above at paragraph 3.35), the Sub-Committee *did* recommend that *"all clotting-factor concentrates derived from US plasma sources and intended for use in the UK be prepared only from material manufactured from plasma collected after new regulations were introduced by the FDA on March 23rd 1983"*. We

advised that this step should be introduced by the DHSS immediately it became feasible, i.e., once supplies of post-March 23 material could be assured.

3.48. I am asked, at question 10(h), whether any of those at the meeting expressed dissent or doubt about the conclusions recorded in the minutes. At the end of the meeting I summarised the conclusions that we had reached. I do not recall there being any dissent from other members of the Sub-Committee or anyone else present at the meeting. I do recall, however, Dr Craske reminding me that we had agreed that the regulatory step of withdrawing imported Factor VIII was not a feasible option in light of the consequences that taking this step would have.

3.49. Question 11 asks about my impression gained from the meeting of 13 July 1983 of the timeframe within self-sufficiency in clotting factor concentrates was expected. As I explained in my written evidence [ARCH0000442_005, at paragraph 13] and my oral evidence [ARCH0000009, pp.121-122] to the Archer Inquiry, from the discussions at the meeting I gained the clear impression that UK self-sufficiency was expected soon. My understanding at the time was that efforts were being made to achieve this within a period of months. I cannot now recall who spoke at the meeting about these efforts, although I imagine that Dr Lane and some of the representatives from the DHSS would have provided information about this. I also cannot now recall exactly what information was provided or what update was provided to add to the information I had gathered on 3 June, but I gained the impression that progress was encouraging. As a result, I thought that self-sufficiency could now be reached in about two further months.

3.50. After a couple of months had passed following the 13 July 1983 meeting, I asked the DHSS if Factor VIII self-sufficiency had been achieved, to be told 'not yet'. Whilst I am not certain to whom I spoke about this, I think that it is likely that that it was Miss Zoe Spencer, who was at both the DHSS AIDS meeting on 3 June and the CSM-B meeting of 13 July; I thought that she was familiar with progress on this issue. She remained positive about progress whilst telling me that self-sufficiency had not yet been achieved. I subsequently made

several such inquiries with the same result. I thought that some serious technical problem must have occurred.

3.51. I am asked, at question 14, about a letter from Dr Galbraith to Dr Ian Field from the DHSS dated 9 May 1983 [CBLA000043_040], in which Dr Galbraith expressed the view that all blood products made from blood donated in the USA after 1978 should be withdrawn from use until the risk of AIDS transmission by these products had been clarified. In particular, I am asked about my oral evidence to the Archer Inquiry [ARCH0000009, p. 123] that, to the best of my knowledge, Dr Galbraith's letter was not put before the CSM or the CSM(B) and that I had only seen it shortly before giving evidence in 2007. In answer to the specific questions posed:

a) Whether this remains my evidence. It does. I learned in 2007 that some people thought that the 13 July 1983 meeting had been convened in order to consider Dr Galbraith's letter. This view was also stated in the 2009 Lord Archer Inquiry Report. However, this was not the case. I had proposed the meeting because of concern about AIDS and licensed blood products, and the Medicines Division helped in its preparation. Neither I nor, I think, Sub-Committee members, knew that Dr Galbraith had written to DHSS and he made no mention of it at the meeting. I suspect that Dr Galbraith may have assumed that the meeting was called in order to consider his letter and passed his belief on to his deputy, Dr Bartlett, who represented GRO-A Dr Galbraith at the Archer Inquiry.

b) Whether Dr Galbraith expressed views at the meeting similar to those that were contained in his letter. When I saw Dr Galbraith letter for the first time in 2007, I then saw that Dr Galbraith's concerns had been very similar to my own in 1983. He participated in the Sub-Committee's 13 July 1983 discussion and would have had an opportunity to raise any views he wished at that meeting, but I do not recall him being an outlier in the discussion at all.

c) Whether Dr Galbraith agreed with the conclusions of the CSM(B) on the question of whether or not US blood products should be withdrawn. As I explained in my oral evidence to the Archer Inquiry [ARCH0000009, p.

124], as far as I remember, Dr Galbraith agreed with the conclusions of the CSM(B) in this respect, in circumstances where about 50% of the material used in the UK was imported so this option could not be advised.

CSM Meeting

3.52. The CSM considered the CSM(B)'s recommendations arising out of the meeting of 13 July 1983 at its meeting held from 21 to 22 July 1983. The CSM's conclusions are summarised in the minutes of the CSM's meeting [WITN5281030] as follows:

> *"5. TABLED PAPER 4 SUMMARY OF MAIN POINTS FROM A CONSIDERATION OF AIDS AND LICENCE* [sic] *BLOOD PRODUCTS BY BIOLOGICALS SUB COMMITTEE 13 JULY 1983*
>
> *5.1 Dr Smith spoke to this paper and reported to the Committee on the above discussion.*
>
> *5.2 The Committee endorsed the recommendations of the Biologicals sub-committee."*

3.53. Tabled paper 4 is the paper prepared for the CSM summarising the main points from the CSM(B) meeting [DHSC0001208]. I am asked, at question 12(a), who prepared this paper. I prepared this paper based on the CSM(|B) meeting minutes.

3.54. I am asked, at question 12(b), what, if any, discussion was there at the CSM of the CSM(B) conclusions and, if there was any discussion, whether there is any reason why it was not recorded in the minutes. I cannot recall there being much discussion on this occasion or indeed on other occasions when the CSM(B) presented recommendations to the CSM. Although the CSM would have read carefully any written information provided, CSM members generally agreed with the CSM(B) in relation to its recommendations.

3.55. I am asked, at question 12(c) whether any of those at the CSM meeting expressed dissent or doubt about the conclusions reached by the CSM(B) and, if so, what was said and by whom. I do not recall there being any dissent or doubt expressed at the CSM meeting.

3.56. Question 12(d) asks, in general, what level of scrutiny reports from the CSM(B) were subjected to by the CSM and whether the approach taken to the CSM(B) report on AIDS and blood products was different to other CSM(B) reports to the CSM. As I have explained above, it was not often that in-depth discussion of reports from the CSM(B) took place at CSM meetings. The CSM generally agreed with the CSM(B)'s view. I cannot recall the approach of the CSM to my report on this occasion being different to the approach taken to other CSM(B) reports, although I note from the minutes of the CSM meeting that I did speak to my report at the meeting, which did not always happen.

3.57. I am also asked, at question 12(e) whether, after being endorsed by the CSM, these recommendations went any further and, in particular, whether the matter went to a Minister for determination. I cannot assist with this question as how the CSM(B) recommendations, endorsed by the CSM, were taken forwards and what level of approval was sought for any decision taken by the Department would have been matters for the DHSS.

European Recommendation

3.58. I am asked, at question 13, about an information paper [DHSC0000717], considered by the Committee of Experts on Blood Transfusion and Immunohaematology in May 1983, and Recommendation No R(83)8 [PRSE0000372] , adopted by the Committee of Ministers on 23 June 1983. In answer to the specific questions about these documents posed by the Inquiry:

a) Whether either of these documents were considered at the CSM(B) meeting on 13 July 1983 or the CSM meeting held from 21 to 22 July 1983 and if not, why not. I had not seen either of these documents before they were provided to me for the purposes of making this statement. As such, I do not think that these documents were considered at the CSM(B) meeting or the CSM meeting and there is no suggestion that they were in the contemporaneous documents I have seen.

b) Whether I became aware of these documents through other channels in 1983 and, if so, how, and what influence they had on my thinking. Given

that I have only very recently seen these documents for the first time, I do not think I became aware of these documents through other channels in 1983. I note that a *proposed* European Council resolution was discussed at the meeting of 3 June 1983 that I attended [WITN5281022], under the agenda item 5 – the implications for NBTS of the line taken by the Council of Europe [WITN5281031] - but I do not recall this discussion. This agenda item, along with a number of other agenda items for that meeting, was not directly relevant to my roles as Director of the NIBSC, Chairman of the CSM(B) or a member of the CSM.

c) In general, whether it was common for Council of Europe Recommendations to be considered by the CSM(B) or the CSM. I do not recall any recommendation of the Council of Europe *ever* being brought to the attention of or considered by the CSM(B) or the CSM.

d) Who was responsible for drawing the attention of the CSM(B) or the CSM to Council of Europe Recommendations. Since I do not think that recommendations of the Council of Europe were *ever* brought to the attention of the CSM(B) or the CSM, I cannot assist with this question.

Developments after the CSM meeting in 1983

3.59. After the CSM endorsed the CSM(B)'s recommendations, on 27 July 1983, I wrote to Professor Bloom to inform him of this and to convey the thanks of Sir Abraham Goldberg, Chairman of the CSM, and his committee for his help with the matter [WITN5281032]. I did so at Sir Abraham Goldberg's request. When asking me to write to Professor Bloom, Sir Abraham asked me to include a reminder to Professor Bloom that the recommendations made were confidential and I did so accordingly. *All* CSM(B) and CSM papers and proceedings were confidential when I sat on these committees and it was standard practice for the Chairman to remind attendees of this at the outset of meetings (which I did at the CSM(B) meeting of 13 July 1983 [WITN5281027] and Sir Abraham did at the CSM meeting of 21 to 22 July 1983 [WITN5281030]).

3.60. I was asked during my oral evidence to the Archer Inquiry whether the recommendations of the CSM(B), endorsed by the CSM, were followed up or reviewed [ARCH0000009, pp. 120-121]. It does not appear from the minutes of the meetings of the CSM(B) held during my tenure as Chairman that there was a further meeting at which the recommendations made on 13 July 1983 were reviewed wholesale. The CSM(B) and the CSM did, however, have further involvement in advising on - and providing recommendations in relation to – a number of the issues that were considered at the 13 July 1983 and 21 to 22 July 1983 meetings.

3.61. Below at paragraphs 3.60 to 3.79, I have addressed in some detail the involvement that the CSM(B) and CSM had in advising on heat-treated blood products. The CSM(B) and CSM also had involvement in advising further on the safety of immunoglobulin preparations and albumin preparations, which I have addressed below at paragraphs 3.85 to 3.98. Where I had involvement in these issues in another capacity, such as in my role as a member of the EAGA, I have included this in the chronology of events.

CSM(B) / CSM involvement in advising on heat-treated blood products from 1984 to 1986

3.62. As I explained in my evidence to the Archer Inquiry [ARCH0000009, p. 121, lines 12-16], the CSM considered the question of heat-treated products again in 1984 and advised the Medicines Division to approach manufacturers and prompt applications for product licences or variations of licences to enable available heat-treated products to be authorised for use as soon as possible.

3.63. Having recently been provided with the minutes of the CSM(B) and CSM meetings held when I sat on these committees, I can see that this issue was raised first by me at the 7 November 1984 meeting of the CSM(B). The minutes of this meeting [WITN5281033] record the following under item 9 of the agenda:

> *"9. Any other business – AIDS*
>
> *The Chairman brought to members attention a recent report in MMWR (1984 33, No 42 page 589). This stated that preliminary evidence concerning the effects of heat treatment on the viability of the AIDS virus*

> *is strongly supportive of the usefulness of heat treatment in reducing the potential for transmission of the AIDS virus in blood clotting factor concentrate products, and suggests that the use of non-heat treated concentrates should be limited.*
>
> *Dr Thomas observed that the US licensed products were all, he believed, heated in a dry state.*
>
> *Members noted these observations and hoped that further evidence would be forthcoming soon."*

3.64. I can see from the minutes of the CSM meeting that took place on 22 November 1984 [WITN5281034] that I raised this issue under item 17 of the agenda. The minutes summarise the discussion and decision of the CSM in the following way:

> *"Dr J Smith informed the Committee that heat treatment of Factor VIII, which is used in the treatment of haemophiliacs, abolished detectable infectivity of AIDS virus added to the preparation. (Source MMWR 1984; 33 No 42).*
>
> *Professor Rawlins reminded the Committee that heat-treated Factor VIII is more expensive than the standards preparation. Widespread substitution of the heat-treated product may cause haemophilia centres to exceed their budgets.*
>
> *The Committee requested that the Licensing Authority propose to the Companies concerned that they make early applications for variations to use a dry heat treating process in the manufacture of their Factor VIII products."*

3.65. I can see from the documents now provided to me that the advice to the Licensing Authority was acted on. A letter from Dr Mann, a Principal Medical Officer at DHSS, to Professor Bloom on 29 November 1984 [WITN5281035] has been brought to my attention. In this letter, Dr Mann relayed the recent advice by the CSM that the Licensing Authority should approach manufacturers of Factor VIII to prompt them to make applications for abridged Product Licences (or variations) so that heat-treated products would be available on formal licences. Dr Mann went on:

> *"This is, as a high priority item, in hand and the Senior Medical Officer dealing with it is Dr Mary Duncan. The Supplies Division of the DHSS is also fully alert to the problem."*

3.66. The first licence application in the UK for a heat-treated Factor VIII concentrate was considered by the CSM(B) in March 1984. This was an application from Hoechst UK Ltd for its product "Factor VIII H.S.". I have exhibited to this

statement the papers for consideration at that meeting [WITN5281036] and the minutes of the meeting, with the relevant Appendix setting out the CSM(B) recommendation, Appendix B [WITN5281037]. The CSM(B) recommended the grant of a product licence on the conditions set out in Appendix B:

> *"1. Satisfactory information was provided on the heat-treatment process; this should include the identify and concentrations of added stabilising agents,*
>
> *2. clarification was given on the electrophoresis data before and after heating, with special reference to the thermal degradation products of Factor VIII and clear statements were given on the change in Factor VIII potency,*
>
> *3. the Finished Product Specification was amended to include: -*
>
> *i) a test with suitable limits for sodium,*
>
> *ii) a clear statement of the acceptance/rejection criteria in the microzone electrophoresis test,*
>
> *iii) an upper limit of Factor VIII activity of not more than 125% of the labelled amount.*
>
> *4. suitable comparative results between the Behringwerke assay for Factor VIII and the BP 1980 assay was provided, together with confirmation that the Behringwerke standard is calibrated in IU against the WHO International Standard,*
>
> *5. additional stability data were provided showing the results of tests for degradation products on storage,*
>
> *6. confirmation was given that the air in the vial is removed or replaced by sterile oxygen free nitrogen,*
>
> *7. an assurance was given that the Albumin would comply, if tested, with all the tests in the BP specification,*
>
> *8. biological evidence of the reproducibility of the inactivation process was provided,*
>
> *9. the Data Sheet and Product Particulars were amended to the satisfaction of the Secretariat, with particular reference to:*
>
> *i) inclusion of a statement that the material was heat-treated;*
>
> *ii) no claims were made that the transmission of hepatitis B and non-A non-B hepatitis had been excluded;*
>
> *iii) no reference to AIDS was included except as a warning that blood products may transmit the syndrome,*
>
> *10. the Batch Release procedure should apply, to include the provision of bulks and in-process samples.*
>
> *Remark*

Further studies on the effectiveness of the inactivation process should be undertaken."

3.67. The CSM considered the application relating to Hoechst UK Ltd's product "Factor VIII H.S." at its meeting on 22 to 23 March 1984 and gave advice to the Licensing Authority in the terms proposed by the CSM(B) [WITN5281038].

3.68. I can see from a product licence grant form recently provided to me that a product licence for Hoechst UK Ltd's product "Factor VIII H.S." was authorised by the Licensing Authority on 6 February 1985 [WITN5281039]. The papers accompanying the grant form suggest that NIBSC batch release procedures were applied to the product as recommended by the CSM.

3.69. The CSM(B) considered a further product licence application for a heat-treated Factor VIII product in 1984, from Armour Pharmaceutical Company in relation to its product "Heat Treated High Potency Factorate". The application was considered at the CSM(B) meeting of 4 July 1984 [WITN5281040]. On the evidence available to the Sub-Committee, members were unable to recommend the grant of a product licence for the product on grounds relating to safety, quality and efficacy. The CSM(B)'s observations and remarks are set out at Appendix C to the minutes of the meeting of 4 July 1984:

"The Sub-Committee considered that:

1. *There was inadequate evidence of safety in clinical use.*
2. *There was inadequate evidence of efficacy in clinical use.*
3. *There was inadequate biological evidence of the effect of heat-treatment on infectivity.*
4. *There was no clinical evidence relating to any changes brought about by the heat-treatment, particularly in relation to the transmission of hepatitis.*
5. *Justification was required for the inclusion and the choice of heat-treatment used.*
6. *The heat treated product should be adequately characterised, supported by suitable data, clearly presented.*
7. *Further details were required on the sterilization of containers, the freeze-drying process and the in-process moisture limit for the product.*

<u>Remarks</u>

1. *With respect to point 3 above, the Sub-Committee considered that evidence of the effect on test viruses would be relevant.*

> 2. *In the event of a Product Licence being granted the Batch Release procedure should apply, to include the provision of bulks and in-process samples."* [WITN5281040]

3.70. The CSM considered the Factorate application at its meeting on 26 to 27 July 1984 [WITN5281041] and gave the following advice to the Licensing Authority:

> *"On the evidence before them the Committee had reason to think that on grounds relating to safety, quality and efficacy they would be unable to advise the grant of a product licence for this preparation and therefore directed the Secretary to notify the applicant in accordance with section 21(1) of the Act."*

3.71. The Committee's provisional conclusions were provided beneath this advice and mirrored the CSM(B)'s observations and remarks, set out above at paragraph 3.67.

3.72. It is my understanding that the NIBSC was involved in evaluating protocols and samples submitted by manufacturers of heat-treated blood products in relation to the licensing process. I can see from the documents now provided to me that Dr Duncan Thomas at the NIBSC wrote to Dr Mary Duncan of the Medicines Division at DHSS on 8 January 1985, reporting on the data provided to the NIBSC from companies Miles Laboratories Ltd, Travenol Laboratories Ltd and Immuno Ltd, who were heat-treating their Factor VIII at the time [WITN5281042]. Dr Thomas was concerned about discrepancies between the three products, including the length of time for and temperature at which the products were heated, and the different ways in which marker viruses had been used. Dr Thomas came to the conclusion that the product supplied by Miles was superior to the others.

3.73. This information was passed on to the CSM(B) at a meeting the next day, 9 January 1985, which I chaired as usual [WITN5281043]. Dr Duncan informed attendees that two manufacturers had submitted abridged applications for Factor VIII products which included a heat-treatment stage as part of the manufacturing process. She conveyed Mr Thomas' concern that manufacturers were using different temperatures and varying lengths of time for the heat-treatment process. Members noted this information and expressed a wish to be kept informed of the licensing position. I note that the CSM(B) considered an application from Miles Laboratories Ltd in relation to its product

"Konyne-HT" at a meeting on 4 September 1985 [WITN5281044]. Members were unable to recommend the grant of a product licence for this preparation on grounds relating to safety, quality and efficacy, one of the observations being that inadequate evidence had been provided of virus inactivation. The CSM(B) remarked that the company should be asked what plans they had for the screening of donors against infectious agents, including HTLV III and that in the event of a product licence being granted, the batch release procedure should apply, to include the provision of bulk and in-process samples. The CSM considered the application for "Konyne-HT" at its meeting on 19 to 20 September 1985 [WITN5281045]. Its advice to the Licensing Authority was that they would be unable to advise the grant of a product licence for this preparation and the Committee's provisional conclusions mirrored the CSM(B)'s recommendations and remarks.[12]

3.74. I have been shown a letter from Dr Harris, the Deputy Chief Medical Officer ("DCMO") to the Chief Medical Officer ("CMO"), dated 4 July 1985, about heat-treated Factor VIII [WITN5281046]. Dr Harris refers to a conversation with me in my capacity as Director of the NIBSC shortly before writing, during which I informed him that, since 19 December 1984, all imported Factor VIII cleared by the NIBSC had been heat-treated. In addition, all Elstree material received since April had been heat treated and Scottish supplies had been heat treated since 23 January 1985. I do not now recall this conversation with Dr Harris, but it is likely that any information I provided was based on information received from Dr Duncan Thomas, who was Head of the Blood Products Division of the NIBSC at the time.

3.75. I can see from the documents now provided to me that I was alerted to a concern about the safety of heat-treated Factor VIII concentrates when I was copied into a letter dated 18 February 1986 from Dr Peter Jones, Director of the

[12] A further example of the CSM(B) considering an application made in relation to a heat-treated Factor VIII product and concluding that they were unable to advise that the application be granted is the application for a variation of the product licence made in March 1986 by Immuno Ltd for its product Kryobulin. The application was considered by the CSM(B) at its meeting of 2 July 1986 at item 5.2, with relevant papers [WITN5281048].

Royal Victoria Infirmary, to the Medical Assessor of the CSM [WITN5281047]. Dr Jones enclosed information which he considered was suggestive of HTVL III conversion in previously seronegative haemophiliacs who had been infused with Factor VIII which had been heat-treated for less than three days.

3.76. Dr Jones' concerns were addressed in detail in a paper prepared by Dr Frances Rotblat, a medical civil servant in the Medicines Division of the DHSS, dated 4 March 1986 [WITN5281049]. This paper was considered by the CSM(B) at its meeting on 5 March 1986 and the Sub-Committee provided advice, the minutes summarising the Sub-Committee's discussion and advice in the following way under item 9:

> *"The Safety of Heat Treated Factor VIII (tabled paper 1)*
>
> *The Sub-Committee considered this paper and made the following recommendations:*
>
> *9.1 The Sub-Committee were glad to receive this data on the follow up of alleged transmission of HTLV-III by heat treated Factor VIII. The Sub-Committee agreed that there was insufficient evidence for action to be taken on any specific product.*
>
> *9.2 Close surveillance should be maintained on the two possible cases of HTLV-III transmission in recipients of Armour material.*
>
> *9.3 The Sub-Committee advised that, if any of the data provided by manufacturers on viral inactivation suggested a danger, urgent consultation should be sought with appropriate members."* [WITN5281050]

3.77. The CSM considered the question of the safety of heat-treated Factor VIII at its meeting on 26 March 1986 [WITN5281051] under agenda item 12. The CSM considered Dr Rotblat's paper and endorsed the recommendations of the CSM(B).

3.78. I can see from the documents now provided to me that Dr Rotblat presented a paper on the safety of Factor VIII to the EAGA at its meeting of 11 March 1986 under agenda item 9.2 [WITN5281052]. As I understand it, this was the same paper provided to the CSM(B) for its meeting on 5 March 1986, the paper dated 4 March 1986. Discussion followed Dr Rotblat's presentation, which I contributed to, and which was summarised in the following way in the minutes of the meeting:

> *"16. In the discussion, members were of the opinion that all except one, the mild haemophiliac who had not received treatment since 1980, could be explained by late sero-conversion which was possibly triggered by an accident such as the road accident. Professor Bloom, whilst agreeing that the clinical evidence pointed to the fact that heat-treated Factor VIII was safe, was concerned that Professor Montagnier had reported at a conference at the College of Pathologists that he had detected reverse transciptase in material heated for 96 hours at 68°C. [Also, the Lancet had reported that the virus was still detectable in spiked material up to 34 hours.]*
>
> *Dr Smith was of the opinion that the safety margins for Factor VIII which related to the source material and manufacturing processes were adequate. However, Professor Weiss thought it essential that since manufacturing processes varied they needed to be tested empirically and liaison with Dr Schild on this matter would be necessary.*
>
> *17. The discussion then centred on whether there was a need to issue a statement on the safety of heat-treated Factor VIII to counteract that made by Dr Jones. Although haemophiliacs and their families were reassured about its safety it was recognised that the media were still interested. It was therefore agreed that a statement which included a reference to Factor IX, used in the treatment of Christmas Disease, should be made as follows:*
>
> > *"The EAGA has carefully considered the safety of currently available Factor VIII and IX concentrates in light of the most up to date medical information. As a result, the EAGA has concluded that there is no evidence that HTLVIII infection has been transmitted in heat treated Factor VIII and IX concentrates."*
>
> *The statement would be subject to clearance in the light of discussions by the CSM."*

3.79. I do not now recall the discussion at the EAGA meeting and am therefore unable to add anything to the summary of the discussion in the minutes set out above.

3.80. I was sent a copy of a letter dated 16 April 1986 from Dr Isaacs, Principal Medical Officer at the DHSS and the Medical Assessor to the CSM, to Dr Jones, in which Dr Isaacs said that the CSM had reviewed the heat-treatment of clotting factors and that the Committee had advised there was insufficient evidence for action to be taken on any specific product [WITN5281053].

3.81. The Armour product, "Factorate", was withdrawn by the company later in 1986 and I note that the CSM was informed of this fact at its meeting on 23 October 1986, a paper on this having been provided to the Committee [WITN5281054]. The minutes of the meeting record as follows under item 9 of the agenda:

> *"9. THE WITHDRAWAL OF ARMOUR 'FACTORATE'*
>
> *9.1 Dr Rotblat informed the Committee of the withdrawal of this product. Since the withdrawal the Licensing Authority were aware of three further seroconversions linked with 'Factorate'."* [WITN5281055]

Issues relating to heat-treated blood products whilst I was Director of the PHLS

3.82. In addition to my involvement in advising on heat-treated blood products when I sat on the CSM(B) and CSM, there were occasions whilst I was Director of the PHLS on which issues relating to heat-treated blood products were brought to my attention.

3.83. In July 1987, I became aware of a letter dated 10 July 1987 from Dr Mitchell at the Leicester Royal Infirmary to Mr Godfrey, a pharmacist at the Infirmary, [WITN5281056]. Dr Mitchell summarised concerns about the Cutter dry heat-treated Factor VIII product that the Leicester Haemophilia Centre had been using in the following way:

> *"Now a report has come from the recent AIDS meeting in Washington showing seroconversion in a patient who had been treated only with Cutter heat treated factor VIII concentrate, i.e. had received no other blood product.*
>
> *HIV is not the only infectious hazard facing recipients of multi-donor concentrates. Many authorities believe that wet heat treated products are safer with regard to non-A, non-B Hepatitis. We have noted with alarm the transmission of Hepatitis B to 2 of our patients. One, a child, was treated with Cutter heat treated factor IX concentrate (prepared identically), the other with our present commercial factor VIII material. Both are now carriers of the hepatitis B virus, a condition associated with chronic liver disease and hepatic cancer.*
>
> *For these reasons I believe that we must now change to the wet heat treated product Profilate."*

3.84. I referred to Dr Mitchell's concerns in a letter I wrote to Professor Buchan on 24 July 1987 [WITN5281057], which I sent a copy of to Dr Rotblat at the DHSS. I wrote in the following terms:

> *"I was very interested to see the letter from Dr Mitchell concerning this difficult problem with which I have in the past been closely involved.*
>
> *If evidence has emerged that the dry heat process used by Cutter fails to inactivate HIV virus reliably, then in my view it would be wrong to*

use it when there are available other products which probably have a higher safety margin. It is to be expected that wet heat processes will be more effective than dry heat processes when applied to Factor VIII, although much would depend upon the time and temperature adopted by the various companies.

The evidence that Dr Mitchell provides relates to a report given at the Washington Aids meeting about sero-conversion in a patient treated only with the Cutter product. The evidence from this case is not known to me, but it should certainly be looked at very carefully because it is always possible that sero-conversion in an individual may be due to exposures other than through receiving Factor VIII injections. The justification for stopping use of the Cutter material therefore depends primarily on the nature of the evidence from this single case.

I would be pretty sure that the DHSS Licensing Authority will be considering this point very carefully, since it will probably have to decide whether the product should be withdrawn. Could I suggest that you get in touch with Dr. Frances Rotblat at the DHSS Licensing Authority. Their full address and telephone number is given at the foot of the letter. Dr. Rotblat may well have more up-to-date information which could be of help."

3.85. I received a response to my letter from Dr Rotblat on 28 July 1987 [WITN5281058]. She informed me she had contacted Cutter and that they were trying to get further information about a suspected seroconversion in Italy. She stressed that it was important to have full details of the case before considering taking action.

3.86. Issues with seroconversion and heat-treated products continued to be discussed into the 1990s. I received a letter from Dr Craske on 17 October 1990 to which he attached an article from Vox Sanguinis highlighting the possibility of transmission of HIV in Factor VIII preparations which had been heated at 60 degrees for 24 to 30 hours [WITN5281059]. I responded to Dr Craske on 22 October 1990 [WITN5281060]. I suggested that there may already be monitoring being done by haemophilia physicians but made clear that if this was not the case then *"we should do our best to contribute to the identification of any problem in this most important area".*

Involvement in consideration of the safety of immunoglobulin and albumin preparations

3.87. I can see from the minutes of the CSM(B) meetings that I have been provided with recently that the safety of immunoglobulins was raised at a meeting of the CSM(B) that took place on 1 May 1985:

> *"8. Any other business*
>
> *Arising from the discussion of the Endobulin application and the written representations for Human Immunoglobulin, the Sub-Committee expressed a wish to reconsider the safety of the currently licensed human immunoglobulin preparations intended for intravenous use.*
>
> *This reconsideration should take into account*
>
> 1. *the evidence of virus inactivation during the preparation of the products, and their final freedom from transmissible agents*
> 2. *the evidence of clinical safety of the products in respect to the transmission of infectious agents*
> 3. *the toxicological evaluation of these products, and the need for any further toxicological requirements for their clinical investigation and licensing."* [CSM(B) minutes bundle/pp. 200-201 (main minutes) [WITN5281061]

3.88. This led to the issue being considered substantively at the CSM(B) meeting of 3 July 1985. The minutes record the following under agenda item 6:

> *"The Sub-Committee considered the factors involved in the risk of infectivity of intravenous immunoglobulins and the reports of transmission of non A non B hepatitis by iv immunoglobulins. In light of these considerations the Sub-Committee made recommendations relating to the preparations of iv immunoglobulins currently licensed in the UK.*
>
> *The Sub-Committee considered that:*
>
> *6.1 <u>GENERAL CONSIDERATIONS</u>*
>
> *Whilst it is probably not possible to guarantee the safety of intravenous immunoglobulin preparations in respect of transmission of infection, an acceptable margin of safety is possible and will be maximised by adoption of the following procedures:*
>
> 1. *The use of healthy donors.*
> 2. *The testing of donor samples for evidence of infections liable to be transmitted by blood.*
> 3. *Use of the cold ethanol fractionation procedure.*

> 4. *The adoption of additional steps known to kill a variety of viruses.*
> 5. *Strict adherence to good manufacturing practice.*
>
> *In assessing the safety of individual products the above points should be taken into account, together with the clinical evidence of safety which should include screening of recipients by means of liver function tests.*
>
> *Tests for evidence of infection in donors are a rapidly developing field. In view of this, licensees should be asked what their plans are for screening of donors."* [WITN5281062]

3.89. The Sub-Committee went on to consider reports of transmission of Non-A Non-B Hepatitis by intravenous immunoglobulins, which included a report of transmission by material produced by BPL, Elstree [WITN5281062 page 3]. The Sub-Committee recommended that materials prepared by BPL should be licenced, and was glad to learn that BPL intended to submit applications for all their products. In light of the reports of transmission, the Sub-Committee considered the evidence already received relating to products licensed in the UK and made specific recommendations for each product [WITN5281062 pages 3-4].

3.90. The CSM considered and endorsed the CSM(B)'s recommendations at its meeting held from 25 to 26 July 1985 [WITN5281063].

3.91. I note from the minutes of a meeting of the EAGA which was held on 26 November 1985 that the EAGA was also considering the safety of immunoglobulin preparations around this time. The minutes of this meeting [WITN5281064] provide the following summary of the discussion on this issue under agenda item 13, a discussion to which I contributed:

> *"54. Dr Sibellas said that Professor Zuckerman had reported that a WHO Consultative Group which had met in 1983 after considering the data before it had concluded that there was no evidence of risk anticipated to the use of normal or specific immunoglobulin prepared by universally accepted methods. He had requested that the matter be discussed by the Group.*
>
> *55. Dr Smith said that the safety of intramuscular immunoglobulin had never been questioned: The Committee on the Safety of Medicines (CSM) had formally reviewed them and any questionable preparation was not released. The Committee was to review next month intravenous immunoglobulins which could have transmitted non A/non B Hepatitis. Professor Weiss then referred to an investigation carried out by Dr Webster at Northwick Park, of patients treated with intravenous*

immunoglobulin. A virus had been isolated from two patients who had received immunoglobulin from two different batches, the source of which was unknown.

Dr Cash informed members that data from America suggested that HTLVIII could pass through cold fractionation 2 which was the basis of the preparation of intramuscular immunoglobulin.

56. According to Dr Tedder one of the problems with the preparation of immunoglobulin was that there was no mean standard and manufacturers should therefore be asked to make known the procedures used. Dr Smith pointed out that the CSM only considered licensed preparations, immunoglobulins produced by the Blood Products Laboratory, Elstree were not licensed. This was an area which needed to be examined. The Chairman thought that NIBSC should be asked to consider the problem and to also to liaise with the JCVI. It was agreed that Dr Tedder, Dr Tyrell, and Professor Zuckerman would provide any necessary input from the group."

3.92. The CSM(B) considered new evidence concerning the safety of immunoglobulin preparations with respect to transmission of infection, presented in a paper produced by Dr Mary Duncan, a medical civil servant in the Medicines Division [WITN5281065], at its meeting of 8 January 1986 under agenda item 6. Having discussed the significance of this evidence, which related to the possible transmission of HTLV III, the following was recorded in the minutes:

6.2 The Sub-Committee was aware of the long safety record of intramuscular immunoglobulins with respect to the transmission of infection. In particular, there has been no evidence of transmission of HTLV III infection by intramuscular immunoglobulins, despite their extensive use and preparation from sources that will have included HTLV III infected donors.

The safety of intravenous immunoglobulins is possibly less certain. There have been only a few documented incidents of transmission of NANB hepatitis and, until the case referred to above, no reported cases suggestive of HTLV III transmission.

6.3 The Sub-Committee noted that immunoglobulin preparations are of considerable clinical value and in some circumstances life-saving.

6.4 The Sub-Committee recommended, on the evidence considered, that no new licensing action to withdraw or restrict supplies should be taken in respect of intravenous or intramuscular immunoglobulin preparations.

However:

6.4.1 All immunoglobulin preparations should as soon as possible and not later than 1 July 1986 for intravenous and 31 December 1986 for intramuscular, be prepared only from donors shown to be HTLV III antibody negative.

6.4.2 As from now no preparations containing HTLV III antibody in the plasma pools, bulks or final product should be released for use.

6.4.3 Manufacturers should provide evidence of the capacity of their process to inactivate viruses by 1 July 1986 in respect of intravenous, and 31 December 1986 in respect of intramuscular immunoglobulin preparations.

6.4.4 The Sub-Committee considered that at present there was insufficient evidence to justify changing the indications for use of immunoglobulin.

6.5 The Sub-Committee recommended that close surveillance should be maintained of the development of any new virological, epidemiological or clinical data." [WITN5281066]

3.93. The CSM considered Dr Duncan's paper and endorsed the CSM(B)'s 8 January 1986 recommendations at its meeting of 30 January 1986 [WITN5281067 at item 7, p. 6].

3.94. Further information about the safety of immunoglobulins was considered at the CSM(B) meeting of 5 March 1986, presented in a paper produced by Dr Rotblat dated 4 March 1986 [WITN5281068]. The minutes of the CSM(B) meeting of 5 March 1986 record the following under item 8 of the agenda:

"The Sub-Committee considered this paper and made the following recommendations:

8.1 The Sub-Committee was glad to see that the use of donor screened plasma was rapidly being introduced. It was hoped that at its next meeting the data submitted on inactivation of virus by the manufacturers' processes would be available.

8.2 The Sub-Committee advised that the information from the manufacturers should include data on the reliability of the methods used for HTLV-III antibody screening.

8.3 It was agreed that the whole question should be kept under review." [WITN5281050]

3.95. At its meeting of 26 March 1986, the CSM noted Dr Rotblat's paper, which had been tabled at the January meeting of the CSM, and endorsed the CSM(B)'s recommendations from its 5 March 1986 meeting [WITN5281051].

3.96. The position in relation to albumin preparations was revisited by the CSM(B) at its meeting of 7 May 1986, presented in a paper produced by Dr Thomas and Dr Rotblat [WITN5281069] and the minutes record the following under agenda item 6:

> *"Manufacture of Blood Products from Plasma Derived from Unscreened Donors*
>
> *The Sub-Committee considered this paper and made the following recommendations:*
>
> *6.1 All imported albumin preparations and the other products listed in this paper should be prepared from plasma individually tested for HBSAg and anti-HTLV-III. The Companies involved should be asked to apply for variations to their Product Licences to cover this point, as soon as possible.*
>
> *6.2 Details of the method of testing of HBSAg and HTLV-III antibody should be supplied.*
>
> *6.3 All preparations not subject to the batch release procedure should be required to comply with it.*
>
> *6.4 Biologicals remark to CSM*
>
> *The attention of the Elstree and Edinburgh Fractionation Centres should be drawn to these recommendations."* [WITN5281070]

3.97. The CSM considered the paper that was before the CSM(B) and endorsed the CSM(B)'s 7 May 1986 recommendations at its meeting of 29 to 30 May 1986 ([WITN5281071] at item 14).

3.98. I can see from the documents now provided to me that Dr Rotblat wrote to Dr Lane at the BPL, Elstree on 13 June 1986 [WITN5281072], Dr Perry at the PFC, Edinburgh on 9 June 1986 [WITN5281073] and the Medical Director of Travenol Laboratories on 25 June 1986 [WITN5281074] to advise them of the recommendations endorsed by the CSM at its May 1986 meeting.

3.99. Dr Rotblat reported back to the EAGA at its meeting on 11 March 1986 on the CSM(B)/CSM recommendations and the actions she had taken in response under agenda item 9.1 [WITN5281052]. Further discussion of this issue followed. It was suggested that an informal group comprising experts in blood products and AIDS including representatives of the Scottish Fractionation Centre, and BPL Elstree might be established and the Chairman of the EAGA

asked if this group would first turn its attention to the problem of immunoglobulins.

3.100. I have been provided with a paper prepared for the EAGA which summarises the conclusions of the NIBSC Liaison Group on the Virological Aspects of the Safety of Blood Products following a meeting of this group on 2 May 1986, held to consider the safety of immunoglobulins [WITN5281075]. I was not a part of this group but note its conclusions that:

a) There was no epidemiological evidence associating the administration of intramuscular immunoglobulin with seroconversion for antibodies to LAV/HTLV III or the subsequent development of AIDS, and there was no reason to believe that intramuscular immunoglobulin, both normal and specific, was anything other than a safe product;

b) While the epidemiological evidence for the safety of intravenous immunoglobulins prepared by conventional Cohn fractionation was somewhat less secure, there was no convincing evidence that such preparations transmitted LAV/HTLV III infection, although certain products has been demonstrated to transmit non-A, non-B hepatitis;

c) The evidence suggested that the LAV/HTLV III virus did not survive cold ethanol plasma fractionation during the preparation of immunoglobulins;

d) The group did not consider that the recall of distributed batches of immunoglobulins for intramuscular use prepared from unscreened donors was warranted on the basis of the available evidence;

e) The group noted that the NBTS, as an added safety measure, had adopted a policy of not issuing immunoglobulins manufactured from a plasma pool to which a donor contributed who subsequently developed anti-LAV/HTLV III antibodies;

f) At that time, all immunoglobulins (both i.m. and i.v.) that were subject to batch release by the NIBSC under the Medicines Act were examined by immune-blotting, and any batch that was positive was not released for distribution, and all licensed immunoglobulins would be prepared from plasma derived from screened donors by the end of June 1986.

Section 4: Other issues

4.1. I am asked, at question 16 of the Rule 9 Request, to explain any other matters that I believe may be of relevance to the IBI, having regard to its Terms of Reference and to the current List of Issues. In particular, I am asked to set out any other involvement I had in (i) providing advice to government in relation to AIDS and (ii) decision-making (whether as part of the PHLS or the CSM or the CSM(B) or NIBSC or otherwise) in relation to AIDS. I have done my best to do so below.

Involvement in issues relating to screening of blood or plasma for relevant viruses

Blood donation screening for HIV

4.2. Routine screening in the NBTS of blood donations for HTLV III was introduced shortly after I took up my post as Director of the PHLS in August of 1985. As I understand it, by 14 October 1985 the Regional Transfusion Centres were screening all blood donations.[13] As far as I am aware, I had no involvement in the PHLS evaluation of test kits that occurred before kits were trialled in the NBTS, as this pre-dated me taking up the PHLS Director role. Once routine screening was introduced, PHLS laboratories had a role in providing confirmatory HTLV III testing for the NBTS.

4.3. I can see from the documents now provided to me that the effectiveness of blood donation screening for HIV was something that was considered by the DHSS on a number of occasions from the mid to late 1980s. Whilst I did not advise on and was not involved in decision-making on this issue, I was sent copies of correspondence relating to it and I have summarised that correspondence below with the aim of assisting the IBI.

[13] This was reported to the EAGA at a meeting I attended on 26 November 1985 (see paragraph 5 of the minutes at [WITN5281064]).

4.4. The question of the efficiency of British donor screening for anti HIV had cause to be analysed in October 1986 when the CMO sought a view from Dr Phillip Mortimer, Director of the Virus Reference Laboratory, PHLS, in the context of the likely performance of the test kits used in the UK when used in Africa. I was sent a copy of Dr Mortimer's letter to the CMO responding to this request, dated 13 October 1986, which enclosed a detailed paper on the issue [WITN5281076]. Dr Mortimer summarised his view on British donor screening in the following way in his letter:

> *"What indicators we have show that British donor screening for anti-HIV is efficient. There are probably very few false negative results and therefore we can only expect minor improvements in the screening programme. In fact the chief concern should be to maintain the present alertness."*

4.5. Dr Mortimer's paper provided the following background on blood donor screening in the UK at paragraph 2:

> *"Since October 1985 all blood donations in United Kingdom have been tested for anti HIV. Most testing is done in large regional centres, of which there are about 20, each doing several hundred tests daily. At present only EIA [enzyme immunoassays] is suitable for donor screening, and the choice of assay is made by the director of each centre. In the first year of donor screening 9/10 of testing has been by the Wellcozyme (type 2) EIA and 1/10 by the Organon (type 1) EIA. Several other EIA are being assessed by the Transfusion Service. Positive screening results in tests on UK blood donations are uncommon and repeatedly positive results rare (Wellcozyme 0.01%, Organon 0.18%*). Repeatedly positive specimins are referred for confirmatory testing: only about 0.003%* are confirmed as positive."*

4.6. Paragraph 4 of Dr Mortimer's report dealt with the accuracy of anti HIV screening tests:

> *"(4) How accurate are anti HIV Screening Tests?*
>
> *The early reports in the lay press that anti HIV assays were inaccurate were ill-founded, but questions about accuracy remain pertinent and are difficult to answer with precision. Accuracy depends upon freedom from false positive and false negative results. In the UK context, false positive results are uncommon both in screening and diagnostic work (<1%). They can usually be easily dealt with by confirmatory procedures and follow up testing. False negative results are of more concern. They arise either because no anti HIV is present (this seems to be unusual in infected individuals and is not the 'fault' of the anti HIV assay), or because the assay is too insensitive to detect anti*

HIV that is present. This latter possibility is being closely studied, especially to determine how early in infection each EIA can detect anti HIV. It appears that the best of the type I assay and the type II assay become positive first, followed by other type I assays. This impression is still too weak to be the basis for choosing a particular assay, however, and the intervals between reactions appearing by different assays are measured in days rather than weeks. Because Wellcozyme has been so much used in UK the most data is available for it and they suggest it is highly accurate under routine conditions (see appendix 1).

Whichever assay is being used, external factors such as clerical and technical error also contribute to inaccuracy. A minimum extrinsic error rate is probably about 1% and it can become much higher if proper procedural checks are not included."

4.7. I can see from the documents now provided to me that by December 1986, consideration was being given by the DHSS to the possibility that there were HIV positive donors who did not have the antibody to HIV. Dr Janet Mortimer provided a note on the issue dated 19 December 1986 following enquiries from Dr Smithies at the DHSS, a copy of which was sent to me [WITN5281077]. The note summarised the position in the following way:

"It is difficult to establish what proportion of those who are infectious do not have antibody to HIV. However :-

1. Antibody production has followed infection within 12 weeks in most cases where the time of exposure has been established.

2. Except for a few relating to ill AIDS patients, there have been no reports of anti-HIV positives becoming anti-HIV negative.

3. Almost everyone with AIDS and AIDS related disease has antibody.

Together these three observations suggest that almost all infected people produce anti HIV soon after infection, and continue to have it throughout the period when they might donate blood. This makes it reasonable to assume that fewer than 5% of those who are infectious lack anti-HIV.

By the end of October 1986 the UK Blood Transfusion Service had tested 2.8 million donations and found 57 anti-HIV positive. If 5% of those who are infectious fail to exhibit antibody, a set of donations containing 57 anti-HIV positives might also be expected to contain 2 or 3 which are infectious but are without detectable antibody. This would give an estimate of about 1 infectious donation without antibody per million screened.

The number of sero-conversions found among previously screened donors is important. There are two reasons for this. Firstly,

> *their own earlier anti-HIV negative donation may have been infectious; secondly, they represent a recently infected group in which the ratio of antibody negatives to antibody positives is likely to be much higher than the 5% quoted above. At present it cannot be reliably estimated how many donors have been tested more than once in the fifteen months since screening was introduced. However, only four have so far shown evidence of sero-conversion. This suggests that the acquisition of HIV infection in existing blood donors is at a low rate at present and that the risk of anti-HIV negative donations from those in the process of sera-converting is correspondingly small. To quantify this risk it will be necessary to know more about the interval between infection and antibody production, and about the distribution of intervals between donation among blood donors.*
>
> *Self-deferral by high risk donors remains the only effective way of minimising the risk of post-transfusion of HIV infection from seronegative donations. The operation of the mechanisms for encouraging self-deferral, and the risk groups definitions upon which it is based, must therefore be kept under review."*

4.8. I note from the documents now provided to me that on 18 April 1988 Dr Mortimer wrote to Dr Pickles at the DHSS, enclosing a revised version of a paper prepared by Dr Mortimer and Dr Rawlinson of the North West Regional Transfusion Centre, Manchester, which estimated the rates of missed HIV positive blood donations in the UK in 1986 and 1987 [WITN5281078]. I have exhibited this document to this statement given its apparent relevance, but I do not appear to have been sent a copy of it at the time and I have no memory of being involved in discussions about this paper.

4.9. Dr Janet Mortimer reported to the EAGA about developments in commercial HIV tests since 1985 at its meeting on 12 December 1989, a meeting which I attended. The following is recorded in the minutes under item 5:

> *"7. Dr Mortimer introduced this paper. It summarised developments in commercial HIV tests since 1985, and new assay formats, reagents and confirmatory tests. The main conclusion was that errors in laboratory diagnosis are more likely now to result from human error than from product failure. There was some discussion about quality control procedures and the importance of the National External Quality Assessment Scheme."* [WITN5281079]

Involvement in advising on the disposal of the "plasma stockpile" at BPL in January 1987

4.10. Although I have no present recollection of being involved in the issue, I can see from the minutes now provided to me that I attended a meeting of experts asked to advise on the disposal of a "plasma stockpile" at the BPL, Elstree on 16 January 1987 [WITN5281080]. Also present at the meeting were: Dr Abrams from the DHSS, who was acting as Chairman; Professor Collee, by then the Chairman of the CSM(B); Dr Gunson, Consultant Advisor in Blood Transfusion; Dr Kernoff, Director of the Haemophilia Reference Centre at the Royal Free Hospital; Dr Lane, Director of the BPL; Dr Mortimer, Director of the Virus Reference Laboratory, PHLS; Dr Schild, Director of the NIBSC; Professor Zuckerman of the London School of Hygiene and Tropical Medicine; Dr Moore and Dr Smithies from the DHSS; and Mr Ayling from the DHSS Medicines Inspectorate.

4.11. Attendees were being asked to advise the DHSS on the disposal of the stockpile of 50 tonnes of fresh frozen plasma ("FFP") and 126 tonnes of time expired plasma ("TEP") being held in cold storage at BPL that was untested for HIV antibody. Dr Abrams asked the group to give advice based on the scientific principles and leave financial, resource and political considerations for DHSS consideration.

4.12. The feasibility of retrospectively validating the FFP was discussed and this discussion is summarised at paragraph 2 to 4 of the minutes. 65% to 70% of the sample of single donations of FFP examined was obtained from donors who had donated again after 14 October 1985 and who had been found anti-HIV negative. Dr Lane considered that it would be operationally feasible for BPL to carry out necessary procedures to select donations of plasma obtained from those donors subsequently shown to be anti-HIV negative. Discussion explored the assumption that plasma obtained from a donor subsequently shown to be anti-HIV negative could be regarded as anti-HIV negative. Professor Zuckerman considered that although scientific evidence to support this assumption was lacking, he would nevertheless be content that the plasma

was used. Other members felt that the evidence from clinical practice supported the assumption and agreed that it would be safe to use the plasma provided that the scheme for sorting donations at BPL incorporated double checking and was carried out off-site.

4.13. Discussion followed on the uses to which the retrospectively validated plasma could be put, summarised in the following way at paragraphs 5 and 6 the minutes:

> *"….. Opinion was equally divided on whether the plasma should be used for the production of albumin alone or whether it could also be used as a source of Factor 8. Dr Smith felt that an albumin-only position was not logical and said it should be albumin and Factor 8 or nothing at all. Dr Kernoff agreed with this viewpoint. Dr Lane pointed out that experimental validation of the virus inactivation heat-treatment process given to Factor 8 would become technically available after May and this should provide further reassurance. Professor Zuckerman said that although the plasma appeared safe he would prefer its use restricted to albumin. However Dr Mortimer and Dr Gunson felt that since the plasma would effectively have the same status as normal donations it should be used for Factor 8 as well. Professor Collee thought usage should be restricted to albumin.*
>
> *6. The final view of the outside experts was; Professor Zuckerman, Professor Collee, Dr Schild, in favour of restricting usage to produce albumin. Dr Gunson, Dr Kernoff, Dr Lane, Dr Mortimer and Dr Smith in favour of using the plasma for fractionation to the blood products albumin and Factor 8. Mr Ayling of the Medicines Inspectorate preferred use for albumin only.*
>
> *All agreed that this plasma could also be used for commissioning the new plant for which some 15 tons of plasma would be required."*

4.14. It was the view of attendees that FFP which could not be validated should only be used for the purpose of commissioning the new BPL (see paragraphs 7 and 8 of the minutes). Specifically the plasma would be used in the early stages of commissioning non-sterile equipment and the plant could be steam sterilised.

4.15. It was agreed that TEP could not be distinguished from unvalidated FFP and should be treated in the same way and should not be used (see paragraph 9 of the minutes). Everyone apart from Dr Kernoff agreed that stocks of BPL albumin made from untested plasma could be safely used (see paragraph 11 of the minutes).

The PHLS role in relation to screening of blood donations for Hepatitis C from September 1991

4.16. As I understand it, routine screening in the NBTS of blood donations for Hepatitis C was introduced from 1 September 1991. As far as I am aware, I was not involved in advising on the policy of screening blood donations for Hepatitis C, although the PHLS had a role to play in providing confirmatory testing services to the NBTS. The way confirmatory testing was arranged was the subject of some debate in 1991 and I exhibit, by way of example, a selection of letters I received on this subject [WITN5281081; WITN5281082; WITN5281083; WITN5281084; WITN5281085; WITN5281086; WITN5281087].

HIV monitoring and surveillance

4.17. On 21 October 1986, I received a letter from the CMO in which he raised concern that the Department was not getting as much information as was needed to determine the extent to which HIV infection was spreading [WITN5281088]. I responded to Sir Donald's letter on 19 November 1986, addressing the points he had raised [WITN5281089].

4.18. In April 1987, a Sub-Group of the CMO's EAGA was set up to consider HIV monitoring and surveillance, which I was asked to Chair. At its first meeting on 28 April 1987 (see the minutes at [WITN5281090]), the CMO set out the Group's objective:

> "… to produce a set of recommendations, applicable throughout the UK, for improving the monitoring and surveillance of the epidemic of HIV 1 infection."

4.19. The minutes provided a useful overview of the various monitoring and surveillance programmes running at the time. The various options for increased screening were considered (paragraphs 21 to 27 of the minutes). It was agreed that mandatory screening was not a realistic or practicable option, given that it would pose considerable practical problems and might lead to concealment of the infection. Named or anonymous testing of pregnant women, patients seen in general practice and hospital patients was considered, along with non-

consensual anonymous testing of blood samples taken for other purposes, but with the patient's identifying details removed. Everyone agreed this triggered ethical problems, which would be thoroughly considered in due course.

4.20. I sent a paper to members of the Sub-Group on 15 October 1987 ahead of our meeting on 21 October 1987 [WITN5281091]. In the paper, I set out the key aims and objectives of surveillance by the Sub-Group, as well as the problems of serological surveillance. These problems included (but were not limited to): the virus' long incubation period and the lack of general availability of reliable tests to detect the virus (as opposed to just antibodies) in infected patients. It was on this basis that the paper dealt with the options for testing at paragraphs 2.4 to 2.6.

4.21. It seemed at the time that the only real option for testing was on a voluntary basis. Compulsory testing (with legal sanctions to enforce compliance) was considered; however, such a procedure was considered unnecessary for the purposes of surveillance in light of perfectly adequate data being secured by other means.

4.22. There were several issues to consider with voluntary testing. Firstly, the patient's consent: ethical questions aside, it was clear that non-consensual testing was not legally permissible and therefore, samples of blood would have to be taken with the patient's consent. The next issue was whether the sample should be named or anonymous. Named testing would have involved the sample being identified through the subject's name and any other details. Anonymous testing would have involved the removal of all identifying details, save for age, sex and Health District of residence. There were a number of important disadvantages to anonymous testing. Where a patient's identity had been removed, there was no possibility of confirming the results of any test or establishing categories of risk behaviour. Where false positive test results occurred, we would have been unable to secure a second sample. There was also no obvious application for anonymous testing: large-scale studies were not practicable because only a small percentage of the population of the UK had tested positive for the virus. A true random sample, therefore, would require the participation of tens of thousands of people.

4.23. Our report was provided to the Department in January 1988 and the CMO wrote to me on 3 February 1988 thanking me and expressing his hope that it would not be long before he could tell me what Ministers had decided about implementation [WITN5281092]. The report was published in May 1988 [WITN5281093].

4.24. We made 26 recommendations, which included the following recommendations in relation to testing:

> *"3. Further information is required to confirm the view that prevalence of HIV infection outside the high risk behaviour groups is at present low in the UK and to provide a baseline which could be used to track prevalence. This further information should in the first place be sought by means of antenatal testing. (4.10)*
>
> > *3.1 Centres participating in antenatal studies should provide compatible basic data and studies in these centres should be co-ordinated. (4.14)*
> >
> > *3.2 Three samples of pregnant women should be studied over a period of a year. The clinics selected to take part in antenatal screening should be both in areas where the prevalence of infection and of high risk behaviour in high and in low risk parts of the country. (4.16)*
>
> *4. The needs for further studies in antenatal patients and/or in other groups representative of the general population should be decided in light of the results of the antenatal testing studies. (4.18)*
>
> *5. Provision should be made for unnamed voluntary HIV testing for those who refuse to have their blood in named schemes."*

4.25. I was informed by the Department by a letter dated 24 February 1988 from Mr Barton of the Department's AIDS Unit of the way in which they intended to take action on each of the recommendations, including their understanding that, in the majority of cases, action taking forward the recommendations would fall to the PHLS and the CDSC [WITN5281094]. I responded to the Department's proposals in a letter dated 16 March 1988 [WITN5281095], outlining the practical requirements for the additional work.

Section 5: Response to criticism from other Inquiry witnesses

5.1. By way of a Rule 13 notification letter dated 3 June 2021, the IBI has drawn to my attention some evidence given by other witnesses that is critical of me and provided me with the opportunity to comment on it.

5.2. The first criticism is made by witness W1055. At paragraph 623 of this witness' statement dated 30 April 2021 it is suggested by the witness that, during a conversation she had with Dr Spence Galbraith, Dr Galbraith asked her to help him *"sue Sir Joseph Smith"* who he *"blamed for blood policy at that time and failing to withdraw the US factor concentrates"*. The paragraph continues as follows:

> *"Galbraith expressed his anger at Smith and in a letter to me talks of giving Smith "a little shock". He alleged Smith received research funding from the plasma companies. I was unable to certify whether this was the case or not."*

5.3. I have addressed the CSM(B)'s consideration of the question of whether US factor concentrates should be withdrawn from the UK market on 13 July 1983 in some detail at paragraphs 3.21 to 3.49 above. Dr Galbraith was at that meeting, at my request, and I do not recall him voicing any dissent to the conclusions and recommendations agreed upon by the CSM(B). I was not responsible for blood policy, at that time or any other time, and the CSM(B)'s only role was in providing recommendations to the CSM and to the Licensing Authority. I do not think I can usefully add to my evidence above relating to the reasons for the CSM(B)'s conclusions and recommendations following the meeting of 13 July 1983.

5.4. As far as I am aware, I have never received research funding or any other funding from plasma companies, in any of the relevant roles I have set out above, or otherwise.

5.5. I note that witness W1055 has provided an earlier statement to the IBI dated 6 November 2018, which is published on the IBI's website. Paragraph 29 of that statement reads as follows:

> *"I also discovered that in May 1983 the British government had been advised by Dr Spence Galbraith (formerly of Public Health Laboratory Service, PHLS) to immediately take the US treatment off the shelves due to the risk of AIDs. Galbraith was in contact with me by phone at the time of the Archer Inquiry and personally sent me his letter to use in our BBC 2007 Newsnight programme. The treatment withdrawal did not happen, Galbraith told me that he was closed down by Joseph Smith in 1983 and asked me years later to help me litigate against him. Joseph Smith also contacted me by phone in a call lasting around 1 and half hours on a Saturday morning and admitted his alleged negligence. Only days later when he was giving evidence to the Archer Inquiry I was surprised at his sudden memory loss as his recall had been amazing; the Medical Defence Union were now involved!"*

5.6. I did not "close down" Dr Galbraith in relation to the question of withdrawal of US factor concentrates in 1983. As I have noted above at paragraph 3.49, I was unaware that Dr Galbraith had written to the DHSS suggesting the withdrawal of US concentrates until I saw his letter many years later. As also noted above, I do not recall Dr Galbraith voicing any dissent to the proposed conclusions and recommendations at the CSM(B) meeting on 13 July 1983.

5.7. I have spent some time thinking about the suggestion that I telephoned witness W1055 before I gave evidence to the Archer Inquiry. The only possible telephone conversation that I recall which might correspond with this witness' account was a call that I received, rather than made. The call was from a woman who raised concern that scientists in general were hiding information about relevant events. She said that if I had any information I should not keep it hidden. I told her that I was happy to tell the Archer Inquiry everything I could remember, which I went on to do. The call cannot have lasted more than several minutes. I do not accept that I "admitted [my] alleged negligence". I feel sure that there was nothing that I said during this short call that could be characterised in this way. It may have been during this call that I first learned of Dr Galbraith's letter to the DHSS.

5.8. The second criticism that the IBI has alerted to me is made in a witness statement provided by witness W1210 dated 27 February 2020. Paragraph 100 of the statement states:

> *"During my work with the national media I have often worked on stories where a right to reply should be given to the individuals involved, this is standard practice in journalism ethics. Examples include: [witness name removed], [witness name removed] and Sir Joseph Smith, all of whom have generally refused to comment and have been very press shy. It appears to me, that they have something to hide."*

5.9. I do not generally provide comment to the press, particularly when the issue I am being asked to comment on is one which is the subject of an ongoing public inquiry. I do not have anything to hide and have done my level best to provide a full account of relevant events in this statement to assist the IBI in its work.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed..... GRO-C .....

Dated..... 11/12/21 .....