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INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF DR DUNCAN THOMAS

I, Dr Duncan Thomas, will say as follows: -

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Introduction

0.1. My full name is Duncan Porter Thomas. My date of birth and home address are known to the Inquiry.

0.2. I am providing this statement in response to the Rule 9 request from the Inquiry dated 1 July 2021.

Opening Comments

0.3. At the time of writing, I am ninety-two. My memory of events and my capacity to process information is not what it once was. I have done my very best with this statement and will assist the Inquiry as much as I can – I am keen to help – but my ability is unfortunately quite limited. I have been provided with the documents that I have cited in this statement and have done my best to read and absorb them but I am acutely conscious that my capacity is lacking and I have relied heavily on help from others to summarise the contents of these documents.

Section 1: Introduction and Professional History

1.1. I began my studies in 1945 at Cardiff University. In 1949, I graduated with a BSc . Between 1949 and 1951, I studied at the Queen's College Oxford graduating with an MSc (Oxon) in 1951.

1.2. From 1951 until 1955, I worked at St Bartholomew's Hospital obtaining a MB,BS (Lond) in 1954. In 1953, I was awarded the Wix Prize.

1.3. Between July and September 1954, I attended Harvard Medical School in Boston, USA, as a visiting medical student.

1.4. I returned to Oxford between 1956 and 1958 completing my DPhil in 1958. During this time, I was a Captain in the Royal Army Medical Corps ('RAMC') seconded to the Medical Research Council ('MRC') Unit.

1.5. In 1982, I became a Fellow of the Royal College of Pathologists.

1.6. In summary, therefore, my qualifications are: BSc (Cardiff) 1949; MSc (Oxon)1951; MB, BS (Lond) 1954; Dphil (Oxon) 1958; MD (Lond) 1963; FRCPath (1982).

Employment History

1.7. The following table outlines my employment history:

Table 1 – Employment History

Date	Organisation	Role
January–December 1955	St Bartholomew's Hospital, London, Professorial Medical and Surgical Units	House Physician/House Surgeon
1956-1958	Royal Army Medical Corps, seconded to MRC Unit, Oxford	Captain
1958-1960	Beth Israel Hospital, Boston, Massachusetts, USA	Assistant Resident / Chief Resident in Medicine
1960-1963	Harvard Medical School, Boston	Instructor in Medicine

Date	Organisation	Role
1963-1970	Lemuel Shattuck Hospital, Boston	Senior Physician, and Chief, Vascular Laboratory
1964-1968	Tufts University School of Medicine, Boston	Assistant Professor of Medicine
1968-1970	Tufts University School of Medicine, Boston	Associate Professor
1970-1971	MRC Headquarters, London	Medical Officer
1971-1974	Committee on Safety of Medicines (Biologicals) Sub-Committee, London	Senior Medical Officer
1974-1976	Thrombosis Research Unit, King's College Hospital Medical School, London	Deputy Director and Senior Lecturer
1976-1991	Division of Haematology, National Institute for Biological Standards and Control ('NISBC')	Head
1982-1983	Bureau of Biologics, FDA, Washington, DC	Distinguished Visiting Scientist
1991	I formally retired	
1991-1995	Bio Products Laboratory, Elstree, Herts	Consultant Medical Advisor
1995-1996	Department of Medicine, University of North Carolina, USA	Visiting Scholar

1.8. My speciality was haemostasis and thrombosis. It is perhaps worth observing, however, that much of my work was research which was unrelated to blood or blood products. While doing national service, for example, I wrote my PhD at Oxford looking into load-carrying by soldiers.

1.9. I was involved in the process of licensing blood products in two of my positions:

1.9.1. SMO on the Secretariat of the CSM Biologicals sub-committee ('CSM(B)'), 1971-1974 and

1.9.2. Head of the Division of Haematology at the National Institute for Biological Standards and Control ('NIBSC'), 1976-1991.

I have therefore focussed on these roles and time periods in this statement.

1.10. As an SMO on the CSM(B), I was not a member of the Committee itself, I was part of the Secretariat. This meant that I would usually be in attendance at the CSM(B) meetings.

1.11. I was a member of various committees and organisations during my career. I have set out below those which may be of peripheral relevance but beyond these, I do not think any others are relevant to the Inquiry's Terms of Reference:

Table 2 – Relevant Positions and Memberships

1976-1991	Chairman of the Blood Products Committee of the British Pharmacopoeia
1976-1971	Member of the International Committee for Thrombosis and Haemostasis, Chairman Heparin sub-committee 1976-1971
1976-1991	Member of the expert committee of biological standards, WHO, Geneva

Litigation History

1.12. Many years ago, I met with Canadian lawyers and Royal Canadian Mounted Police in relation to a criminal prosecution. They visited me on two occasions and asked questions about Factor VIII made by Armour which the CSM(B) had refused to license because we did not consider that it had been sufficiently heat-treated (it had not been made hot enough). I understand that the product was sent to Canada where Canadians were infected as a result. I understood at the time that the litigation was settled out of court (although I have since been told that there was some sort of prosecution in which Armour and others were acquitted: I do not know if this was the same litigation). To the best of my recollection, I did not draft a witness statement and I certainly do not have any papers relating to this case. I have been told that a letter from the Government Legal Department to NIBSC dated 9 June 2006 suggests that I met with the defence lawyer for Dr Furesz, one of the four doctors who was prosecuted and I may have submitted a statement. I have no recollection of whether this is

correct. Beyond this, I have not provided any written or oral evidence on these matters.

Early Career

1.13. In the summer of 1970, I returned from working in America and started work for the MRC as a medical officer in Park Crescent, London. About a year later I was offered a role as a Senior Medical Officer for the CSM, part of the Medicines Commission. John Holgate was the Principal Medical Officer with responsibility for the biologicals. 'Biologicals' is the term for products of biological origin such as vaccinations and blood products whose purity or potency cannot be adequately tested by chemical means. This role was as part of the Secretariat to the CSM(B). We would advise the CSM(B) about licences. This was how I first became involved in NIBSC and met the then-director Sir David Evans. I talk about the role of CSM(B), its responsibilities and the work I did in more detail below.

1.14. Having worked as SMO for over three years, in 1974 I left the Department and spent two years working as a Deputy Director in Thrombosis research at King's College Hospital under the late Professor Vijay Kakkar.

1.15. I have been shown a letter dated 21 January 1975 from Dr J.A. Holgate (Department of Health and Social Security ('DHSS')) to Dr W.d'A. Maycock (the Lister Institute of Preventative Medicine, Elstree) **[CBLA000252]**. Dr Holgate wrote:

> *My concern is growing daily as there are no apparent moves whatsoever to obtain a replacement for Dr. Duncan Thomas. I am sure you will agree that any replacement we eventually may get is unlikely to have his stature and I feel his absence most acutely.*

1.16. At the time that this letter was written, I had already left my DHSS role. I was not aware of any concerns about my replacement (or lack of replacement).

Working in the United States 1982-1983

1.17. I have spent several periods in my career working in and visiting the United States. These are set out in Table 1 above but it is worth flagging one particular visit. Between 1982 and 1983, I was a distinguished visiting scientist working at the Bureau of Biologics, Food and Drug Administration ('FDA') in Washington, DC. This was during a leave of absence from NIBSC. I was employed by the FDA for a year with a salary. While I was working in the States, the recognition of the AIDS virus was emerging. It was a hot topic but initially it was not known that it was even a virus, everything was obscure. It was not known that it was a virus until 1983. I was based on the National Institute of Health campus and there were people on campus doing AIDS work; I would speak to them out of interest but it was not my field.

1.18. You can see a reference to this period of working in the States in a letter I have been shown dated 13 January 1983 from David L. Aronson, Director, Coagulation Branch, Division of Blood Products, Office of Biologics, National Center for Drugs and Biologics, Bethesda, US, to Dr John Cash of the Scottish Blood Transfusion Service, Edinburgh **[MACK0001314].** In that letter, Dr Aronson wrote:

> *All rumors to the contrary, Duncan Thomas is not lost in the wilds of the Midwest but is in the process of settling in here. Hopefully, we can do some thrombosis experiments between taking care of AIDS and other routine crises.*

1.19. This reflects the reality of the situation that I found in Bethesda: the AIDS crisis had broken and many of those working on the campus were dealing with it but it was not my focus. I describe the impact of my work in the States below.

Section 2: The Licensing Process in general, including the role of NIBSC

2.1. While I cannot assist with the roles and functions of the Licensing Authority or NIBSC overall and changes throughout time, the following is a broad outline of my understanding and the work that I was doing during my tenure on the

Secretariat to the CSM(B) from 1971 until 1974 and then during my time at NIBSC from 1976 to 1991.

Licensing Authority

2.2. The Licensing Authority was created in 1968 by the Medicines Act 1968 thereby establishing the licensing regime. Section 6 stated that:

> *(1) …the authority responsible for the grant, renewal, variation, suspension and revocation of licences and certificates shall be a body of Ministers consisting of all the Ministers specified in paragraphs (a) and (b) of section 1(1) of this Act[1].*
>
> *(2) Any function conferred on the licensing authority by or under this Act may be performed by any one of those Ministers acting alone or by any two or more of them acting jointly.*
>
> *(3) In accordance with the preceding provisions of this section, in this Act "the licensing authority" means any one or more of those Ministers, and, in the case of anything falling to be done by the licensing authority, means any one or more of those Ministers acting as mentioned in subsection (2) of this section.*

2.3. This accords with my understanding: the Licensing Authority itself was the term used to describe the ministers. It was also, however, colloquially used – often without capitalisation – to describe the entirety of the bodies involved in the licensing process.

2.4. The Licensing Authority was ultimately responsible for granting, varying or refusing licences for medicines which included drugs and biologicals.

Committee on Safety of Medicines

2.5. The Licensing Authority would be advised by a committee of experts called the Committee on Safety of Medicines ('CSM') which was set up as a response to the Thalidomide disaster. It was a committee of the Medicines Commission (which was established under the Medicines Act 1968). The CSM would make recommendations to the Licensing Authority about granting or refusing new

[1] This meant the Health Ministers and the Agriculture Ministers.

product licences or varying existing product licences. To the best of my knowledge, these recommendations would normally be accepted. I was never a part of the CSM and cannot give further details on its workings.

Biologicals Sub-Committee: Secretariat

2.6. There were other sub-committees of the CSM, but the sub-committee with which I was involved was the Committee on the Safety of Medicines Sub-Committee on Biologicals ('CSM(B)'). I was on the Secretariat which included Senior Medical Officers such as me who would assess the clinical trial and medical data that the manufacturers[2] sent in with their application. I would describe myself as a medical assessor.

Product Licence Applications

2.7. Manufacturers would send the CSM their product licence application and this would include a protocol setting out how they had created the product. All manufacturers would be required to provide detail of the procedures used to create the product. This applied to all drugs as well as blood products. The application for the licence would include information about donors (such as how they selected the donors, how the donors were tested for hepatitis B and how they excluded people who should not give blood), the manufacturing process and what tests they had carried out. I mention hepatitis B because at the time I was involved with the CSM(B), hepatitis B was well-known and there were tests available whereas the same was not true of hepatitis C or HIV until later (I discuss testing further from paragraph 2.39 below).

2.8. The information and evidence submitted by manufacturers would be large quantities of documents which would be distributed to the CSM(B)'s Secretariat. The sort of material provided would include:

2.8.1. Product particulars;

[2] I use the term 'manufacturers' throughout my statement as this is how I would have referred to pharmaceutical companies who were manufacturing products at the time. It is synonymous with 'pharmaceutical companies'.

2.8.2. Copies of proposed product labels;

2.8.3. Data sheets;

2.8.4. Scientific evidence such as:

2.8.4.1. Method of manufacture

2.8.4.2. Methods of analysis;

2.8.4.3. Stability report; and

2.8.4.4. Copies of clinical studies.

2.9. The professional assessors on the Secretariat then considered the application and evidence, judged it and wrote a report to the members of the CSM(B) which included some of the leading pharmacologists in the country. The report would contain a summary of the application and the recommendation – you can see an example of a Summary and Report that I drafted while serving on the Secretariat in 1974 at **[MHRA0000091_012, page 17]**.

2.10. There was a close working relationship between NIBSC and the CSM(B) with mutual interaction and coordination; representatives from NIBSC would attend the CSM(B) meetings. The applications would also be passed across to NIBSC for their input and the NIBSC team would usually record their assessments in letters. This was very common. As the NIBSC Annual Report 1991-1992 **[WITN6405002]** stated on page 6:

> *The MCA frequently seeks the advice of NIBSC scientists on technical aspects of applications. The advice given includes some comments on the nature and suitability of source materials, the manufacturing strategy, in-process control and final product specification and product. Another important issue is the appropriate standard preparations in the manufacturer's quality control processes.*

2.11. It was also quite common, if there was an issue with the licence application, that the Secretariat would liaise directly with the manufacturer to understand and resolve it. This might entail asking questions or seeking undertakings. An example of this, from after my time on the Secretariat, can be seen in the letter of 18 January 1985 written by Dr Mary Duncan to Mr Hince at Armour requiring

an agreement about the length of time and temperature for which a product was to be heated [**ARMO0000161].** Such communications were commonplace and, while on the Secretariat, I would often be asked to contact the manufacturers to clarify matters or reach agreements on areas that needed resolution at all stages of the licensing process. An example of this can be seen in a letter I received from J. Middleton (I have no recollection who he or she was) dated 26 February 1973 asking me to 'endeavour to obtain the applicant's written agreement to the following provisos' from Serological Products Limited regarding Kryobulin **[WITN6405003]**).

2.12. As part of this process, I also recall that the Medicines Inspectorate would visit factories and ensure the manufacturers were doing what they should do. This work would be carried out by the pharmacists who were part of the CSM. This was true of all products, from drugs to blood products and included new types of blood products such as heat-treated products.

2.13. The process in summary, therefore, was that the application would arrive and be passed to the Secretariat for our assessment and any liaison with NIBSC and / or the manufacturers. The Secretariat would report to the CSM(B) and then the application would be discussed at the Committee stage, first by the CSM(B) and then by the main CSM. NIBSC did not attend the CSM meetings; NIBSC representatives only attended the CSM(B) meetings. Recommendations would be made by the CSM(B) and they would then be considered by the CSM. Finally, on the CSM's recommendation, the Licensing Authority would issue product licences. Once a licence had been granted for a biological product, it would be subject to a batch release procedure which was carried out by NIBSC. I have described this further from paragraph 3.1 below. Batch release was applied to all blood products.

2.14. We were unable to test blood products virologically in those days, in particular for hepatitis C and HTLV-III. At an earlier stage we were able to test donors (not the products themselves) for hepatitis B but you would need to ask a virologist for the details of this. While we were able to test for certain blood borne infections (such as the hepatitis B antigen), we could not test for hepatitis C or the HIV / AIDS virus. Later, in the late 1980s, virologists at NIBSC would test

samples of the pools of donated blood but this was not something that we did in my department. I know from an article that I wrote when I was at NIBSC (discussed in full from paragraph 6.1 below), that by 1988 we were screening plasma pools used by the NHS fractionation centres and samples of all blood products distributed in the UK for HIV antibodies and HBsAg at NIBSC **[DHSC0001008**]. I cannot recall the exact dates when this started. I cannot say for sure whether this would have included unlicensed products; on the whole we were not sent unlicensed products and doctors prescribed them on a named-patient basis. Even at that time, there was no universally agreed approach to removing or inactivating viruses in plasma pools used by manufacturers of clotting factor concentrates although some techniques were emerging as safer than others.

Interaction with the Licensing Authority

2.15. I cannot comment on how NIBSC and the CSM worked with and exchanged information with the Licensing Authority. (I do not think they did, the Licensing Authority were the ministers and we never met them. It was the civil service acting on behalf of the minister. When I was on the Secretariat, I would pass information to the CSM(B) and when I was at NIBSC, we would report back to the CSM(B) or occasionally the CSM itself.)

Conflicts of interest

2.16. During my time on the Secretariat, on the CSM(B) sat two individuals who worked for UK manufacturers: John Watt from Edinburgh who ran the Protein Fractionation Centre ('PFC') and Richard Lane, who was the Medical Director at BPL in Elstree. Having manufacturers on the CSM(B) had the advantage of meaning that it was kept abreast of commercial developments and received informed insight into production but it also presented its own problems of conflicts of interest. I know that all interests would be clearly declared during meetings and minuted accordingly. Additionally, a record of interests was kept and I have also seen a note of declared personal interests on which I was included: **[WITN6405004**]. This document is not dated but I think it must have been from when I was at NIBSC and would attend CSM(B) meetings.

Foreign licences

2.17. It was not uncommon for products the CSM was considering to have already been licensed abroad. As I remember it, these products were American and, in one case, Austrian. During my time on the Secretariat, I think they were the only manufacturers involved in importing blood products to the UK. We would liaise closely with the FDA but this was not a rubber-stamping exercise. We still checked every application carefully and we would not be influenced or swayed by licensing within another jurisdiction. From my perspective, I recall that occasionally we were reluctant to accept evidence from the Americans where they said a product had already been licensed for a few years without causing problems and that we should take this into account. We would look at all the evidence carefully but we were not influenced by other jurisdictions' licensing processes or decisions.

CSM(B) liaison with the FDA

2.18. On the CSM(B) Secretariat, we spoke to the FDA frequently. I knew my opposite number there and we would have conversations by telephone. That said, this was not a formal process and the work on licences we carried out was all in-house.

2.19. I cannot speak to what access other individuals or the Licensing Authority itself had in relation to submissions and considerations received by the FDA or others.

Applications, variations and abridged product licences

2.20. Where manufacturers asked for a variation of their licence (for example, when a blood product that had previously been licensed was now to be heat-treated or where a licensed product was now to be used to treat a different condition), they would have to reapply and get approval for the new variation of the product. Applications for new product licences and for variations or amendments of existing product licences were treated the same. Everything would go to the CSM unless it was something truly trivial. In the same way as with a new

application, we would prepare a recommendation for a variation. We applied the same level of scrutiny.

2.21. The same was true of abridged applications, but they were shorter as they dealt with specific issues. Nonetheless, they fundamentally went through the same procedure.

2.22. When heat-treatment was introduced, it was recognised that this process was very important and we carefully considered the applications for variations (though it is possible that some were abridged licences, I cannot now recall). There were issues about what heat treatment was sufficient: the method; the temperature; the duration and the number of viral markers used. We were conscious that the process of heat treating meant that manufacturers lost some of the product which of course affected profits. At no point was I aware of any manufacturer putting profits over safety. They wanted to be confident they were eradicating viruses, whilst minimising the loss of product (the yield) via heat treatment. Nobody had a clear answer as to what was the correct process when heat-treatment began. This is discussed further at paragraphs 6.2 to 6.3, 6.7 and 6.21 below.

Assessment and scrutiny of applications

2.23. I cannot of course speak for others but I felt that there was a clear process in place that brought together experts in different disciplines to assess each application fully. I had many dealings with manufacturers over the years and I recognised that they knew what they were doing and understood the detail of how they produced their products. The CSM(B) – both in the form of the Committee and the Secretariat – would look at applications thoroughly and would not hesitate to ask questions.

2.24. While I was on the Secretariat, we would carefully scrutinise applications for product licences for blood products and were able to identify incomplete applications or other shortcomings. Manufacturers would sometimes submit clinical studies and other information and we would carefully consider this material. We would consider these clinical studies if they were applicable and we were not afraid to check the information provided by manufacturers. While

clinical studies could be helpful, we had the requisite knowledge and expertise to look at how they were conducted and identify any shortcomings. There was a range of people with different expertise on the Secretariat, CSM(B) and CSM who would bring their own knowledge to bear. The Secretariat and CSM(B) scrutinised everything that was presented and where something appeared incomplete or there seemed to be shortcomings with a study, we would go back and ask questions. Licences were often given with conditions which demonstrated the CSM spotted deficiencies and ensured they were rectified before the product was released on the market. There was often an exchange and discussions with manufacturers who had to satisfy the CSM that they had done whatever was required.

NIBSC

2.25. NIBSC was formed in 1972 and was managed by the National Biological Standards Board ('NBSB'). As I have explained, the work of the CSM and CSM(B) was to assess a product's safety, efficacy and quality. NIBSC's role, meanwhile, was as part of the assessment of safety and quality: NIBSC assessed the composition of the product, in particular, its potency. NIBSC would examine the product protocols to check the product's composition against the manufacturer's specification and to ensure that the manufacturers were doing what they said they would do. There were often complexities and difficulties relating to standardisation of assays, especially for clotting factors, and we would liaise with the manufacturers about such issues.

2.26. We would liaise closely with the Secretariat of the CSM(B) and assist if we could at the application stage, as I have already described.

2.27. If we (at NIBSC) were unhappy with the potency, we would raise our concerns with the manufacturers and CSM(B) and the manufacturers might be required to amend the proposed labels.

2.28. Beyond what I have explained (which goes to the assessment of the quality and safety of a product by virtue of a product's composition and potency), I cannot assist with the assessment of safety, quality and efficacy of blood products

because NIBSC's only involvement related to potency and checking the protocol documents.

2.29. NIBSC's primary role was to carry out potency testing for the batch release procedure which I set out at paragraph 3.1 below onwards. If a product did not meet the specification, we would not issue a Batch Release Certificate meaning that the product would not be released onto the market.

Official Medicines Control Laboratory

2.30. I understand that the Inquiry has received evidence to the effect that NIBSC became an Official Medicines Control Laboratory in 1981. As far as I was concerned, it was always an Official Medicines Control Laboratory. I cannot recall it making any practical difference to NIBSC's role in examining blood products.

International Standards

2.31. I can assist with regards to my recollections about establishing the international standards but this only related to potency (rather than other aspects of quality, safety and efficacy).

2.32. At NIBSC, we had the responsibility for establishing the international standard and we were the WHO laboratory for the International Standards on behalf of the WHO. We would produce the international unit (a yardstick against which other samples of the same product could be measured) and send it around the world. We would establish the standard by asking all the laboratories that we knew about to assay a sample and then our statisticians assessed the best mean. Once the original standard ran out, NIBSC would produce another identical one and so on.

2.33. The system of international standards started with insulin in the 1920s. Everyone was using different units which made it very difficult for prescribing doctors and for patients. Sir Henry Dale from the MRC went to Geneva and worked to agree and establish international standards for biological substances such as hormones, antitoxins, vaccines and blood products. The process was

used for drugs and in due course, Factor VIII. I used to attend the annual Expert Committee on Biological Standardisation in Geneva to establish international standards for all biologicals.

2.34. During my time at NIBSC I was able to persuade American manufacturers to adopt the international standard for Factor VIII. They were not keen on using international standards and preferred to use their own 'house' standards. For example, Armour wrote to me in September 1978 suggesting that the two units were identical and requesting dropping a second assay and thereby not using the International Standard **[WITN6405005]**. I responded saying that we were not prepared to accept that the two standards were equivalent and setting out the data to support my position **[MHRA0000085_010]**. Armour ultimately agreed to assay their product against the International Standard: **[MHRA0000085_003]** but it did not happen overnight and involved visits from their 'key personnel' to NIBSC such as in September 1979 **[MHRA0000084_011]**.

2.35. In the NIBSC Report for 1978-1980, there is some record of the issues and work that led to this change in relation to Factor VIII concentrate **[WITN6405006** at internal pages 29-30**]**. In particular there is reference to a meeting with US drug company representatives at NIBSC in October 1980. Following this meeting and as a result of the lengthy discussion in this meeting, NIBSC made the international standards available to US manufacturers for calibrating their house standards.

2.36. The international standard for Factor VIII was established before I joined NIBSC. I think this happened in the late 1960s or early 1970s under Dr D. R. Bangham, who was responsible for blood products at NIBSC before I joined in 1976.

Extensions of Shelf-Life

2.37. One other thing that I recall from my time at NIBSC and have seen in the documents is that we were often consulted about extensions of a product's shelf-life. By way of example, on 27 April 1982, E.R.James, a Quality Control Manager at Armour, wrote to me saying that two of their batches of HP

Factorate were approaching their expiry dates **[MHRA0000081_010]**. The batches had been re-assayed by the Oxford Haemophilia Centre and Mr James set out the results and said they proposed to extend the shelf-lives from one year to two years. He wrote 'This proposal is based on the assay results obtained above and upon the data submitted to the Licensing Authority to support a request for a shelf-life of two years for this product; I understand that the data has been provided to you for review'. On 29 April 1982, I responded saying I had no objections **[MHRA0000081_009]**.

2.38. I continued to make these sorts of assessments throughout my time at NIBSC (I have seen further examples such as in May 1990 when I expressed concerns about Factor VIII batches which had been stored at ambient temperature: **[MHRA0000010_028]** and **[WITN6405007])**.

Sources of donated blood in relation to licensing of blood products

Testing

2.39. From the beginning of my time working on the CSM(B) and while I was at NIBSC, there was already a test for the hepatitis B antigen and all donors had to be screened.

2.40. You can see that this testing was taking place – and was a requirement needed for a licence to be approved – if you look at a Report and Summary that I prepared for Antihaemophilic Factor (Human) made by Abbott Laboratories in August 1974 while I was on the CSM(B) Secretariat. Under 'Method of Manufacture', I have recorded at paragraph 9.1 that 'Plasma meets the requirement that each donation shall be individually tested, using the radioimmunoassay method, and found to be non-reactive for hepatitis associated antigen' **[MHRA0000091_012, page** 20**]**. Under '10.2 Quality Control', I have written:

> *Active Constituent: Plasma for fractionation meets the requirements that each donation shall be individually tested and*

> *found to be nonreactive for hepatitis-associated antigen. The Austria (Abbott) test is used.*
>
> *The donors meet the criteria of the regulations.*
>
> *The blood from each donor is tested for syphilis (serological test), for blood group and for rH factor.* **[MHRA0000091_012, page** 21**]**

2.41. The label of the product was to warn:

> *This product is prepared from units of human plasma which have been tested and found nonreactive for Hepatitis Associated Antigen. However, it is recognised that presently available methods are not sensitive enough to detect all units of potentially infectious plasma and the risk of transmitting hepatitis is still present.* **[MHRA0000091_012, page** 19**]**

This demonstrates that the plasma had been screened for hepatitis B but we still felt it was necessary to warn about the risks in the 1970s.

2.42. In the 1980s, a test was developed to screen donors for HIV and then in the late 1980s, a test for hepatitis C became available when the virus was isolated. I am not sure when these tests were first in use in the United Kingdom. These were gradual developments and as the science developed, it was applied and donors and then products were tested. I can see from the documents that by at least 1986, we were being sent some blood products at NIBSC to test for HTLV-III/LAV antibodies **[WITN6405008]** .

2.43. On 27 April 1987, Dr Schild and I prepared a paper for the CSM(B) on 'The Need for Validation of In Vitro Screening Tests for Viral Contamination of Blood Donations Used in the Manufacture of Blood Products' seeking the views of the CSM(B) **[DHSC0002374_041]** (pages 2-4). I have no recollection of going to a meeting with Dr Schild (if, indeed, we did attend a meeting). As a result of the paper, Dr Purves, Dr Jefferys and Dr Rotblat prepared a draft recommendation **[DHSC0002374_041]** (page 1). They recommended that all manufacturers applying for new licences for blood products should supply information about their screening procedures for HIV and HBsAg and information about the quality assurance and performance evaluation of their test kits. They recommended ongoing monitoring of current licence holders and

for all new licences by submission of quality assurance and performance evaluation data with the protocols supplied for the batch release process. Finally, they recommended that the Licensing Authority should write to individual manufacturers and ask them to provide quality assurance information.

2.44. I have also seen a letter which I wrote on 16 July 1990 to Mr David Donald at BPL **[BPLL0003236]** confirmed that:

> *…tests for the presence of HIV/2-antibody are carried out as part of our release procedure on all plasma pools and finished product sent to us by BPL. We are also able to carry out confirmatory tests for anti-HIV/1 or anti-HIV/2, in the event of any positive results appearing on the initial screening tests.*

I cannot, however, recall when we started using these tests.

2.45. As soon as tests became available, manufacturers would begin to apply them. They did not want to sell products that were infected and I felt they were doing their best. In my dealings with them, I found them to be highly responsible (and I include here my time on the Secretariat, at NIBSC and the time that I spent as a consultant at BPL after I left NIBSC).

Conditions

2.46. I have mentioned above that conditions could be imposed but what types of conditions were imposed for product licences to be granted varied on the blood products. There would have been pharmaceutical issues that the pharmacists would have addressed and later, when blood products were heat-treated, there would have been technical requirements about temperatures and pHs on which the manufacturers would need to satisfy the CSM but this was all outside my competence.

Sources of donated blood

2.47. The main issue about screening donors related to the American and Austrian donors because they were often paid unlike the voluntary donors in the UK. The rules about this were tightened up in 1983 (see further paragraph 5.12 below) at which point the Americans started to exclude prisoners and high risk donors.

We relied on what was written on the protocol rather than conducting checks on the donors ourselves.

2.48. On one occasion, in 1973 when I was still on the CSM(B), the Department sent me to San Francisco to speak to Cutter. I know that efforts have been made to locate any documents about this trip but so far, nothing has been found. Nonetheless, I recall that the purpose of the visit was to ensure that Cutter were really doing what they claimed to be doing. This was before AIDS or hepatitis C were issues and my focus was on hepatitis B. I met with a Cutter committee and questioned them about their processes. They assured me that they were not using dubious donors but I never interviewed any donors. I was reassured by their answers and could not find anything to fault them on. I wrote up my findings in a report but unfortunately, I understand that this has not been located.

2.49. I have given some thought as to why I might have been sent to check on Cutter. We may have been more suspicious as there was a so- called 'Cutter incident' in relation to the polio vaccine. Some live polio got into the vaccine and paralysed patients. As a result, all polio vaccines were tested on monkeys at NIBSC to make sure none were paralysed before a vaccine was released.

2.50. Although I have very little recollection of this now, I know that manufacturers would provide us with information about the source of the blood they used. By way of example, in one Report and Summary that I prepared for Antihaemophilic Factor (Human) made by Abbott Laboratories in August 1974 while I was on the CSM(B) Secretariat, I stated:

> *11. Selection and Screening of Blood Donors*
>
> *The controls applied in the collection of plasma for AHF* [Factor VIII] *manufacture are detailed in the copies of the forms used to collate the information on the medical history, physical examination and laboratory data of a proposed donor; the Donor medical history cards; the plasma donor list and daily donor rejection list. (see pages 29-37 of the submission).* **[MHRA0000091_012,** page 21**]**

2.51. We would not be given names and addresses (and indeed, I do not think we ever asked for them) but the manufacturers assured us that they were screening donors and testing their blood with the tests that were available at the time. They were recruiting for plasmapheresis and donors could make donations as often as twice a week. To the best of my recollection, we did not do any dip sampling of donors; we relied on the manufacturers to follow the processes that they had set out in their applications that they were obliged to follow under the conditions of their licences. We were a licensing advisory body rather than an inspection body and had no statutory power to conduct inspections.

2.52. Although I cannot recall whether visits took place in general, I had a distant recollection that I once visited a plasmapheresis centre. I have since been shown a copy of a report that I drafted for the CSM for its meetings in December 1972 and January 1973 **[DHSC0105593_006]**. This document is a summary and report about an application for a product licence made by Travenol for a product called Hemofil. The final page of this report is a 'Summary of Inspection Report' that I have written about the Hyland Laboratories, Costa Mesa, California which I recorded as having inspected on 24 October 1972. It appears that I conducted this inspection. In this report, I wrote:

> *The donors were all men, mostly middle-aged, and predominantly of Mexican origin. They were euphemistically described to me as 'people who need $5' […] from what I saw, they were certainly not affluent, although they could not fairly be described as down-and-out alcoholics. Neither did they seem to be youthful hippies, for the most part. […] medical screening of the donors was rudimentary: a microhaematocrit determination of ear lobe capillary blood, blood pressure and temperature, and that was about all. Probably the most important screening carried out was routine testing for hepatitis-associated antigen, using Hyland's own counterelectrophoresis kit. The testing is carried out on all blood that is collected, on every visit, and before the plasma leaves the blood bank. Several aspects of the whole operation do not meet T.S. Regulations. For example, the transfusion needle is not inserted by a doctor, the donors are not screened for syphilis, more than 420ml blood is removed at once session, and haematocrit and not haemoglobin*

> *determination is made. However, it is hoped that the sub-committee will advise the licensing authority on the relevance of some of these requirements in the present context.*
>
> *[…] The fractionation process is carried out under excellent conditions in a modern, well-equipped plant. The personnel seem highly competent and informed. My only criticism was that the aseptic filling area was small and overcrowded, and they placed too much reliance on laminar flow cabinets. However, a new filling area was due to be built within a matter of weeks.*
>
> *Standardization of the Factor VIII concentrate is carried out using a house standard, and not the International Standard. They promised to mend their ways, but I am doubtful if they will, unless required to do so.*
>
> *In conclusion, obviously the main problem with this product is the hepatitis hazard. The donors do not inspire confidence, and Factor VIII concentrate is prepared from very large plasma pools. Despite the HAA testing, the risk of hepatitis must still be considered to be present. However, the firm make no attempt to disguise this potential hazard.*

2.53. It is clear from this summary that I had some concerns about Hyland's factory and donors which I conveyed to the CSM.

FDA Standards v International Standards

2.54. I have been shown an application from 1974 by Abbott Laboratories for a product licence for '*antihaemophilic factor (human)*' **[MHRA0000091_012]**. Although I have no direct recollection of this, I can see from reading the documents that in the application, it had not been clear to me whether Abbott had used the FDA standard or the WHO standard (known as the International Standard) when carrying out the assay. I therefore flagged this concern under Medical Comment. This touches on a general issue I mentioned above of American manufacturers preferring to use the FDA Standard rather than the International Standard (which I also mentioned in the report quoted at paragraph 2.52 above).

2.55. As a result of this comment, the CSM granted the licence but specified the condition that 'potency and dosage are expressed in units with reference to the International Standard' **[MHRA000091_012, page** 16**].** This is recorded

in Dr Mary Duncan's letter to Dr J.V.R Marriott dated 10 December 1974. You can see from a follow up letter from Dr Marriott to Dr Duncan dated 14 January 1975 that they had discussed this issue over the telephone in December 1974 **[MHRA000091_012, page 1].** Despite Dr Marriott's assertion that the two units were the same, there could have been a difference (although it may have been slight). While Dr Marriott states that he would be proposing that the International Standard be mentioned on their labels, this was in fact a clear condition of the licence so he did not have discretion to make that decision.

Donors

2.56. I have been shown a document showing the CSM's proposal in January 1976 to grant a licence in respect of Bayer's Koate product on the condition (amongst others) that satisfactory information be provided on the 'number of donations in each pool' **[MHRA0009305]**. This recommendation was made while I worked at Kings College Hospital so I was not in post either at the CSM(B) or NIBSC and was not involved. From looking at it, it appears that the CSM(B) wanted to know how many donors had contributed to each pool.

2.57. We knew the American manufacturers used paid donors and so I can only assume that the CSM must have accepted this. No one ever concealed the fact: it was known all along. I have been shown a copy of a memorandum dated 23 February 1976 from J. Kris Piper at Cutter Laboratories to someone called Lowell Crow (I do not recall who this was) advising that they do not collect information on the rate of rejection of donors and explaining that this was because such information would 'be of dubious value in evaluating a plasma derivative product's safety or efficacy' and because all donors had to be 'acceptable according to the criteria described in [the US Code of Federal Regulations] [BAYP0000020_014]'. Beyond this, I cannot comment on the extent to which it was considered relevant whether the identity, nature and appropriateness of the blood donors could be scrutinised by the CSM when considering product licence applications. This was not something with which I was involved.

2.58. It is worth adding that clinicians and haemophilia centre directors all knew that there was a risk of hepatitis from blood products. The ones I knew had told their patients there was a risk of getting hepatitis. Because Factor VIII was so life-changing, my understanding was that their patients were prepared to accept the risk.

Section 3: Specific Matters relevant to the functioning of the Licensing Process

Batch Release Procedure

3.1. Batch release procedure was where, once a product had been licensed, manufacturers had to send NIBSC samples of each batch of the product which we would then test to ensure that its composition matched that of the manufacturers' specification. We would then check the protocols and specification and confirm that all licensing conditions had been met (for example, that the product was correctly labelled). We would test the potency of each batch. We would do this by taking a sample and measuring it against the international standard using established international procedures. Undertaking a Factor VIII analysis in the laboratory is a technical process and Trevor Barrowcliffe was the individual at NIBSC who worked 'at the bench' and undertook the actual testing. In the case of blood products, when the tests were available, we started testing the samples for non-A non-B hepatitis (hepatitis C) and HTLV-III (HIV).

3.2. Until we were satisfied by the potency, specification and that the licensing conditions had been met, the batch of the product would not be released to the market. You can see an example of a NIBSC 'Examination of Samples' from 30 May 1978 which relates to a product called Proplex **[MHRA0033317_014]**. As these forms show, at NIBSC we would carry out tests relating to identity, and potency. We would examine the protocols for completeness, compliance with the specification and licence and trends or comparison. If the findings were not satisfactory, we would recommend that the batch not be released for sale.

3.3. I have been shown a document entitled 'Additional Notes for Guidance: Biological Medicinal Products' from 1976 **[MHRA0033773]**. This sets out the outline of the process and part 3 of this document states that the licensing authority's power to require protocols and samples came from the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1976. This also allowed batches to be withheld until a certificate of authorisation had been issued by the licensing authority.

3.4. I have been shown a document described in a handwritten annotation as being a 'Handling Brief' and dated 31 January 1991 which also describes the batch release process: **[DHSC0004324_017]**. This sets out various different types of batch release procedure including:

A. *The company supplies samples of the product and batch documents to the Institute. In addition, the company cannot sell the product until approval has been given.*
B. *The company supplies batch documents to the Institute. In addition, the company cannot sell the product until approval has been given.* [...]

Although I have little recollection of these different procedures now, this appears correct.

3.5. Somewhat confusingly, I think that the term 'stop order' related to the batch release procedure where a manufacturer was directed that a batch must not be sold or supplied or offered for sale or supply until it had been issued a certificate by the Licensing Authority (see for example **[DHSC0002229_006]** or **[MHRA0036365_018]**). This would be procedure A or B in the list at paragraph 3.4 above. I have little to no recollection of the term 'stop order' being used generally.

3.6. Batch release procedure might be applied to a product for a limited period but as I recall, for blood products, it was applied indefinitely for safety reasons; I explained these reasons in more detail in my letter sent to Mr Cox at DHSS on 19 April 1988 **[MHRA0000093_007]**.

3.7. When a licence was granted, the product would be issued only if the manufacturer agreed to participate in the batch release procedure. It was, or

became, a routine condition for all product licences to have to apply the batch release procedure as a condition but may have originally been a less formal process. I have seen for example the Cutter memorandum that I have referred to in paragraph 2.57 above **[BAYP0000020_014],** from 1976, which seems to suggest that Cutter was asked to agree to the imposition of the batch release procedure and declined.[3] Similarly, a letter from Travenol shows that they were asked to apply the batch release procedure before the L icensing A uthority would agree to the licence. Nonetheless, it does appear to have been included as a formal condition of a licence from as early as 1976 (you can see it featuring on **[ARMO0000004],** which related to a licence application for Factorate, and **[BAYP0000001_110]** issuing a licence to Bayer for Koate, also in 1976). Manufacturers would first be asked to comply and this would then be recorded on the licence and, if they refused to comply, the licence might not be granted.

3.8. As far as I am aware, it was not the case that certain scenarios gave rise to batch release; I think it was used for all biological products. Adverse Reaction Reporting was entirely separate from batch release and I have covered it from paragraph 3.17 below.

3.9. I believe that despite batch release procedures being in operation, companies might provide vials from batches that were in the process of undergoing batch release testing to be prescribed on a named patient basis. By way of example, I have seen a letter dated 8 June 1979 to which I was copied where Armour provided 200 vials of Dried Human Antihaemophilic Fraction (Sterile) BP to Dr Rizza at the Oxford Haemophilia Centre before it had been released by the DHSS but 'they have agreed that the material can be forwarded to you because it is urgently required to meet a patient need' **[MHRA0000084_018].** It seems to me that this batch was undergoing batch release but while the outcome was awaited, Armour provided it to Dr Rizza to prescribe on a named patient basis. They undertook to inform him of the outcome. This goes to show

[3] I have also seen that D.R. Bangham from the MRC wrote to an SMO at DHSC saying that without batch release, he would not agree to licensing Koate **[MHRA0009293]** so it looks like this was not the end of the story.

how high the demand for these products was at the time and the efforts to meet that need.

Information required for batch release

3.10. At NIBSC, we would require the full protocols of the tests which had been applied to each batch of product and details of the potency. The protocols gave the full details of the assay and test conditions, the methods which had been employed and the results obtained (see **[MHRA0000091_012, page** 14]).

Issues with potency or the protocol

3.11. Once the Licensing Authority had granted the licence, NIBSC confirmed that the potency was correct and that the protocols were acceptable; if the product met the specification, the batch would be released onto the market. If it did not, we would sometimes go back to the manufacturer to resolve the issue, for example by relabelling the batch. Alternatively, we would refuse to issue the Batch Release Certificate and the batch would not be released.

3.12. As I recall, it was unusual that we would find something wrong with the potency; manufacturers would be careful to ensure that the potency was correct.

Named Patient Prescriptions

3.13. I do not think that the batch release procedure applied to blood products which were to be used on a 'named patient' basis. The named patient process was where a doctor prescribed a product to a specific, named, patient and that product did not need to be licensed. Doctors were able to prescribe drugs that had not gone through the CSM. It gave doctors clinical freedom by allowing them to circumvent the regulatory and licensing process and assume the responsibility themselves.

3.14. An unlicensed product might treat a rare condition which would mean it was not cost-effective for the manufacturer to make the huge investment of going through the licensing process. I understand that the same system operates in the United States.

3.15. Occasionally, and usually as a matter of courtesy, manufacturers might send samples of unlicensed products to NIBSC for batch testing or write and tell us that they were importing or dispatching a product for prescription on a named patient basis. This was unusual and I do not think that NIBSC actually had any power to say 'no'.

3.16. In 1986, NIBSC started testing samples of unlicensed blood products produced by BPL. Before this time BPL had claimed 'Crown privilege' for their products, and did not send samples to NIBSC. I have seen a minute from Dr Alison Smithies to Dr Harris dated 1 August 1986 saying, 'I have confirmed with Dr Schild and Dr Thomas that they are willing to take on the testing of BPL's batches of coagulation factors for anti HIV. However they would wish to make it clear to DHSS that they cannot provide a guarantee for a product which is not licensed.' **[DHSC0003962_117]**. This suggests to me that we were agreeing to test unlicensed BPL products for HIV antibodies to assist DHSS and BPL. This view is confirmed by a letter written by Dr Schild to Dr Snape at BPL on 20 August 1986 in which he discussed this arrangement and said, 'we are most anxious to help the Department in our role as a national control authority' **[DHSC0001054]**. In September 1986, Dr Harris, DCMO at the DHSS directed BPL to submit samples and protocols for all batches of blood products manufactured at Elstree for us to examine 'with immediate effect' **[DHSC0001069]**.

Adverse Reaction Reporting and Yellow Card Reports

3.17. Adverse Reaction Reporting was a different process to the batch release procedure. When a clinician became aware of an adverse reaction, they would complete a yellow card or some other form of report and this would go to the CSM for consideration (in the early days, I think they would more often simply write a letter). Yellow Cards were a formal way of submitting an adverse reaction report: they were yellow forms that were available to clinicians and others.

3.18. When I was on the Secretariat, we would have routinely seen the yellow card reports and any other adverse reaction reporting relating to blood products. One

such example of how this would come to us is a letter dated 23 August 1974 sent to me by Norman Berry, the British Director of Serological Products (Immuno) **[MHRA0033322_006].** I cannot say whether I would have seen this letter. The letter recorded that Dr Crowley from the Liverpool Royal Infirmary had a patient who had been given a particular batch of a Factor VIII product called Kryobulin in 1974 and who had contracted hepatitis later that year. We would have made a note of this and probably told the CSM(B) that a patient on Kryobulin had seroconverted. I do not think this would have given enough evidence to recall the product. It was not clear that the seroconversion was caused by the Kryobulin given the short incubation period. If we had received any more letters, yellow cards or other reports about Kryobulin, the Licensing Authority would have stepped in and recalled the product but of course, I am saying this with the benefit of hindsight. Such questions would have been complicated at the time by whether there was enough of other Factor VIII products to treat patients, some of whom would have needed them to prevent life-threatening or severely debilitating complications. What it does show is that the pharmaceutical industry were taking their responsibilities seriously in reporting the possibility of an adverse reaction.

3.19. When I worked at NIBSC, we were not directly informed of adverse reaction reporting but would usually have been notified if it was a blood product. One example of how we might have been notified is following a suspected adverse reaction when the Medicines Division would write to a manufacturer and request that they sent NIBSC samples along with the full protocols with an instruction that none of the batch be sold or offered for sale until a certificate authorising the sale had been issued by the licensing authority. You can see one such example of this at [**ARMO0000035**] where Armour was told specifically to send the batches to me at NIBSC after a suspected adverse reaction report.

Section 4: Working relationships with manufacturers

4.1. While I was on the Secretariat, we had a professional working relationship with the manufacturers. We got to know the individuals who represented the firms as they came to see us and sometimes we visited them. We were the point of contact for the regulatory side of the necessary process for them marketing their product. The main CSM itself met once a month and there was nobody on the CSM to whom they could ask general questions about the process (each member of the CSM was an expert in their own field) so the Secretariat would advise them. I continued to help with this work even after I moved to work at NIBSC because after I left, there was no one with the same knowledge of the blood field (this is why John Holgate made the comment referred to at paragraph 1.15 above). NIBSC, the Secretariat and the CSM(B) also had a very close working relationship and we all worked together.

4.2. I have seen an internal Travenol memorandum dated 22 September 1986 **[SHPL0000409_132].** This refers to a meeting that I appear to have had with three Travenol employees to discuss the registration of a product called Method M. I remember Martin Lee who sent the memo was based in California. The memo seems to record a discussion and route forward in order for them to get an abridged new licence.

4.3. These meetings were not unusual but, because the companies did not change their products that often, such meetings were infrequent. If they wanted to change a product, they would often get in touch with the Secretariat and I would give them a steer on what to do. There was nothing untoward or covert about this – manufacturers were encouraged to iron out issues before making applications and it was in everyone's interests that manufacturers provided the CSM with the information they needed to make an informed decision on licensing; I was assisting with that process.

Meeting on the Infectious Hazards of Blood Products: February 1984

4.4. I returned from the United States in late 1983. As I described in paragraph 1.17 above, while working there I had seen the impact of the early identification of

AIDS. While I did not work on AIDS myself, I could see that it was significant. However, I wanted to ensure that we were considering the evidence for viral infections for blood products in the UK. The Penrose Inquiry's Final Report says 'although the trends were beginning to be well established in the USA, it remained the position that, at the end of 1983 and into 1984, AIDS was still not seen by clinicians and officials in this country as presenting a major threat to haemophilia patients in the UK' (paragraph 9.142). That certainly seemed to me to be the case and I wanted to ensure that we were having the conversation about infection and blood products in the UK.

4.5. As I explained in the introduction to the meeting (see the draft minutes at **[PRSE0003071, page 1]** and what appears to be my speaking note **[MHRA0000076_022]**.), while Factor VIII's therapeutic benefits were significant, infection with hepatitis had long been a known side-effect. Now infection with AIDS and non-A non-B hepatitis (later called hepatitis C) were becoming recognised side-effects too.[4] New information indicated that 21 haemophiliac patients in the United States and 11 in Europe, two in the UK, had contracted AIDS, presumably through transfusions of Factor VIII concentrates. It is important to recognise that at this point, we did not have full understanding of how terrible the AIDS virus was, nor of the damage that hepatitis C did to the liver. Nonetheless, I felt this was very worrying and was something that we needed to be aware of in the UK. When I returned from the States, I said that we needed to talk about the issue and so I was responsible for calling the meeting that took place in February 1984.

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[4] I note that the Penrose Inquiry Report commented:

> *15.133 At the meeting of the UK Blood Transfusion Services' Working Party on Transfusion Associated Hepatitis on 27 September 1983, there was discussion of 'apparent non-A non-B hepatitis-like illnesses' in patients receiving high doses of intravenous human normal immune globulin. Incidence of infection was higher than in intramuscular infusion, the other standard route of delivery. The signs noted were early transaminitis. Dr Thomas thought that the picture was similar to that seen of commercial Factor VIII concentrates from the USA.*

(It cited the Notes of the Minutes of the UK Working Party on Transfusion Associated Hepatitis Held at Edgware on Tuesday 27 September 1983 **[PRSE0002278]** at 3444–45.)

4.6. Sir Joseph Smith chaired the meeting. I think that this was probably the first time in the UK that there was a meeting of the relevant people to discuss the problem. It brought together all the relevant parties working in the field. The agenda contained a list of participants **[I MHRA0000076_018, page 2]**: including virologists such as Dr Tedder, he was an expert virologist those working for SNBTS, and individuals from NIBSC, PHLS, BPL; Haemophilia Centre Directors such as Professor Bloom; manufacturers (Cutter, Immuno, Travenol, Alpha Therapeutics and Armour) and Dr John Petriccianni from the Office of Biologics at the FDA. While we often worked together across these organisations and areas of expertise, it was unusual to have a meeting this large and with such an international attendance. There were a range of presentations and contributions from specialists attending. The manufacturers were alive to the problem, they understood its importance and seemed to be doing their utmost to deal with it; they wanted to make sure that they were selling safe blood products.

4.7. As is recorded in the note of the meeting and the introduction I gave, my aim in calling the meeting was to discuss three questions:

1) Can AIDS be caused by transmission of an infectious agent in blood or blood products? (The question I posed as recorded in my speaking note was: 'What is the evidence that AIDS resulting from the transfusion of fresh blood, blood components, or blood products, is due to an infectious agent?')

2) Can virus inactivation methods, such as heat treatment, reduce the risk of transmission of hepatitis and/or AIDS? (The question I posed as recorded in my note was: 'What is the evidence that heat or other treatment of therapeutic concentrates reduces the risks of transmitting hepatitis or AIDS?')

3) Are the steps currently being taken by transfusion centres and manufacturers of blood products adequate to minimise the risks? (The question I posed as recorded in my note was: 'Are the steps currently being taken to exclude as donors those individuals at high risk for developing AIDS adequate in the light of current knowledge? Do the manufacturers carry out any screening in addition to that recommended by the FDA?')

I did not know the answers to these questions, nor did I think that the meeting was able to answer them conclusively but I thought it was crucial that those working in this field turned their minds to these issues.

4.8. At the meeting there were presentations from attendees touching on many issues including: recent and current clinical studies; issues relating to pool sizes; the aetiology of AIDS; the impact of immunological suppression in blood transfusion-related cases; FDA strategies for identifying and excluding high-risk donors; long-term research into AIDS and transfusion in the US; in vitro testing; collection procedures at plasmapheresis centres; problems with paid donors; data about haemophilia transmission; fractionation and processes to minimise infectious hazards; variety and characteristics of viruses in plasma and laboratory testing for infectious hazards. There followed discussion on 'four main issues' (though there appear to be six recorded):

4.8.1. What should be done about blood products made from plasma pools when one of the donors to that pool subsequently develops AIDS?

4.8.2. Only the test for hepatitis B core antibody was thought to be of value as far as laboratory testing for AIDS was concerned but there was no general agreement that such testing should be part of the routine screening of all donors.

4.8.3. Optimal size of plasma pools with no agreement that reduction of pool size would be practicable or a successful way to reduce AIDS or hepatitis transmission.

4.8.4. The MSD hepatitis vaccine was regarded as safe following three separate virus inactivation steps.

4.8.5. Safety of specific immunoglobulins.

4.8.6. The need for continued research in particular looking at the capacity of the various fractionation steps to inactivate viruses and the effects on the properties of various blood products of these and other procedures to inactivate viruses.

4.9. The results of this meeting was that the MRC set up a committee to consider the whole issue of AIDS and blood products which was chaired by Geoffrey

Schild of NIBSC. I had started the ball rolling and the matter was taken out of my hands and passed to the virologists who were better placed than me to address it.

Product recall or withdrawal

4.10. I have been asked about 'Stop orders/product recall or withdrawal'. As I have said above, I think that the term 'stop orders' just referred to batch release.

4.11. As to product recall or withdrawal, this would be an order telling manufacturers to stop selling a product or to recall a particular product. With one exception, I do not recall such an order ever being issued for a blood product during my time although I am not sure that I would necessarily have been aware of it had this occurred. NIBSC had no powers to recall or withdraw products; if we had had any concerns, we would have raised them with the CSM. I have a memory of a product of Armour's being withdrawn or recalled when they did not heat a product sufficiently and that is what led to them selling the product to the Canadians leading to the litigation I mentioned at paragraph 1.12 above. There was a meeting in the UK at which it was decided that their way of heat-treating the product was not acceptable but I do not remember any further details.

4.12. If a haemophilia centre director had a patient who seroconverted, they would tell the Secretariat and the CSM about it and in due course, NIBSC would probably have been informed, but I cannot say more than that about how safety concerns were raised or reported to NIBSC. I have seen that I was copied into a press statement issued by BPL on 20 June 1991 which reported a batch of Factor VIII product had been recalled pending investigations after two haemophiliacs had been treated with it leading to 'two serious adverse events' **[DHSC0042680]**. I left NIBSC around this time (around September 1991) so I may not have seen this press release; I do not recall what happened, whether I knew about it at the time, nor do I remember the outcome.

Special Reporting Requirements

4.13. I have been shown the 1985 internal Immuno correspondence referring to 'special reporting requirements' **[SHPL0000221_001]** but this is not

something of which I have any recollection. Feiba was a novel product and it was not a Factor VIII product so it seems that there were some particular requirements placed on it. This was long after I had left the Secretariat so there may have been new processes in place. It may be that a witness giving evidence about the CSM can provide assistance.

Research and Development

4.14. I have been shown the minutes of the nin th meeting of the Central Blood Laboratories Authority ('CBLA') from 23 November 1983 **[DHSC0001670].** These minutes record at item 91.3:

> *Dr Thomas expressed concern that the Authority's budget did not adequately cover Research and Development at the current time and he stressed the importance of devoting adequate resource to this activity.*

4.15. This was the first meeting I attended after I returned from working in the United States. Before I left, or perhaps after my return, I must have realised that the CBLA was not doing much research and development. I cannot now say what impact the limited budget had, save for the obvious observation that with limited funding, there would have been limited research. This was a general concern I had and so I raised it at this meeting but I do not know what came of it.

Section 5: Knowledge of and Response to risk of infection associated with blood products

Hepatitis

5.1. There was a test for hepatitis B from before I started working on the Secretariat. From the start, people were tested for hepatitis B when they were donating blood and it was accepted that this was a necessary part of the process.

5.2. Hepatitis C came much later and at first it was considered to be a mild illness like hepatitis A. It was not until later that the serious liver damage it caused became apparent.

5.3. In the introduction to the Meeting on the Infectious Hazards of Blood Products on 9 February 1974 (which I described in detail from paragraph 4.4 above), I said that it was 'now well-recognised that, while the screening of donors for hepatitis B is relatively effective, the risk of a haemophiliac contracting non-A, non-B hepatitis is virtually 100% on first exposure to Factor VIII concentrate, from whatever source the product is obtained' **[MHRA0000076_022 .]**. That reflected my knowledge of hepatitis contamination of blood products in relation to Factor VIII at that point in time and shows that screening for non-A non-B hepatitis did not take place until later.

5.4. I remember visiting Paris, I think in the late 1980s but I have not been able to verify the date. While I was there, I saw that they were testing for the hepatitis C antigen and I remember telling Dr Gunson about it. I felt that we were slow at getting testing underway but implementing testing was not my responsibility.

5.5. I have been asked about screening for hepatitis at NIBSC. First of all, there would not have been screening of donors at NIBSC: it would have taken place at the blood transfusion centres. I have no knowledge of the history and development of screening: this was a matter for the virologists such as Howard Thomas.[5] Secondly, when I was at NIBSC, there was no way to test the final product for viruses; I do not know when this became possible. While I was there the virologists were starting to test plasma pools but again my recollection is hazy and I was not directly involved. We did not test donors,

Meeting about the standards of processing blood and blood products: 1977

5.6. I have been shown a brief note of a meeting I attended that took place on 6 October 1977. This meeting was to discuss the standards of processing of blood and blood products and the manufacture of sterile fluids in the Regional Blood Transfusion Service **[CBLA0004181]**. This meeting was discussing good manufacturing practice and people would be expected to follow it. It

[5] I was asked about the Advisory Group on Testing for the Presence of Hepatitis B Surface Antigen and its Antibody and have been referred to **PRSE0000862**. This mentions Howard Thomas and again, I had no involvement with this Group and cannot comment on its work or the development of the HBsAg test.

seems that regional blood transfusion centres did not have large aseptic facilities to pool plasma so they were understandably reluctant to pool individual donations and instead wanted individual units to be sent to BPL for pooling. The meeting was not about anything specific to infected blood as far as I can remember or tell from the note. I do not remember anything about the discussion, the reasons for the course of action chosen or what action was taken to implement the decision. Implementation would have been a matter for the Medicines Inspectorate (and if my memory serves me, the note-taker J Flint was a pharmacist from the Medicines Inspectorate).

US protocol for hepatitis study: 1983

5.7. As mentioned at paragraph 1.18 above, I have been shown a letter dated 13 January 1983 from the FDA to John Cash at SBTS **[MACK0001314]**. This letter sets out an example protocol that a FDA hepatitis group recommended for a study using chimpanzees. It seems that the focus was on developing ways to kill viruses in products which duly led to the process of heat treating blood products. This protocol and study differed from work done in the UK because, for a start, we never did any chimpanzee studies (though for completeness, as described in paragraph 2.49 above, I believe that we had previously used monkeys for polio studies). I cannot judge whether this protocol was reliable or effective – this would be the work of a virologist.

Blood Products Panel: 1977-1978

5.8. I have been shown a hand-written note that appears to have been from November 1977 or perhaps early 1978 **[MHRA0014314_020].** This states:

> *5. …Dr Thomas feels that most haemophiliacs are v. well aware of the hepatitis risk – and a lot of them have had hepatitis. Therefore he does not agree with the argument (feels older generation would be more inclined to keep patients in the dark whereas younger practitioners would hold the view that patient should be made fully aware of risk). He also said that (subject to confirmation) all [samples] from USA have warning on label – FDA requirement – if we hear nothing leave in for Factor VIII…*

5.9. I am unable to recall what 'leaving in for Factor VIII' meant). The context of this remark was that at around this time, I was friends with several haemophilia centre directors: Drs Arthur Bloom; Roger Hardisty (Great Ormond Street Hospital); Illsley Ingram (St Thomas's) and Frank Hill (Birmingham). We had discussions and their view – as I recall it and as I appear to have stated here – was that patients should be made aware of the risk. I understood (second-hand) that patients were prepared to take the risk because the effects of Factor VIII were so life-changing and at this point, the full horror of AIDS and hepatitis C had not emerged. Factor VIII concentrate had transformed their lives. The life expectancy for a haemophilia sufferer in 1962 was just 37 years old but by 1984, it was almost normal **[PRSE0003071, page** 1]. It was considered worth the risk but of course, nobody knew how bad the risk actually was at this time. I did not personally know any directors who thought that it best not to tell their patients but somebody must have told me that there were those of the older generation who did not agree. I understood that they felt it was better not to worry the patients.

5.10. I was not present during these consultations and have no personal experience; I was only going on what I had been told. In the introduction to the meeting on the Infectious Hazards of Blood Products on 9 February 1984 (as described from paragraph 4.4 above), according to my note, I quoted Dr Peter Jones in a BMJ editorial who said 'People with haemophilia, their families, and their doctors feel threatened by the deluge of speculation about the possible side effects of treatment with blood products. Two topics hold their attention: the risk of contracting the acquired immunodeficiency syndrome (AIDS) and the risk of developing hepatitis and subsequent chronic liver disease' **[MHRA0000076_022].** That accorded with my understanding at the time: that haemophiliacs and their families were being told the risks. I am acutely conscious that the Infected and Affected may have very different views on this and they, of course, can offer first-hand evidence that I cannot.

AIDS

5.11. In the introduction to the Meeting on the Infectious Hazards of Blood Products on 9 February 1974 (again as described from paragraph 4.4 above), I said that

'[i]n the past two years or so, a new hazard has arisen in relation to the infectious hazards of blood and blood products' **[I MHRA0000076_022];** I was referring to AIDS. I described how there were 20 cases of AIDS in haemophiliacs reported in the States, eleven cases in Europe and two in the UK (one of which I said may have resulted from a blood transfusion). I cited a recent CDC report that stated that 31 out of 3000 AIDS cases had received a blood transfusion within the preceding five years. I explained, 'I mention these recent findings because I believe we need to consider the evidence that AIDS may develop as a result of blood transfusion, as well as following the administration of blood products.'

Matters arising while I was in the US: 1982-1983

5.12. I was working in the US in 1983. I have been asked about some documents from this period which I discuss below but generally speaking, I would not have been party to any correspondence or discussions during this period.

5.13. On 23 March 1983, the FDA issued new guidelines as a result of the emerging AIDS crisis **[HCDO0000392_089]**. An extract of a press release I have been shown from this time summarises the guidelines as follows:

> *The new FDA guidelines say plasma centres and blood banks should:*
> - *set up educational programs to inform persons with increased risk of AIDS that they should refrain from donating plasma or blood;*
> - *instruct plasma centre and blood bank personnel in how to use medical history questions to uncover the early symptoms of AIDS – such as night sweats, unexplained fever and sudden, unexplained weight loss – or exposure to AIDS;*
> - *and establish procedures for the handling and disposition of plasma and blood collected from known or suspected AIDS patients.*

5.14. I have been shown some correspondence which refers to plasma collected before the new guidelines were introduced: **[DHSC0001394], [DHSC0002229_006]** and **[DHSC0002229_019].** The documents discuss concerns about American companies 'dumping' product manufactured before the changes on the UK market which might not be recorded on the product labels. In a minute from Dr Diana Walford dated 16 May 1983 to an unidentified

recipient (and which I would not have seen) (**[DHSC0001394]**), Dr Walford wrote:

> *Products manufactured from plasma taken before the new regulations were introduced have to be labelled to indicate this. However, the UK product licenses [sic] do not contain this requirement and there are fears among haemophilia centre directors that the more 'dangerous' material may be dumped in the UK.*

5.15. Dr L.K. Fowler (DHSS) seems to have responded to this minute (**[DHSC0002229_006]**) saying that manufacturers could identify those batches of plasma collected after the new guidelines were issued and could therefore identify the concentrate made from it, but notes, '[w]hether or not they would be prepared to release this information is another matter'. Dr Fowler continued:

> *All FVIII concentrates are subject to full 'Stop Orders', which require the manufacturers to submit protocols and samples from every batch they propose to sell in the UK, to Dr Duncan Thomas's department at NIBSC. The content of an individual manufacturer's protocol is very much a matter for agreement between Dr Thomas and the company. I do not think that date of plasma collection is a requirement at present, but I see no reason why it should not become so if it were thought desirable. The Licensing Authority would then, on the advice of Dr Thomas, be able to reject those batches which did not comply.*

5.16. Although this letter mentioned me and my department, as I have said, at this time I was working in the States. I have no recollection of speaking to either Dr Fowler or Dr Walford about this letter or its contents. To be clear, the basic protocol requirements were established by CSM and Medicines Inspectorate, not by NIBSC. I would advise the manufacturers on the protocol requirements and then the applications would be approved by the CSM(B). I might, for example, point out that their protocol was inadequate in some way or that they failed to meet the requirements and they would make the requisite changes to their applications. In my experience, the manufacturers went to great lengths to describe their processes in their licence applications. I would not have initiated any requirement to do something else – anything of this nature would have gone to the CSM.

5.17. I have no recollection of asking manufacturers to label a product with its manufacture date but this might have been imposed on them while I was

abroad. My impression is that the manufacturers followed the FDA's rules and so they would apply these new guidelines across the board. It is worth adding too that Factor VIII was a popular product that was in high demand. There would not have been a large (or even any) backstock of Factor VIII which means that by the time I returned from the States, this issue was probably a moot point.

5.18. I have no knowledge whether any 'dumping' actually happened, nor do I remember there being any discussion of concern of this happening after I returned to NIBSC. I suspect that the manufacturers did not try to do it because they knew they would not get away with it as we were the only country outside the USA, testing for anything, to the best of my knowledge: no other country had any equivalent organisation to NIBSC. I have mentioned the Armour product which the UK rejected being sold to the Canadians but this was later and concerned a heat-treated product.

5.19. I have also been shown a 'Background Paper I: Acquired Immune Deficiency Syndrome (AIDS)' **[DHSC0002229_019]** which I am told was circulated in or around May 1983. Again, this was while I was out of the country and I would have had no knowledge of it.

5.20. I have been shown an incomplete letter from Dr Winstanley to Dr Walford dated 10 May 1983 **[DHSC0002227_035]** but I cannot comment on what conditions were implemented and when or how compliance was scrutinised as this all took place while I was away. Obviously the CSM would issue conditions when they reviewed the application and then NIBSC would check the potency and protocol to ensure that they had followed the requirements through the batch release process. My recollection is that batch release was in place by 1983.

5.21. Again, I played no part in the meetings of 3 June 1983 **[DHSC0002229_030]** and 13 July 1983 **[ARCH0001710]** or the correspondence between Sir Joseph Smith and Professor Bloom dated 27 July 1983 **[DHSC0001207]** and that of 17 May 1983 **[DHSC0001395]**. Having been away around this time, I had no involvement in these issues and cannot comment further.

Matters arising following my return to the UK: late 1983 onwards

5.22. I have been shown a copy of a paper drafted by Dr Fowler entitled 'Acquired Immune Deficiency Syndrome (AIDS): A New Hazard for Haemophiliacs?' which I am told was probably dated in late 1983 or early 1984 **[DHSC0002229_059]**. I have been asked whether the paper accurately addresses the steps which might have been taken at that time to reduce the transmission of AIDS in blood products. This is impossible for me to answer now because I cannot now recall my exact state of knowledge, or that of the medical community at the time and I am not a virologist nor a specialist or expert in AIDS.

5.23. On 23 January 1986, I attended the second[6] meeting of the NIBSC AIDS Working Party **[MHRA0000074].** The minutes of this meeting show that we were discussing the ELISA testing kits which had been used on panels of reference sera and freeze-dried reference sera, presumably to assess their reliability. I do not recall the outcome of this meeting.

5.24. I had no involvement in the Ad Hoc Working Group on the Evaluation of Anti-HTLV III Kits (I have been provided with the minutes of the 3 March 1986 meeting **[DHSC0002343_007]**). This was a technical matter which would have been considered by virologists (Dr Schild, who attended the meeting from NIBSC was a virologist) but it was not my area of expertise.

5.25. I have also been provided with the minutes of a NIBSC Liaison Group on the Virological Aspects of the Safety of Blood Products meeting on 2 May 1986 **[DHSC0002345_017].** The document does not record attendees, but I was probably present. I can see that we seem to have been insisting that all immunoglobulins should be from screened donors – a decision which makes sense – by the end of June 1986. We had been focussing on blood clotting factors. I cannot think why June 1986 was the date on which this happened – I would have assumed that by that time, all donors should have been screened.

[6] I understand that the minutes of the first meeting or any subsequent meetings have not been located.

5.26. I have no recollection of the paper 'Manufacture of Blood Products from Plasma Derived from Unscreened Donors' which I appear to have drafted in around May 1986 for the CSM(B) **[MHRA0028426]**. Nor can I recall the circumstances in which I drafted it. By 1986, the tests were all agreed and I felt that there would be a risk of mixing screened and unscreened donors and so it was much safer to have all the plasma tested. This is simply good manufacturing practice. I can only assume that I wrote this paper as advice to the CSM(B) and they subsequently endorsed it but I have no recollection.

5.27. I have seen a letter from Dr Rotblat to Dr Rizza dated 9 June 1986 **[HCDO0000271_064]**. Dr Rotblat was an SMO and worked for the Secretariat and Dr Rizza was a Haemophilia Centre director in Oxford. In the letter Dr Rotblat said:

> *...there is no date from which this requirement [that all batches of commercial factor VIII concentrate released by NIBSC have a protocol stating they were from donors tested for HIV] was made. However I have discussed this with Duncan Thomas and he feels that all companies have been complying since early this year.*

5.28. Although I have no direct recollection now of why I thought this was the date from which manufacturers had been compliant, I have been shown a draft letter which I appeared to have written (my initials appear after the word 'Draft') **[MHRA0000075_019]**[7] which states that from 1 January 1986, 'all protocols will be expected to confirm that the product has been manufactured from source plasma that, when tested, was found to be negative for anti-HTLV-III antibodies'. This suggests some sort of formal change took place on 1 January 1986.

5.29. It is difficult to say now whether this requirement could and should have been established earlier. As I recall, tests for AIDS / HTLV-III only became available during around 1985 and these were tests on donors. Of course such tests should have been adopted as soon as they were available but it took time for it to be established that the tests worked. Of course there can be no argument: it

[7] Please note that this draft is only on page 1. The selection of pages which follow were notes from a meeting at NIBSC on 7 February 1986 with suggested amendments in handwriting from Dr R. J. Perry, the Director of SNBTS.

should have happened sooner if that was possible, but that might have been unrealistic.

5.30. I have seen another letter from Dr Rotblat dated 24 October 1986 in which she wrote to inform me that three patients from Birmingham had seroconverted all of whom she said had received the same batch (Y83006C) of Armour Factorate **[MHRA0000078_002]**. She suggested carrying out further tests on this batch. I think I had already been informed of this by a letter from Rorer Health Care dated 7 October 1986 which mentioned my having had a telephone call from N. Randall saying that Factorate was being withdrawn from the UK market **[ARMO0000602].** I vaguely remember being notified of this (whether by these letters or the telephone call) and thinking that it was a red light.

5.31. Until we had tests available to test the individual blood products (as opposed to testing the donors or plasma pools), the only way to know that a virus was in a blood product was if patients seroconverted. We would only be sent a sample as part of the batch release procedure and not the totality of the batch, no more than a dozen. Although I think we would have retained the leftover portions of samples for a while thereafter, I cannot now say how much of this sample (if any) remained after the original testing, if it had been retained and whether it still existed two years later to allow us to run any tests on it. I am afraid that I cannot now recall what happened.

5.32. It may be that the Licensing Authority would have duly prevented Armour marketing that batch or later batches if they had not taken the immediate action of recalling the product. I do not know what size the batch was and given the demand for Factor VIII, it would be likely that it had all been used on patients long before this letter reached me. My memory fails me on what we did at the time. It is possible that Frank Hill who ran the haemophilia centre at the children's hospital in Birmingham would remember and might be able to assist.

5.33. I have been shown a minute from Dr Rotblat to Dr Jefferys dated 23 March 1987 (I was not copied into this minute, nor would I have been aware of it) **[DHSC0002374_044]**. The minute refers to a meeting of the Liaison Group on the Virological Aspects of the Safety of Blood Products which took place at

NIBSC on 20 March. It records that, because of concerns about HIV, Dr Schild and I had decided to put 'a small paper to biologicals [CSM(B)] in May suggesting that we could ask the commercial manufacturers to use particular kits for the testing of their donors'. This is what led to the paper I have described at paragraph 2.43 above.

Section 6: Viral Inactivation/Heat Treatment

Reducing the Risk of Virus Transmission by Blood Products (British Journal of Haematology, 1988)

6.1. In 1988, I wrote an 'Annotation' for the British Journal of Haematology entitled Reducing the Risk of Virus Transmission by Blood Products **[DHSC0001008]**. This is a helpful demonstration of the state of my knowledge relating to the risk of virus transmission by blood products at that time (1988) and in particular, my observations about heat-treatment. You can also see from this article that by the time of writing, NHS plasma pools and samples from all final blood products distributed in the UK 'are screened for HIV antibodies and HBsAg' at NIBSC (opening paragraph).

6.2. In this article, I observed that:

> *…there is as yet no generally agreed approach to removing or inactivating viruses in plasma pools used by manufacturers of clotting factor concentrates. Currently, a variety of techniques is being employed, including dry heating the final product; heating in solution or with steam; employing various solvents; and using partitioning during purification by immunoabsorption, as well as a combination of two of these techniques….Certainly, there is as yet no universally agreed method for inactivating viruses in clotting factor concentrates, although a consensus is emerging that some techniques may be safer than others.*

6.3. I went on to observe that 'wet heat', where products were heated for 10 hours at 60˚C, had an excellent safety record but 'a penalty has to be paid in terms of a lower yield'. I set out that dry heat treatment for 30 hours at 60˚C was 'inadequate as a method of inactivation of HIV, even with screened donors' and

later in the article I noted that '[c]laims concerning the relative superiority of one or other technique of viral inactivation must still be viewed with caution'. I described that dry heating at 75 or 80˚C for 72 hours by the NHS fractionation centre (BPL) was believed to provide a 'wider safety margin' with encouraging but inconclusive clinical data on the lack of transmission of HIV and non-A non-B hepatitis.

6.4. I was optimistic that 'the risk of HIV seroconversion among patients treated with heat-treated products made from screened donors is now undoubtedly very small,' but warned of ongoing problems with the more resistant hepatitis viruses and the lack of a conclusive test for non-A non-B hepatitis in blood donors. Furthermore, I observed that there was no 'universally agreed criteria for determining the adequacy or otherwise of screening test-kits for HIV 1' and there was no licensing system for diagnostic test-kits in the UK. I noted that the CSM had required each manufacturer to validate his own procedures for viral inactivation and confirm that all blood was free of anti-HIV antibodies and HBsAg. I anticipated that the UKBTS / NIBSC Liaison Group would be likely to recommend that each manufacturer should provide data demonstrating that one single stage in the manufacturing process is capable of inactivating at least 10^5 infectious particles of HIV per ml of solution and requiring documentation showing the production process overall resulted in substantially greater level of virus decrease. I said that '[o]n current knowledge, this should give an adequate safety margin with plasma derived from screened donors.'

6.5. I concluded that:

> *...there are no quick or easy answers to the problem of viral contamination, and it is only the gradual accrual of data from long-term clinical studies that will enable the present uncertainty to be replaced by general agreement... While battles are being won, the fight against contaminating viruses in blood products is far from over, and there remains an urgent need for further scientific and technical progress in this field. The goal of completely safe blood products may be unrealistic (Bove 1987), but the risk of viral transmission can surely be reduced to an absolute minimum.*

Applications for heat-treated products

6.6. The question of how applications for heat-treated products (whether blood or otherwise) were scrutinised and whether they were treated as new applications or variations is really a question for the virologists – I do not think I would have been asked for specific comment at the time. I think that they would have been scrutinised with the same care and attention as new applications but I do not now recall whether manufacturers made applications for variations or abridged applications; I have summarised my understanding at paragraph 2.22 above.

6.7. The question of how much heat was needed, the form and duration were all technical questions although I was aware that there was an inconsistency in approach across manufacturers. I describe viral inactivation further from paragraph 6.9 below but was in no position to judge the efficacy of heat-treatment methods. In fact, until tests became available, there was no way at that time of telling categorically whether heat-treatment had worked or to verify the safety of each method of heat treatment: the only way to know for certain was for the clinicians to monitor the patients, which was why adverse reporting was essential. Of course, when testing was developed, that would have been applied but that came later. We tested for potency as usual and in the late 1980s pools were being tested: I remember 5,000l of plasma being tested before being put into bottles but cannot recall when this was. I have seen from the documents that in April 1990, L.R. Whitbread, the Assistant Secretary of the CSM, wrote to manufacturers saying that the CSM had recommended manufacturers of blood products submit samples of plasma pools to NIBSC **[MHRA0034935_042]**. We progressed from testing donors to testing pools but I am unclear whether we ever tested the product for viruses, this will have been the virologist, Dr Trevor Barrowcliffe's area.

Batch testing heat-treated products

6.8. In relation to batch release testing, this would have been performed generally with respect to heat-treated products because by the time heat-treatment came along, blood products were all, or almost all, being subjected to the batch

release process. I do not think that it is likely that any batch release procedure would have been applied to any products prescribed on a named patient basis for the reasons I have given from paragraph 3.13 above onwards.

Viral inactivation

6.9. Viral-inactivation was a developing area of knowledge. The manufacturers would describe on their product licence applications how they were heat-treating the product and we at NIBSC would see that when it came to us from the CSM. We would report back to the CSM(B) and might have discussions with the manufacturers where appropriate. We were not at that stage, however, in any position to decide which processes were more effective, whether 60 degrees for 2 hours or 80 degrees for 8 hours was better for example. Manufacturers would use viral markers (so they would infect the product with a known and test-able virus, then heat-treat it and test again for the presence of the virus). This was the only way to give some indication that heat-treatment was inactivating viruses but of course it was not foolproof because not all viruses behave the same way. Other than this, there was no way for us to judge the efficacy of heat-treatment in the laboratory; the only way was to look at what happened subsequently. This is all as described in my 1988 article.

6.10. Manufacturers would submit clinical studies on their applications and these would be considered by experts on the CSM and CSM(B) (as I have described at paragraph 2.24 above). The experts would comment on the applications and such studies. The CSM would assess the application and would take into account the clinical studies if they were relevant and they would critically assess the studies and/supporting evidence filed with the application. If the CSM was concerned that the information submitted was incomplete, unbalanced or otherwise lacking, they would ask questions of the manufacturers before granting any licence.

6.11. There probably was a point in time when heat-treating a blood product became a prerequisite for a licence to be granted. This was probably sometime in the mid-1980s but I cannot be sure. As I have mentioned, manufacturers would use

marker viruses: some would use two, others six. It was not consistent and was a matter for the manufacturer and then the CSM to evaluate the likely efficacy.

6.12. Factor VIII was in short supply and used very quickly. I do not recall if there was any recall process after heat-treatment became mandatory but, if not, this might explain the rationale (though I was not directly involved and am speculating). I think that on some occasions Haemophilia Centre directors were told 'do not give out more of batch X' but it is difficult to be more precise.

6.13. I was never aware of any pressure being exerted on anyone to recommend the licensing of heat-treated products. If there was any such pressure, it was not exerted on me.

Concerns about heat-treatment discrepancies

6.14. I have seen the letter I sent to Dr Duncan dated 8 January 1985 [**MHRA0019502**]. In this letter, I set out my concerns arising from three sets of data for heat-treated Factor VIII provided by Miles, Travenol and Immuno. I describe the discrepancies between their methods when it came to temperature, length and use of marker viruses. I said, 'I must confess that I find this all rather worrying, particularly as the Licensing Authority has decided to deal with the matter "in house" and not refer to the Committee for advice.'

6.15. I cannot remember exactly what prompted me to write this letter but I do remember that I was worried about the discrepancies between the processes of different manufacturers. My reference to the Licensing Authority which had 'decided to deal with the matter "in house" and not refer to the Committee for advice' is very puzzling. I do not know exactly what issue I was referring to there but whatever it was, it seems that I was concerned by it at the time. The process was normally that the Secretariat to the Licensing Authority would seek advice from the CSM(B). Dr Mary Duncan was an SMO on the CSM(B) and she would have been used to sending up advice and recommendations to the CSM. The Licensing Authority itself, as I have mentioned, was really the ministers; it was a nominal concept rather than an actual group that met as far as I know. The ministers and the Secretariat to the Licensing Authority did not have virological expertise (again, as far as I know) so I am surprised that they did not seek

advice. It seems to me that in retrospect they should have done. It was obviously a very active area of research and there was no generally accepted 'correct' way of doing things. I am not aware of how my concerns raised in this letter were responded to or taken forward.

PFC Samples

6.16. I have been shown a letter from Dr Bob Perry at PFC which he sent to me on 8 January 1985 **[PRSE0002706]**. I am afraid I cannot recall when PFC started routinely sending NIBSC samples for routine assessment and I do not remember what the batch release process was around this time. His request for live HTLV-III would have been dealt with by the virologists at NIBSC – I don't know the outcome.

CSM(B) Meeting: January 1985

6.17. I have been shown the minutes of the CSM(B) meeting held on 9 January 1985 **[DHSC0001799]**. I am recorded as having been present at this meeting although I was not a member of the CSM(B) at this time. As I said above, it was quite common for representatives from NIBSC to be invited to attend CSM(B) meetings so I expect I had been invited. I have no recollection of this meeting or the discussion but I can see from the minutes that Dr Mary Duncan informed the meeting that two manufacturers had submitted abridged applications for Factor VIII products including heat-treatment in the manufacturing process and one had submitted a variation. She observed that 'all the manufacturers were using a different temperature for the heat-treating process and varying lengths of time'. This was an issue that I was aware of as I have said but I cannot assist further on the discussion at this meeting.

Abridged application by Alpha: January 1985

6.18. I have seen a letter that I wrote to Dr Duncan on 17 January 1985 about an abridged application for a heat-treated product by Alpha Therapeutics **[MHRA0033388_026]**. This letter offers a helpful example of how NIBSC interacted with the CSM(B). You can see in the letter that I have been shown a copy of the application and I offered my assessment of the processes that were

being undertaken. Everyone was trying to reduce the viral risk within the product whilst also trying to maintain the effectiveness of the Factor VIII itself. As I said in the letter, 'the main worry about these heat-treated products is whether evidence will emerge from long-term studies of the formation of neo-antigens and, particularly, antibodies to Factor VIII'. This was the risk on one side of the equation: that Factor VIII would stop benefitting haemophiliacs. On the other side was the 'very definite hazard from unheated Factor VIII' and I felt that the risk of heat-treating was worth taking at that time. This letter was a fair summary of the sort of considerations in play at the time as to the potential advantages and risks of heat-treated blood products; there is nothing I would add.

6.19. The virus testing would have been carried out by virologists, this was not something that we could do in my department, and I do not know what was done to develop a standard assay between 1984 and 1985 (or at any time).

Variation application by Armour: January 1985

6.20. I have been shown a copy of another letter sent to me by Dr Duncan dated 17 January 1985 **[MHRA0000078_034]** in which she mentioned a variation application from Armour in which it was suggested that 'given the right conditions, 60˚ for 5 minutes is enough to inactivate the HTLV-III virus!'. I can tell that she was sceptical about this suggestion – as I would have been. She asked, 'When are you going to have that meeting at NIBSC?!' I cannot recall what this meeting was or whether it took place but I think it would have been the same meeting that I suggested in the letter of 17 January 1985 **[MHRA0033388_026]**. In that letter I had written, 'I think the idea of a scientific meeting between NIBSC and manufacturers has merit, although I cannot see it taking place before late spring…'. I believe this meeting did take place at NIBSC.

SNBTS and NIBSC

6.21. While NIBSC operated across the rest of the United Kingdom, health matters were devolved when it came to Scotland so we did not operate there. We

therefore felt it was important to help whenever we could and work closely with our Scottish colleagues at the Scottish National Blood Transfusion Service ('SNBTS'); I used to visit them in Liberton. If they asked for any help, we would try to assist.

6.22. I have been shown some extracts of the evidence that Professor Cash gave to the Penrose Inquiry on 8 September 2011 [**PRSE0006043** page 114] and that of Dr Perry from 13 September 2011 [**PRSE0006045** pages 115-116].

6.23. Professor John Cash, the Medical Director of SNBTS was a friend. He mentioned the 'informal support' that we offered which I have described above. NIBSC did not have any authority to approve license applications and SNBTS would still need to make formal applications to the CSM to licence their products but I was able to cast my eye over their proposals and identify if there were shortcomings and give them a steer. They were looking at heat-treating the entire supply of Factor VIII in Scotland which was a big step and they wanted advice and, as Dr Perry said, 'some sort of framework'. I would have explained to them what other manufacturers were doing, what I thought was sensible, how they could go about sending licence applications to the CSM, what requirements they needed to fulfil etc. I could not decide or approve anything – that was not my responsibility – but I could say whether their proposals struck me as sensible and I could offer suggestions. Professor Cash summed it up when he told the Penrose Inquiry, 'he couldn't speak officially but as a professional he had listened to the data of Bob [Dr Perry] and his team, and said in his personal view he thought it was okay'. Dr Perry is correct in saying that it was not a formal process; it was about sharing knowledge. I was not helping SNBTS to strategise in any way, merely to make effective applications which was in everyone's interests; whether they would be granted was another matter. I would have given this advice to anyone who asked; I did not have the same close relationship with commercial manufacturers as I had with SNBTS colleagues, although my door was always open.

Section 7: Distribution of unlicensed products

7.1. As I have said above, I do not think batch testing would generally have taken place on unlicensed products. As I further explained at paragraph 3.15 above, I recall that manufacturers would sometimes contact us at NIBSC about using or importing a product for use on a named patient basis but this was just a matter of courtesy; we did not have any power to stop them.

7.2. I have been shown the correspondence between Trevor Barrowcliffe from NIBSC and Armour (which was owned by Revlon) **[MHRA0000079_005, MHRA0000079_006]** in which it appears Armour were sending NIBSC batches of Factorate for testing despite the product only being supplied on a named-patient basis. This included batch Y69402 among others. I think that we were probably trying to assist and be helpful but you would need to ask Dr Barrowcliffe for the details as I have no recollection. It seems from these letters as though Factorate – or at the very least, these batches of Factorate – were being prescribed on a named patient basis but I have no more information than what is in the letters to assess this. It was not a common arrangement for a manufacturer to come to NIBSC to discuss any unlicensed product (heat-treated or otherwise) but shows goodwill on the part of Armour. We would encourage a formal product licence application to be made and I think any such work would have been short term. I imagine we would have tested the batches for potency as we did for licensed products. I am sure that Dr Barrowcliffe would have discussed this unusual testing with me and others within NIBSC but again, I have no direct recollection.

7.3. I have been shown a Revlon HealthCare Limited memorandum dated 15 July 1985 **[ARMO0000417]**. This refers to having sent batch Y69402 to NIBSC despite it having been released for sale only on a named patient basis. This is one of the batches referred to in the correspondence above. The memo refers to 578 vials available for distribution and gives their expiry date as February 1986. I do not know what, if any procedures would have been applied by NIBSC to this batch.

Section 8: Specific Companies

Armour / Factorate

8.1. I have been shown a spreadsheet relating to Armour Factorate [**MHRA0000048**]. This records the substance (Factorate), batch numbers, dates on which the protocols and samples were received, the numbers of samples and units and the date on which the substance was released. There is a column for recording 'Comments'. Next to nine batches of heat-treated Factorate, someone has written 'already released as untreated batches' [**MHRA0000048, page** 8] but I do not know what this means. Below that, another comment says 'new heat-treated batches, named patient use' and while again I do not know what was meant by this, it might mean that we had been informed that the product had already been prescribed on a named-patient basis.

8.2. I have been asked to comment on a remark apparently saying 'named patient normal release'. Although I cannot be sure, I think that in fact these were two remarks, the first simply saying 'named patient' and relating to batch X52209. This batch might not have been released for some reason which is why no release date is entered. 'Normal release' seems to apply to the batch on the row below: A26005. For the avoidance of doubt, 'named patient normal release' would not make any sense as named patient would not equate to normal release.

8.3. Contained within the product licence application for Factorate, dated January 1985, is a letter from Dr Evatt at the Centre for Infectious Diseases to Dr Fred Feldman at Armour [**ARMO0000164,** pp22-23]. The letter discusses experiments that were carried out by the CDC in the US on heat inactivation of LAV (Lymphadenopathy Associated Virus[8]). I have no recollection of this but I know that the CDC did tests on chimpanzees and it looks like they were trying to inactivate the virus which would have been of interest to the UK Licensing

[8] This was later identified as being the same, or virtually the same, as HTLV-III and the two were renamed HIV. LAV emerged first in around 1983 with HTLV-III being first described in April 1984 by Robert Gallo in the States. There was then a period of time before it was established that it was this virus which went on to cause AIDS.

Authority. The US manufacturers were the frontrunners and they would liaise closely with the Bureau of Biologics at the US National Institute of Health. I do not recall our having contact with the CDC itself, we would deal with the Bureau of Biologics.

8.4. I was not part of the Licensing Authority or its advisory committees at this time (I was at NIBSC) so cannot comment on whether these experiments or clinical trials were available to the UK Licensing Authority. Speaking from my time on the Secretariat, such clinical trials might be sent to the UK Licensing Authority by manufacturers during the licensing process or they might come to the attention of those on the CSM at conferences or in journals but there was not a way in which they were formally promulgated internationally or passed on to the Licensing Authority.

8.5. While I was on the Secretariat, we would certainly have looked at foreign studies with interest. I think it is fair to say that the CSM(B) and we would be influenced but we all tended to be a little sceptical of work done by others. I can recall at least one occasion on which we turned down an application despite some supportive evidence from the US.

8.6. I have seen Dr Alfred M. Prince's study 'Safety of Blood Derivatives Pasteurized in the Dry State' which considered viral inactivation via heat treatment [**PRSE0004828**]. Dr Prince was a famous virologist and I think the experts on the Secretariat, CSM(B) and CSM would have considered a report such as this carefully and given it a lot of weight.

8.7. Given the number of experts on the CSM(B) and the CSM, I think it is likely that any significant studies would have come to the Licensing Authority's attention. That said, there was no formal process that I recall for the manufacturers sending the UK Licensing Authority studies, such as this one, after the granting of a licence.

8.8. It is also worth observing that studies and similar publications often took many months to be peer-reviewed, edited, and published. This meant that they were not always the most efficient method of gaining up-to-date information and this why the yellow card system and adverse reporting was so important, as well as

attending conferences and the personal relationships with contacts working in the same field both nationally and internationally.

8.9. I have seen a letter from the Medical and Technical Director of Armour, Dr P.A. Harris dated 11 July 1986 and copied to NIBSC among other recipients [**MHRA0000078_008**]. The letter says that there had been a reported HIV sero-conversion relating to Factorate Heat Treated of which they had notified UK Haemophilia Centre Directors and the Department of Health in March. It said that on 23 June 1986, their American parent company had recommended the return of any non-donor tested material and they were now recommending the return of all non-donor tested Factorate. The letter requested the return of Heat Treated Factorate and said that since January 1986 all Armour material had been donor-screened. I have no recollection of the process by which Armour went from providing the 'informatory letter' to requesting the return of the material (and I think it is quite unlikely that I would have had any involvement).

8.10. I do recall that there were lots of concerns about Armour and discussions about this issue. I cannot recall exactly what happened or whether we thought, at the time, that the actions they were taking were sufficient. Clearly, as soon as there was confirmed evidence of seroconversion, Armour should have withdrawn the product and / or the Licensing Authority should have considered recalling the product and revoking the product licence.

Cutter: Humanate

8.11. I have seen the minutes of a board meeting of Cutter Laboratories Limited from 16 December 1980 [**BAYP0000021_063**]. I was not present at this meeting. The minutes record that 'NISAC [*sic*] and Doctor Duncan Thomas were very concerned regarding Humanate and the impossibility of tracing its manufacture back to its source.' I have no recollection of this at all and given this was before AIDS, I do not know or remember the exact nature of my concern. I obviously queried someone from Cutter and expressed whatever my concerns were. I am puzzled by why they were unable to trace the source as they must have known

their sources but perhaps I had asked for more information. I do not know what practical steps, if any, were taken to address my concerns.

8.12. I have seen a further spreadsheet that shows two batches of Humanate from Speywood Laboratories **[MHRA0000049].** Alongside batch number 2805 under 'Comments', someone has written 'RELEASE NOT RECOMMENDED'. It appears that batch 2805 was not recommended for release but it is not clear if this also refers to the batch listed above (4802) as well. I cannot recall why it would not have been recommended for release. Speywood was an English company but they imported and labelled some American products (this is something I have learnt since and is not something I now recall).

8.13. Once this conclusion was reached, the product would be withdrawn or steps would be taken to remedy whatever issue had led to that recommendation.

Shire-Baxter: Gammagard and Prothromplex

8.14. I have been shown a 'Briefing Note for CPMP' dated 3 May 1994 **[MHRA0014242_013]** and a letter from Dr Susan Wood to Brian Hartley dated 24 March 1994 **[MHRA0014242_019]**. I do not now recall what CPMP stands for so cannot explain anything about the background to this briefing note. These documents relate to the worldwide recall of a product called Gammagard after patients developed hepatitis C following their treatment. They record that Gammagard was not licensed in the UK due to concerns about the viral inactivation process but the manufacturer Baxter supplied 8,883 vials for use on a named patient basis.

8.15. As I have explained above, doctors have the clinical freedom to prescribe an unlicensed product on a named patient basis. There were no controls in place in relation to unlicensed products: the prescribing doctor takes the responsibility and there was no mechanism for preventing doctors from prescribing on this basis (which I believe remains the case today).

8.16. I see that in her letter, Dr Wood said, there 'would seem to be a need to review the area of named-patient usage and assess whether there is grounds now for

tightening the law in this area', but I do not know about any review nor the outcome of any such review.

8.17. I have seen an internal Immuno Memo recording a discussion on 12 February 1990 (to which, again, I was not party) [**SHPL0000177_001**]. This regards a product called Prothomplex. My recollection is that Prothomplex was an unusual product in that it was a combination of other products. I do not now know how it came to be licensed untreated in 1990 but what seems to me most likely is that it was from a different part of the fractionation process which perhaps was known not to have viruses in it.

8.18. As far as I know, the Licensing Authority said that untreated Factor VIII products should not be used once the heat-treated products were licensed.

Section 9: Reflections

9.1. From my recollection, I consider that the licensing authorities responded to the risks posed by infected blood products in a timely and appropriate manner. It is all too easy to look at these issues with the benefit of hindsight and in the knowledge of the terrible outcome where patients were infected. That was far from clear at the time. Much of what happened took place before there were available tests and before we knew the full extent and horror of AIDS and hepatitis C. Once tests were available, they were applied and the CSM responded appropriately. It is very hard to assess the timing of all of this, some forty years later.

9.2. While of course it is terrible that anyone was infected, I do not think that there were any steps that could and/or should have been taken at the time – when considered without hindsight and with the knowledge then available – to prevent or minimise the extent to which patients received blood products infected with HIV and Hepatitis C. We did our best with the knowledge that we had.

9.3. As I mentioned briefly at paragraph 5.4 above, I believe the French were testing for hepatitis C before the UK. I visited France, in the late 1980s and was informed that they were already testing for hepatitis C before we were. This

suggests we could perhaps have started testing for Hepatitis C sooner. I believe I told Dr Gunson, but I do not know to what extent he responded.

9.4. With the benefit of hindsight, clearly un-heat-treated blood products were given to patients in the UK which should not have been, either on a named patient basis or following the issue of a product licence. It is particularly upsetting that while BPL produced a safe Factor VIII (8Y), there was never enough of it. This is the real sadness. Because of this lack of availability, the Haemophilia Centres needed to find alternative foreign sources of Factor VIII product and that is what they did.

9.5. It should be acknowledged that the arrival of Factor VIII concentrate so transformed the lives of Haemophiliacs that doctors felt great pressure to prescribe them despite the known risks. With the benefit of hindsight it would have been better to wait until heat-treated products became available, the devastating long term effects of AIDS and Hepatitis C only became fully apparent with the passage of time. Fortunately, the arrival of recombinant technology for Factor VIII has now at least removed the hazard of contaminating viruses for haemophiliacs. In my opinion, while there are certainly no heroes in this sorry saga of infected blood, it is also true that there were no real villains. What happened to those patients given infected blood products was certainly a major tragedy, and remains a matter of the deepest regret. The suffering of these patients and their families was immense, and elicits my deepest sympathy.

Statement of Truth

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

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

Dated..... 17 May 2022 .....