Witness Name: Dr Trevor William Barrowcliffe
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INFECTED BLOOD INQUIRY

FIRST WRITTEN STATEMENT OF DR TREVOR WILLIAM BARROWCLIFFE

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Section 1: Introduction and opening comments

Introduction

I, Dr Trevor William Barrowcliffe, will say as follows: -

1.1. My name is Dr Trevor William Barrowcliffe and my date of birth is GRO-C 1944 and my home address is GRO-C North Yorkshire GRO-C GRO-C

1.2. I am providing this written statement in response to the Inquiry's Rule 9 request dated 13 May 2022.

Opening Comments

1.3. I would like to begin my witness statement by saying that 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 limited by the fact that most of the relevant events took place 35-40 years ago and my memory is not what it was. I have been provided with the documents that I have cited in this statement and have done my best to read and absorb them within my limited capacity.

1.4. I fully support the aims of the Inquiry and would like to contribute towards the unravelling of events that led to this awful tragedy. Having met some haemophiliacs and their families during the early stages of my career, I really sympathised with them in their suffering from this dreadful condition; indeed, it is one of the reasons I took up a career in this branch of medical science. When a university student, I was myself at the Churchill Hospital in a ward with haemophilia patients. I heard from those patients about this mysterious substance called Factor VIII, the lack of which caused their condition. I met some of the scientists carrying out research; not much was known at this time and I found it really interesting. I decided that after I had finished my degree I would try to obtain a scientific post in this area, to see if I could contribute to increase knowledge and improvement in the treatment of patients. Although nothing can compensate for the loss of loved ones, I can understand the desire of bereaved families, and others affected by these events, to seek the truth of what happened, and I will do my best to help, especially considering the awful

circumstances of the transmission of infectious viruses to patients by some of the products.

Section 2: Professional history

Qualifications

2.1. My professional qualifications are as follows: -

a. MA (Oxon), Chemistry – 1966

b. PhD (London), Medicine – 1972

c. Dip. Mus. (Middlesex) – 1983

d. MA (Durham), Music – 2014

Employment history

2.2. The following table outlines my employment history:

Table 1 – Employment History

Date	Organisation	Role
January 1967 – January 1969	Sterling-Winthrop Co.	Information Scientist. To provide background information on the Company's products to internal staff.
January 1969 – January 1972	Royal Free Hospital	Research assistant. To develop a process for manufacture of Factor IX concentrates which could be carried out in a local blood bank.
January 1972 – November 1974	Royal Free Hospital	Post-doctoral scientist. To pursue research into the purification and characterisation of coagulation factors, particularly Factor IX.
November 1974 – January 1991	National Institute for Biological Standards & control (NIBSC)	Scientist, then Senior Scientist, in the Division of Hormones & Blood Products (subsequently became the Division of Blood Products, then Division of Haematology). Roles: 1) to establish and perform tests for potency and safety of blood products and related materials; 2) to establish and

Date	Organisation	Role
		maintain International and British Standards in the field of thrombosis and haemostasis.
January 1991 – January 2006	NIBSC	Head, Division of Haematology. To oversee and administer the Division, comprising around 20-22 scientific staff.
January 2006 onwards	Retired	

Memberships

2.3. The following table outlines my relevant memberships:

Table 2 – Memberships

International Society on Thrombosis and Haemostasis ('ISTH')	Member, 1975-present; Member, ISTH Council, 1997-2003; Member ISTH Congress Organising Committee, 1997-2003; Chairman, ISTH Scientific and Standardisation Committee, 2003.
Scientific and Standardisation Committee of ISTH ('SSC')	Member, 1990-1996. Chairman, SSC Subcommittee on Control of Anticoagulation, 1994-1997. Member SSC Subcommittee on Factor VIII and Factor IX, 1979-2005. Member, SSC Subcommittee on Heparin, 1979-2005.
British Society for Haemostasis and Thrombosis ('BSHT')	Member, 1979-present; Secretary, BSHT Committee, 1991-94; President, 1996 – 1997.
British Pharmacopoeia Committee H, Biological Materials	Member, 1980-1985
British Committee for Standards in Haematology - Haemostasis and Thrombosis Task Force	Member, 1985-2003

Steering Committee for UK National External Quality Assurance Scheme ('NEQAS') in Blood Coagulation	Member,1985-2004
European Pharmacopoeia Group 6B	Consultant, 1988-2003
Biochemical Journal Editorial Review Panel	Member, 1991-1997
Thrombosis and Haemostasis Journal Editorial Review Panel	Member, 1995-2001

I have seen references which suggest that I may have attended the Haemophilia Centre Directors Working Party on Factor VIII Assay but I have no recollection of this. I have also seen that I attended the second meeting of the NIBSC AIDS Working Party on 23 January 1986 but again, I have no recollection of this. Finally, I have seen a summary of the AIDS Scientific and Technical Working Group dated 2 May 1986 (this is described as 'NIBSC Liaison Group on the Virological Aspects of the Safety of Blood Products') in a document that the Inquiry has shown me and which I discuss at paragraph 7.38 below) which, again, I attended but do not recall.

Litigation history

2.4. In May 1996, I was asked by Dr Rejman (SMO at the NHS Executive) to prepare an expert witness statement regarding recombinant Factor VIII and plasma derived Factor VIII, to be considered by the VAT Tribunal in respect of an appeal by Baxter Healthcare Limited [DHSC0003540_036]. On 14 October 1996, having received comments on a draft, I provided my final report [WITN6408002] (p.3-7). This was about a hearing to determine whether their product could be regarded as a blood product, and hence not subject to VAT. I think I gave evidence but I am not absolutely sure.

2.5. Other than this, I have not provided evidence or been involved in any other inquiry, investigation or litigation relevant to the Inquiry's Terms of Reference.

Section 3: Product licensing process in the United Kingdom

NIBSC and product licensing

3.1. The 1995-2000 NIBSC Corporate Plan gave the following helpful summary:

> *The National Institute for Biological Standards and Control ('NIBSC') is managed by the National Biological Standards Board (NBSB — The Board). NBSB operates as a Non-Departmental Public Body of the UK Department of Health and was established as a body corporate by the Biological Standards Act 1975. The Board's functions are set out in Statutory Instrument (1976) No. 917 (The NBSB [Functions] Order). The Board fulfils these functions through its management of NIBSC* [WITN6408003] (p.4).

3.2. NIBSC's mission was '*...to safeguard public health through the standardisation and control of biological substances used in medicine*' [WITN6408004] (p.1). Its role and function were to provide the scientific basis for ensuring that all biological medicinal products intended for use in the UK were of acceptable purity, potency and, where appropriate, safety (as described in the Introduction to the NIBSC Report for April 1984 to March 1985 [WITN5281006]). More of NIBSC's functions can be found in NIBSC's Corporate Plan 1995-2000 [WITN6408003] (p.5) which states:

> *Biologicals are substances used in the prevention, treatment or diagnosis of human disease that cannot be adequately defined using chemical analysis alone, and thus require biological testing for their characterisation and quality assurance. In general, biologicals are derived from cells or animal tissues and are (in molecular terms) highly complex. They require special quality control procedures because of the biological nature (and intrinsic variability) of the starting materials and of manufacturing procedures. Some of the most complex biological medicines are living entities, such as the bacteria and viruses used as live attenuated vaccines. Many biological medicines are now prepared by recombinant DNA technology. Because biological substances cannot be characterised chemically, their biological activity and thus potency has to be measured against that of a known standard of the same substance. The preparation and use of Biological Standards is fundamental to NIBSC's work. Well-characterised preparations of biological substances are used as actual physical standards against which to compare the properties of manufactured products. The authoritative, global reference materials for the majority of biological medicines are the International*

Standards produced at NIBSC on behalf of the World Health Organization (WHO).

3.3. Blood products were one of the biological medicinal products that we assessed.

3.4. When I joined NIBSC in November 1974, blood products were dealt with in the Division of Hormones and Blood Products, under the leadership of Dr Derek Bangham. After about 2 years, Blood Products was established as a separate Division, with Dr Duncan Thomas as Head of Division. In 1984, when Dr Schild became Director, the Division of Blood Products was renamed Division of Haematology. Dr Thomas remained in post until the early 1990s and then I took over from January 1991 until January 2006. The Division was divided into Scientific Staff (of which I was a member and of which Dr Thomas was the head), Technical Staff, and about one member of Administrative Staff (see for example page viii of the NIBSC Annual Report [WITN5281006] (p.6)). The scientists were each responsible for one particular area, e.g. I was responsible for blood coagulation and Dr Patrick Gaffney was responsible for Fibrinolysis. The technical staff were the ones who did the practical work, under the supervision of the scientists. This remained largely unchanged during my time at NIBSC.

3.5. A more detailed overview of the work of the Division of Haematology can be found in the Scientific Policy Advisory Committee's 'Review of the Division of Haematology', December 1993 [WITN6408005].

3.6. The Divisions of Virology and Retrovirology were also involved in the assessment and testing of blood products.

3.7. My role was limited to establishing and performing tests for potency of the products on a batch by batch basis after the products had been granted a licence. These tests were highly technical assays. Initially, NIBSC as a whole was involved in only a limited way in the licensing process, but this increased as time went on. To clarify, we did not have a formal role in the licensing process, but we became more involved in discussions with the Licensing Authority when manufacturers recognised the need to introduce viral

inactivation methods into their production processes. I was not personally involved in these discussions.

3.8. In explaining my role and the wider role played by NIBSC, I have considered a copy of a July 1977 leaflet to which the Inquiry referred me, produced in by the Medicines Division of the Department of Health and Social Securities ('DHSS') [MHRA0004773].

NIBSC Liaison

3.9. I have been asked how NIBSC worked and exchanged information with the Committee on the Safety of Medicine ('CSM') and unfortunately I cannot comment as I was not involved with the CSM at all. I have no knowledge of how NIBSC and the CSM worked and exchanged information. I do however recall that the head of the Division of Haematology at NIBSC, Dr Thomas, would often attend the CSM Biologicals Subcommittee. I do not think he was actually a member, more an expert who would attend and assist as required.

3.10. NIBSC worked with the Licensing Authority on an informal basis – we would respond to requests for scientific help and guidance when asked. At NIBSC we would correspond directly with individuals at the MCA (which, as far as I was concerned, was the Licensing Authority) and I refer to some of that correspondence here. Beyond this, I do not have any knowledge of how NIBSC and the CSM worked and exchanged information, if at all, with the Licensing Authority.

3.11. In regard to how NIBSC co-operated with the Blood Products Laboratory ('BPL') and the Protein Fractionation Centre ('PFC'), when I first joined NIBSC, the products of BPL and PFC were not initially subject to batch release. This did however change in the mid-80s when they started to submit their products for batch release, although I cannot specifically remember when.

3.12. Before we started batch releasing their products, I collaborated scientifically with the two laboratories to establish a British Working Standard for Factor VIII Concentrate, and subsequently a similar Standard for Factor IX concentrate. A 'standard' is a sort of yardstick against which potency can be accurately and universally measured. In each assay the test sample is compared to a Standard of known potency – this is known as a 'Working Standard'. It was impossible to

use the actual International Standard for each assay as stocks would be rapidly depleted, so NIBSC needed a Working Standard, as did BPL and PFC – it occurred to me that if we all used the same Working Standard it would be much more convenient and would lead to improved harmonisation of assays, and so the British Working Standard for Factor VIII Concentrate was born.

3.13. In 1987, a Working Group on Plasma Fractions was formed, with representation from NIBSC, BPL and PFC, under the chairmanship of Dr Thomas. I was a member of this Working Group, whose remit was to develop Guidelines for Plasma Fractions, as part of the broader aspect of collaboration between NIBSC and the Blood Transfusion Service ('BTS') in developing Guidelines for all their activities.

3.14. NIBSC co-operated with the BTS by collaborating in the development of national guidelines for all BTS activities. There were three technical Working Groups: Plasma Fractions; Blood Components and Blood Group Reagents; and an overall Liaison Group. The benefit of this was that all the individual Blood Transfusion Centres would be operating with the same set of written guidelines.

NIBSC and Product Licence Applications

3.15. I have been referred to section 19 of the Medicines Act ('MA') 1968 in order to answer how the quality, safety and efficacy of blood products were assessed in respect of product licences for blood products. I was not involved in the licensing process and therefore unfortunately cannot answer this question, nor can I answer what the criteria meant in practice nor by what process(es) such matters were assessed. I did not have any role in the assessment of product licence applications except occasionally providing scientific advice, if requested. While I cannot think of any specific examples, that advice would have been in my area of expertise, i.e. the biological activity of coagulation factors and the methods of their manufacture. The same applies for NIBSC as a whole because NIBSC did not have any formal role but would have provided scientific advice when requested.

3.16. The sources of evidence and expertise relied upon in order to make licensing assessments of quality, safety and efficacy were the responsibility of the Licensing Authority, of which again I have no knowledge.

3.17. I have been asked what international standards applied in this context of assessing product licence applications. The term 'international standards' is a broad and ambiguous term as it could mean either written standards or physical reference materials. In regard to written standards (which is what I think applies here), initially assessors would have followed World Health Organisation ('WHO') guidelines and requirements for blood products. Later on, the European Guidelines would have been taken into account. The increased role of European requirements, as established by the European Pharmacopoeia, and later the European Medicines Agency, took place over several years during the 1980s and 1990s, and it is difficult to give an exact time frame. The term 'house standards' refers only to physical reference materials, and should not be confused with written standards, which I think is what is being referred to here.

3.18. There was no statutory requirement for products to be tested by NIBSC as part of the application for a product licence. During the mid-80s, when manufacturers were exploring various forms of virus inactivation, some manufacturers submitted samples pre-licensing on an informal basis, but this was not a legal requirement. Nor was there any requirement for manufacturers to submit information to NIBSC as part of the licensing process.

3.19. As I was not involved with the licensing process, I do not have the knowledge to comment on whether I was confident that those involved in product licensing in the UK had the sufficient expertise, resource and time to make an effective evaluation of the applications made by pharmaceutical companies nor can I comment on the extent of scrutiny involved in the applications for product licences for blood products.

3.20. Neither do I have the knowledge to comment on the information which was shared between the licensing authorities in other jurisdictions or the level of access the UK Licensing Authority had in relation to submissions and consideration received by the FDA or other licensing authorities.

3.21. As far as I am aware, there was no statutory requirement for NIBSC to be involved in an application for a new product licence, an application for a

variation, an amendment to a product licence or an application for an abridged product licence.

3.22. While I cannot comment on the types of conditions that could be imposed for a product licence to be granted for a blood product, NIBSC was involved in the batch release procedure. I therefore know that licences could be granted on the condition that they were subject to the batch release procedure which I discuss in detail below. This was a condition that samples from each batch of a product and accompanying documentation on quality control had to be submitted to NIBSC for approval before the rest of the batch could be released to the market. This was a requirement for all blood products and did not require any recommendation from myself or NIBSC.

3.23. To my knowledge, NIBSC did not have any role in evaluating blood products produced by BPL, PFL and PFC during the period in which Crown Immunity meant that such products produced by those laboratories did not require a product licence. Nor am I aware of any other regulatory checks during this period.

Section 4: Specific matters relevant to the functioning of the licensing process

Batch release procedure

4.1. As outlined above, the batch release procedure involved manufacturers submitting samples of each batch of their product to NIBSC, on behalf of the Licensing Authority, together with the associated quality control information ensuring that its composition matched the manufacturers' specification. It was intended to provide assurance that all the appropriate tests had been done by the manufacturer and that each batch was satisfactory in terms of quality and safety. However, having seen the document 'Medicines Act 1968, Additional Notes from Guidance – Biological Medicinal Products', I would add, '*it should be emphasised that operation of the batch release procedure by the licensing authority does not absolve the licence holder from ensuring that his product meets the specification and requirements of the product licence*' [MHRA0033773] (p.9).

4.2. Once the batch release procedure had been imposed on a product, it was carried out on samples from every batch.

4.3. In practice, NIBSC would scrutinise the documentation that accompanied the batches and would then carry out the appropriate tests on each sample. If everything was satisfactory, a release certificate would be signed and sent to the manufacturer and the MCA.

4.4. The appropriate tests included potency testing where we would take a sample and assay it against the International Standard, or an internal Standard calibrated against the International Standard, using established international procedures. I talk further about testing blood products specifically at paragraph 4.13 below.

4.5. The information which typically accompanied the batches in order to comply with the batch release procedure included information about electrolytes, pyrogenicity, abnormal toxicity, potency, total protein and viral markers. The main changes over time were related to viral markers – initially this was only hepatitis B surface antigen, but as knowledge evolved, additional viral marker tests were added, namely for HIV and hepatitis C.

4.6. Other information which accompanied the batches can be found in a letter I have been shown from the Medicines Division to Bayer UK Limited granting a product licence and imposing the batch release procedure at the Licensing Authority's discretion [BAYP0000001_110]:

> *(a) the number of donations in each pool;*
>
> *(b) the method of assay, the standard used and its calibrations;*
>
> *(c) batch to batch reproducibility.*
>
> *...*
> *3. The expiry date is given together with temperature at which the investigation was performed.*
> *4. On-going information is provided on the reasons for, and the rate of, rejection of donors or donations, centre by centre.*

4.7. The batch release procedure did not apply to products used on a named patient basis (I discussed the 'named patient' process further below from paragraph 4.1).

4.8. Throughout the time I was at NIBSC, I believed it was an absolute requirement for blood products to participate in the batch release procedure (as indicated by an internal minute dated 10 May 1983 regarding the import of blood products [DHSC0002227_035] (p.2)) and that it was a condition in order to be granted a product licence for a blood product. I have also been shown a letter dated 18 March 1976 from Dr Bangham, the Head of Division of Hormones and Blood Products at NIBSC, which suggests that the batch release procedure was a strict requirement: '*I would not agree to the licencing [*sic*] of this product unless Batch release for this product is implemented*' [MHRA0009293].

4.9. I have noted the 'Medicines Act 1968, Additional Notes For Guidance – Biological Medicinal Products' which states:

> *Although holders of product licences are required as a condition of licence to comply with the standard provisions (unless it has been agreed that any particular standard provision should not apply) the need for the holder of the licence to submit protocols or samples and protocols of each batch of the product or refrain from marketing each batch until a certificate has been issued will not take effect until such time as a direction has been issued by the licensing authority specifically invoking the powers of the regulations. The arrangements set out in the direction will continue in force until such time as they are amended or rescinded by the licensing authority* [MHRA0033773] (p.8).

I interpret this as a way of saying that manufacturers have to comply with the batch release procedure once this has been stipulated in the product licence.

4.10. In the late 80s and early 90s, when the EC Directives 89/342 and 89/381 were discussed with the view of being implemented, Article 4.3 altered the batch release method. The effect of this was to '*…permit batch test of, respectively, immunologicals and medicinal products derived from blood only where another Member State has not previously examined the batch in question*' [DHSC0004299_032] (p.1). I can see from the draft minutes of a meeting I attended on 30 October 1992 where the batch release provisions of the EC Directives 89/342 and 89/381 were discussed, we at NIBSC made the argument that:

> *…there was a good case for batch release of blood products, on the following grounds:*
>
> *a. there was not necessarily greater batch-to-batch consistency in blood products because:*

i. *manufacturers started with entirely heterogeneous starting materials;*

ii. *new infectious agents were emerging all the time;*

b. *the risk of viral contamination in blood products (Factor VIII has recently been shown to have transmitted Hepatitis A in four EC countries);*

c. *the inadequacy of selective product monitoring in terms of gaining expertise and being able to examine trends over a number of years;*

d. *the contribution made by NIBSC's current procedures in terms of deterring manufacturers from cutting corners;*

e. *evidence that EC countries without batch release (eg Denmark) became dumping grounds for products unlikely to be released elsewhere;*

f. *the difficulties associated with withdrawing batches from the market where contaminants were discovered in the course of product monitoring;*

g. *the significant financial advantages of carrying out potency assays on batches.*

Given these arguments for batch testing blood products, there was then a strong case (comparable to that for vaccines) for not recognising other Member States' batch testing. In particular, there were safety risks other than contamination by HIV or Hepatitis that were not adequately checked for by other Member States [DHSC0004299_032] (p.3).

4.11. At the conclusion of this meeting, NIBSC was required to provide more information about batch testing. We provided that information on 12 November 1992: [WITN6408006]. In that further information, we identified three instances in which plasma pools submitted in the four years since testing began which had been found by NIBSC to be HIV+, two of which were for Factor VIII products [WITN6408006] (5). I cannot remember specifically what happened afterwards (save that I would have expected these batches referred to would not have been released).

Adverse Reaction Reporting

4.12. Adverse reaction reporting was completely separate from batch release and did not involve NIBSC. Adverse reactions were reported to the CSM and / or the MCA.

Testing

4.13. My colleagues and I undertook the actual testing of blood products in order to implement batch release procedures. We carried out potency testing of each batch and any other tests which involved the haemostatic system, e.g. thrombogenicity tests for Factor IX concentrates.

4.14. We did not use the International Standards directly in assays of products, as the International Standards were intended to be used by the whole world, and should last for at least 5 years. We used the British Working Standards.

4.15. I have been referred to the following documents [MHRA0009885; BAYP0000020_014] and I can confirm that other than reviewing these documents most recently for the purposes of preparing this statement, I had not seen of any of the documents prior to this time and have no further comments on them.

4.16. We often reflected on our testing methods, results and experiences at NIBSC. As such, I have seen a document entitled, 'Independent Product Testing at NIBSC: A. Summary of Recent Results' [WITN6408007]. The document considers the '*…number of samples of biological products and other materials tested at NIBSC during 1994/5 and 1995/6…'* The document goes on to say:

> *The majority of batches of product examined for batch release or other purposes have been found satisfactory. However, testing continues to reveal problems where quality does not match up to requirements. Experience has shown that manufacturers respond rapidly to technical and scientific information fed back to them regarding the outcome of testing and many issues are satisfactorily resolved by the industry and do not recur.*
>
> *Table 1 shows the number of instances over the past two years where 'interventions' were made i.e. where issues were raised with manufacturers on protocol data or where testing suggested there were issues of quality or lack of compliance with product specifications which needed addressing. Over the past two years, interventions were made on 6% of the almost 4000 protocols and/or materials tested. In the*

majority of these interventions issues were satisfactorily resolved by discussion with, or provision of further data by, manufacturers. However, in some cases the outcome was that a release certificate was not issued. This was the case for a total of 26 materials examined in 1994/5 (1.3%) and 34 in 1995/6 (1.8%).

In the face of increasing recognition of the risks of transmission of viral infections by blood and blood products, testing of plasma pools (used in the manufacture of blood products) for viral markers (anti-HIV-1/2, anti-HCV, HBsAg) was commenced in 1986 and was universally applied in the UK from 1989 for HIV and HBV; anti-HCV testing was routinely applied from 1993. Instances in which pools were unsatisfactory in respect of these markers have become progressively less frequent since 1989…

4.17. Table 1 (as referred to) is shown below:

Table 1

SUMMARY OF RESULTS OF TESTING

OF BIOLOGICAL PRODUCTS at NIBSC, 1994/95 and 1995/96

	1994/1995		1995/1996*	
Product Type	Number of Batches Tested	Number of Interventions	Number of Batches Tested	Number of Interventions
Viral Vaccines	446	27	409	25
Bacterial Vaccines	429	35	432	28
Immunoglobulins	331	5	289	13
Coagulation Factors	230	22	304	15
Albumins	239	26	258	33
Antithrombotics & Thrombolytics	205	5	93	3
Others (Hormones, Cytokines etc)	130	not applicable	95	not applicable
All	**2010**	**120(6%)**	**1881**	**117 (6%)**

* Data for the first 10 months of the year

4.18. Similarly, at paragraph 8.33 below I discuss a paper I co-authored entitled 'Testing of Blood Products & Plasma Pools for Viral Markers – NIBSC Experience From 1986 – 1993' which reflects on the number of plasma pools and final products from UK licensed blood products manufacturers submitted to NIBSC for batch release testing over the years. It showed that since 1986, a total of approximately 4,700 plasma pools and final products from UK-licensed blood product manufacturers were submitted to NIBSC for batch release

testing. The document concludes with, '*...control authority testing for viral markers should be mandatory as part of the European batch release procedure for blood products*' [DHSC0006465_037] (p.2).

Plasma and Concentrate Standards

4.19. In 2013, after I had left NIBSC, I wrote an article in *Haemophilia* entitled 'Laboratory testing and standardisation' where I described my role in the development of plasma and concentrate standards, including British and International Standards:

> *When I joined NIBSC in 1974 my remit was to establish a laboratory for testing clotting factor concentrates and other coagulation-related products such as heparin, as well as to organize the development of national and international standards for these products* [RLIT0001382] (p.2).

4.20. To offer a bit more detail, when I arrived at NIBSC, the First International Standard for Factor VIII, a concentrate, had been established for several years, and was coming to the end of its life, especially as it had been found positive for hepatitis B surface antigen ('HBsAg'). My first job and role was to establish its successor, the Second International Standard. This involved organising a major international collaborative study, collation of the results, and the submission of a report to the WHO Expert Committee on Biological Standards, which was the body responsible for establishment of International Standards.

4.21. A British Standard for Factor VIII in plasma had also been established, and my job was to organise the British collaborative studies for the replacement of successive batches. During these studies, it became apparent that the calibration of British plasma standards against the International Standard, which was a concentrate, was subject to large variability among laboratories. There was also a discrepancy between the two assay methods for Factor VIII. An assay is a measurement of the potency of the product, and the two methods for assaying Factor VIII were the 1-stage and the 2-stage method. I therefore proposed that a separate International Standard should be established for Factor VIII in plasma. This was agreed and after a large international collaborative study, the First International Standard for Factor VIII in plasma was duly established by WHO. While it was largely my work, it was overseen

by Dr Thomas, and I would have discussed the design and analysis of the collaborative study with him.

4.22. The same process was also applied to Factor IX, with the establishment of International and British Standards for both plasma and concentrates, and eventually International and British Standards were established for most of the coagulation factors.

4.23. The Standards that I established were purely for the measurement of potency, which was related to efficacy of the products but not to their safety. The main development over time was the production of Working Standards, which could be used in much larger quantities than the International Standards.

4.24. The International Standards took precedence over all other Standards. The British and European Standards were calibrated against the appropriate International Standard.

4.25. NIBSC in the course of the licensing process used British Working Standards for Factor VIII and Factor IX concentrates in routine assays for batch release.

4.26. Individual manufacturers were expected to establish in-house Standards, calibrated against the International Standards, for routine use in assays of their products. For the American manufacturers, they had to comply with the requirements of the FDA, whose Standard for Factor VIII was a plasma, and this sometimes caused discrepancies with the use of the International Standard, which was a concentrate. Because of this, some manufacturers, notably Armour Pharmaceuticals, used a contract laboratory in the UK to assay their product before sending samples for batch release.

4.27. I have been shown a letter that Armour wrote to Dr Thomas in September 1978 which said:

> *Recently, I have discussed informally with Dr. Barraclough, the possibility of using our parent company's potency determination as the only assay in the protocol submission to you for release of batches of our Factorate.*
>
> *This follows assays of the International Standard against the American standard by Armour Pharmaceutical Company in Kanakee, and a statement that they have received from the Bureau of Biologies which states unequivocally that, in their opinion, the two units are identical* [WITN6405005].

4.28. I have seen some of the correspondence which followed ([MHRA0000085_010] and [MHRA0000085_003]) and can see that Dr Thomas did not agree with Armour's assessment and that eventually, they agreed to calibrate their house standard against the International Standard. As referenced in Dr Thomas's letter to Armour on 26 September 1978 [MHRA0000085_010], the use of the FDA plasma standard instead of the International Standard for calibration of their house standard would have led to a 30% increase in the labelled value of their product. All manufacturers were persuaded to calibrate their house standards against the International Standard, and eventually this whole issue was resolved when the FDA were persuaded to establish a concentrate standard, the 'Mega' Standard, calibrated against the International Standard, for use on a large scale by themselves and all the US manufacturers.

4.29. I have been shown a letter that TBL Kirkwood and I sent to Dr Cash of the Regional Blood Transfusion Service in 1975 where I discuss the proposed Fifth British Plasma Standard for Factor VIII, in particular the positive / negative antigen results in plasma standards. I noted, '[w]*e would remind you that the International Standard gives a positive result for hepatitis B antigen; the proposed 5th British plasma standard is [HBsAg] negative'* [SBTS0000309_141] (p.1). It was undesirable for any standard to be positive for HBsAg from the point of view of the safety of the laboratory staff handling these standards. To my knowledge, there were no positive results in any plasma standards.

4.30. The test for HBsAg was an absolute test, yielding a positive or negative result. It was not measured against a reference standard in the way that potency tests are.

4.31. The only Standard which gave a positive result in any of the virology tests was the First International Standard for Factor VIII, which as indicated above, was positive for HBsAg. As soon as this information became available steps were taken to establish a replacement.

4.32. The virology results on Standards were irrelevant to the testing of Blood Products – in the first place these Standards were only used for determination

of potency, and in the second place plasma standards were not used for concentrate products.

Stop orders, product recall and withdrawal

4.33. I am not familiar with the term 'stop order' and to my knowledge, batch release was not called anything else but I gather from the documents that it may be an alternative description of 'batch release' (see for example [DHSC0002229_006]).

4.34. I have no knowledge regarding how safety concerns about a blood product would be reported to NIBSC – I do not think they would have been because such concerns were reported to the MCA and/or the CSM. I am unaware of whether these bodies subsequently informed NIBSC.

4.35. When it came to withdrawing or recalling a blood product, or even revoking a product's licence following a safety incident, NIBSC were not involved and so I cannot comment on what considerations were applied to such decision-making. Nor can I comment on how the procedures evolved over time. I believe it was entirely the responsibility of the MCA.

4.36. NIBSC were able to withhold a batch of a blood product if any of the tests or protocol information was unsatisfactory although, in practice, this happened only rarely. I have seen a letter I sent to Mr Ivan Bryant, Regulatory Affairs Manager at Alpha Therapeutic Europe Limited, dated 5 April 2002, as an example of how '*…following discussions with the MCA, we will not be issuing release certificates for any of the batches of Albutein currently under test, until more information is available*' [MHRA0009194]. This occurred where we saw particulate contamination in bottles of Alpha Albutein 5% from Batch NF 1079A.

4.37. I have also seen another example of where I did not recommend the release of a '*…batch of Stable Plasma Protein Solution, because of concern about the microbiology results*' [WITN6408008]. In this letter to Dr Bruce Cuthbertson dated 19 October 1994, I suggested that he take this matter up with the MCA and requested I be informed of any discussions.

4.38. I have been asked to look at a copy of the 1985 internal Immuno Ltd correspondence [SHPL0000221_001] which I had not seen prior to this Inquiry.

Having looked at the document, I can confirm that NIBSC were not involved in the adverse reaction reporting and so I cannot comment on how '*...special reporting requirements*' [SHPL0000221_001] (p.1) differed from the general adverse reaction reporting. Nor can I comment on when such special requirements were implemented or the aim of these requirements or the consequences of a licence holder not complying with the special requirements.

BTS/NIBSC Interactions and guidelines

4.39. The BTS saw the need for the development of National Guidelines for use in transfusion centres around the country and, to satisfy regulatory requirements, they asked NIBSC to help. This is confirmed in the minutes of a meeting dated 17 June 1987: *'The UK BTS had approached NIBSC to seek help in formulating "guidelines" for BTS activities which would be accepted as national guidelines in due course'* [NHBT0007598] (p.1).

4.40. As a result, in 1987, the BTS/NIBSC Liaison Group ('the Liaison Group') was established alongside three technical Working Groups: the Working Group on Blood Components; the Working Group on Blood Group Reagents; and the Working Group on Plasma Fractions ('WGPF') (as discussed in paragraph 2.14 above).The relationship between these three groups was collaborative.

4.41. I was a member of the WGPF. The purpose of the WGPF was to produce guidelines on the manufacture of Plasma Fractions, to be included in the National Guidelines for the BTS. The WGPF's role was advisory. I attended meetings several times a year and minutes of these meetings were recorded, for example: [NHBT0007574; NHBT0007575; NHBT0007576; JPAC0000043_048; JPAC0000043_047].

4.42. I have been shown the minutes of a Liaison Group meeting in June 1987. Although I was not present at this meeting, the minutes say *'...donor selection and procedures, documentation and handling of plasma donations'* [NHBT0007597] (p.1) would overlap with the work of the WGPF. In the UK, plasma for fractionation was collected largely from regular blood donors, and these would be subject to donor selection procedures, as set out by the Liaison Group. In my experience there was no confusion over the role or the responsibilities of the respective working groups.

4.43. I can see from the minutes dated 25 November 1987 [NHBT0007638] (p.2) that I attended a WGPF meeting, during which I was allocated the role of commenting on standards and assays for dried Factor VIII concentrate. As it was my area of expertise, it was understandable that I was asked to contribute.

4.44. In the minutes of a WGPF meeting which took place in October 1988, it recorded that the BTS / NIBSC would develop guidelines to *'...describe conditions, conduct and products that should be obtained in the service, rather than what exists at present'* [JPAC0000043_047] (p.2). I have described the events and / or policy considerations that prompted the development of the guidelines, including NIBSC's interest, in paragraph 4.39 above.

4.45. I have no knowledge about why during that meeting it was stated that the BTS / NIBSC document could only be guidelines as opposed to '*requirements*' [JPAC0000043_047] (p.2) but it may be because the latter would require DHSS approval and legislation.

4.46. The final product that resulted from the development of the guidelines, was the Guidelines on Plasma Fractions which were incorporated in the overall National guidelines, and were implemented by BPL and PFC. I think that this was what eventually became known as the 'Red Book'.

4.47. To my knowledge, no other bodies were materially involved in the development of the guidelines. The relevant WHO documents on Blood Products were noted and taken account of in the development of the Guidelines.

Section 5: Use of unlicensed products

The 1978 Order – named patient basis

5.1. The Amendment of the Medicines (Exemptions from Licences) (Importation) Order 1978 ('the 1978 Order'), introduced a method of exempting products from licensing provided they were being sold on a 'named patient' basis only.

5.2. As far as I am aware, NIBSC did not play any role in restricting the blood products used on a named patient basis. I think this was within the remit of the MCA. As I had no involvement, I cannot comment on the type of information other relevant bodies required in order to consider potential exemption, nor can

I comment on the considerations that applied when considering whether to raise an objection on the ground of safety.

5.3. I have seen the minutes of a Haemophilia Reference Centre Directors meeting held on 14 September 1981 where Dr Bloom was recorded as saying that *'…NIBSC would expect the manufacturers to prove the claim for each batch of concentrate produced, but it could not prohibit the use of the material for named patients*' [LOTH0000012_122] (p.8).

5.4. NIBSC would have expected manufacturers to prove the claim made on each batch of concentrate i.e. whether it was either hepatitis-free or hepatitis-reduced as far as it was possible by in vitro tests, but final proof could only be determined in clinical use.

5.5. Before the development of a test for non-A non-B hepatitis, there was no means of demonstrating freedom from or reduction of hepatitis transmission other than by clinical studies. NIBSC's role was limited to in vitro testing when a test for hepatitis C became available.

5.6. NIBSC could not prohibit the use of blood products on a named patient basis because we did not have the legal authority to do so.

5.7. I have been shown a letter sent from Cutter Biological to the DHSS in 1985, providing notification of a proposal to import a heat-treated Factor IX product under the exemption provided by the 1978 Order [BAYP0000004_269]. Following receipt of such notification, the process which would have been adopted thereafter would be a matter for the Licensing Authority. NIBSC were not involved.

5.8. I have also been shown a ministerial briefing from June 1983 in which it was argued that the 1978 Order had inadvertently permitted the importation, without detailed control, of large quantities of medicines that were already available under licence in the United Kingdom [DHSC0101977]. While I am unfamiliar with the 1978 Order, I do agree that this procedure could have affected patient safety. While the 1978 Order created a risk to blood products in particular, it is however also worth recognising that, in relation to HIV and hepatitis C, there were no in vitro tests available at the time to prevent such batches from causing

an infection. It is also worth recognising that it was up to the Licensing Authority to ensure that manufacturers did not take advantage of this apparent loophole.

The 1984 Order

5.9. I understand that the 1978 Order was later replaced by the Medicines (Exemption from Licences) (Importation) Order 1984 ('the 1984 Order'), where an exemption could only apply if certain conditions were fulfilled i.e. if no product licence for the medicine had been granted in the UK. I have no first-hand knowledge of the 1984 Order.

5.10. I am told that for an import exemption to be granted it was necessary that, first, a written notice was given to the Licensing Authority (Article 4(1) (a) 1984 Order) and, secondly, that the Licensing Authority had not issued a notice stating that they had reasonable cause to believe that the medicine should be regarded as unsafe or of unsatisfactory quality (Article 4(1) (c) 1984 Order).

5.11. While I have no knowledge of the 1984 Order, I presume that, provided manufacturers complied with the UK licensing regime, it meant that all batches of licensed products were subjected to the batch release procedure by NIBSC.

5.12. I cannot speak to what considerations applied when raising an objection on grounds of safety or issuing a notice under the 1984 Order or what information was required from manufacturers; this would have been the remit of the Licensing Authority and not NIBSC.

5.13. In the event that a product has already been introduced to the UK market via the named patient route, it would have been the Licensing Authority's remit to consider whether this affected the decision to approve a product licence. NIBSC would not have considered any issues about granting product licences or carried out any enquiries as to the consequence of using the product on a named patient basis as this was outside our remit.

5.14. I have been shown two letters between Dr N Randall, Quality Control Manager, Revlon Health Care and me, in December 1984, where I wrote that manufacturers were not obliged to send products used on a named patient basis for batch testing: [MHRA0000079_005; MHRA0000079_006]. This was broadly the case. This correspondence was the initiative of the manufacturer

who appears to have sent us batches of heat-treated Factorate for testing. It was not a common arrangement to send us batches for testing in this situation.

5.15. The process and approach for testing these samples under the batch release procedure, even if there was an absence of requirements, would have been the same as testing any product as described above in Section 4: Batch release procedure.

5.16. The correspondence suggested that heat-treated Factorate was being used on a named patient basis at this stage. While NIBSC may have had knowledge of this, it would not have had any input, as it was a decision made by the manufacturers.

5.17. While I cannot recall how long this arrangement exactly lasted, I presume it would have applied until the heat-treated product obtained a product licence, which would have been a matter of months rather than years.

5.18. At the time Factorate was being batch tested (1984), there were no in vitro tests which could have identified a potential infection by HIV or hepatitis C.

5.19. I have seen a memo from Armour Pharmaceutical Company dated April 1985 which states *'Dr Trevor Barrowcliffe of NIBS & C has expressed concern over the use of Named Patient Supplies to provide our H.T. Factorate to the UK market as we now have Product Licence for the supply of heat-treated product. He has advised that NIBS & C are seeking, with the DHSS, ways of applying pressure upon supplying companies to have this product released by the procedure detailed on our licence'* [ARMO0000374]. While I am unsure how knowledge of this procedure came to my attention, once it did, I would have flagged my concern to the manufacturers and the MCA, as it appeared that the manufacturer was trying to evade the batch release process.

5.20. Despite the condition in the 1984 Order and holding a product licence, pharmaceutical companies breached the rules therein by continuing to use the named patient exemption. Enforcement of such conditions were a matter for the MCA.

5.21. I believe the main reason as to why a pharmaceutical company continued to use a product via the named patient basis despite having a product licence for

the product was because the former process had a rapid turnaround by avoiding the batch release procedure and it is possible that this was pushed by some haemophilia doctors.

5.22. Apart from letters like the one quoted above in paragraph 5.19 ([ARMO0000374]) where I am shown to have expressed concerns, there was no other action NIBSC could take: enforcement would have been a matter for the Licensing Authority.

5.23. I have been shown a memorandum dated 15 July 1986 from Revlon Healthcare Limited (UK) which states that batch Y69402 was released for sale on a named patient basis, and that samples had been sent to NIBSC in the way normally adopted for batches released under a product licence despite there being no obligation to do so [ARMO0000417]. As I have said, I believe such a practice was uncommon and unusual. I think pharmaceutical companies chose to adopt this practice because some, at least, respected the batch release process and felt reassured if batches used on a named patient basis had been passed by NIBSC.

5.24. We examined Feiba, a product for treatment of patients with Factor VIII inhibitors which was available on a named patient basis as early as 1976, as confirmed by a Pharmaceutical Examiner's Report dated 10 June 1985 [SHPL0000078_010]. I do not know if there were any restrictions on how long a product could be used on an unlicensed basis.

5.25. I have been shown 'Examination of Samples and Protocols' [MHRA0000066]. This document is the same as the protocols which would have been applied in the batch release procedure, but presumably in this case, it was being applied to samples used on a named patient basis.

5.26. The document refers to '*release authorisation*' being restricted to '*in patients to be named*' [MHRA0000066] (p.4). This is an example of the oversight of the named patient procedure. The testing would have been applied in the same way as for testing samples under the batch release procedure, and the results would have been reported to the manufacturer and the Licensing Authority.

Section 6: Relationships with pharmaceutical companies

6.1. The relationship between NIBSC and pharmaceutical companies was generally informal and limited to occasional meetings and telephone calls.

6.2. I have been shown a note of a meeting with Armour dated 25 March 1983 [MHRA0000080_002] which I exhibit as an example of one of the more formal kinds of meetings that we might have had. This was a meeting that had been called to discuss discrepancies between our NIBSC assays and the labelled potencies of Armour Factorate. This minute illustrates the following:

a) NIBSC kept potency under constant review and challenged pharmaceutical companies where there were issues;

b) NIBSC would hold batches where the potency differed significantly from the labelled potency;

c) Where issues such as this arose, there would often be careful testing conducted by both manufacturers and NIBSC until some agreement could be reached (here, some batches were to be relabelled, some were to be retested, and one batch was to be released as the potency match was close (92%));

d) Efforts would be made to identify the cause of discrepancies (see the final section headed 'Action in Future').

Information Sharing

6.3. Beyond this, we did not have regular meetings with manufacturers, but would meet to discuss specific issues if requested by them. These meetings were infrequent and usually related to information that manufacturers wanted to relay, such as changes to their manufacturing process, like the introduction of viral inactivation methods. The meetings would not have been minuted. They were informal and not subject to any guidelines or protocols.

6.4. To share knowledge between the pharmaceutical industry and NIBSC / licensing authorities, other scientists from NIBSC and I regularly attended international congresses such as those of the International Society on Thrombosis and Haemostasis and the World Federation of Hemophilia, at which manufacturers presented their latest data. At these congresses, it was possible to have informal discussions with scientists from the various companies.

6.5. The relationship between NIBSC and pharmaceutical companies only changed between the 1970s and 1990s to the extent that, during the AIDS crisis in the mid-80s, there were increased discussions between NIBSC and manufacturers about virus inactivation methods and their evaluation; these mainly involved colleagues in the Division of Virology.

6.6. Although actual methods of viral inactivation were investigated and developed by the manufacturers, as they were specific to the composition of each product, NIBSC did contribute to the development of methods to assess the efficacy of viral inactivation processes.

Influence

6.7. I recall no occasions when pharmaceutical companies attempted to improperly or inappropriately influence decisions made by NIBSC, or any other bodies involved in the licensing process.

6.8. That said, we did occasionally get phone calls or letters enquiring about the progress of our batch release testing on a particular batch; these were mainly in the early stages of the batch release procedure, and became less frequent once manufacturers had become more familiar with our operation of the batch release process. I did not regard such enquiries as inappropriate.

6.9. There were occasions when manufacturers requested we expedite products submitted for batch release. While I do not recall if we gave them any formal timeline, they generally knew how long it would take us to conduct our checks and release the batches. They might therefore get in touch if we were taking too long or if, for any reason, they wanted their batches released more quickly. I did not think this was inappropriate and I do not feel that they put undue pressure on us. Where this sort of thing happened, I thought they were unwise

to send us batches too late when their supplies were running low and they were trying to get them cleared quickly because we could not always assist. Some examples of this happening can be found here:

a) A letter dated 17 May 1993 from Dr Terry Snape to myself drawing my '*attention to four batches of factor VIII type 8SM… which fall below the lower limit of the potency range defined for the product…*' The letter concluded:

> *Please let me know if you would wish to have more data to facilitate your review of the batches. With the exception of FHM4180, to which attention has already been drawn, we are aware of no reason why these batches should not be released for sale* [MHRA0000008_022].

On the same day, Dr Terry Snape faxed a handwritten letter to me requesting I expedite a batch referenced in the letter above, as BPL were '*…effectively in a stock-out position*' [MHRA0000008_020].

b) A letter from BPL dated 25 May 1993 [WITN6408009] saying they were anxious for particular batches to be released. I have also seen a letter dated 18 November 1993, faxed to me from Dr Terry Snape, Technical Director at BPL, requesting we '*…expedite these batches [of 8SM] through the NIBSC process*' because '*…there is now considerable pressure on 8SM stocks, with any delay to batch progression causing stock-out and customer dissatisfaction*' [MHRA0000012_005].

6.10. I have also seen a memorandum dated 1 December 1993 from Geoffery Kemball-Cook to myself regarding the '*Release of 3 BPL 8SM Batches*' which shows how Dr Terry Snape telephoned NIBSC '*…to ask for an urgent release*' despite only having the product for a number of days [MHRA0000012_002] (p.1). Mr Kemball-Cook set out the efforts that NIBSC had gone to in order to assist and warned '*I think you should be aware of the circumstances surrounding this rather dangerous precedent'.* I do not remember receiving this letter but I know that Mr Kemball-Cook was probably the one doing the tests (or overseeing them) and he was probably concerned that if we expedited a batch for one manufacturer, others would ask for the same assistance. When we would receive requests similar to the ones above, we would try to help but we

would not be pressured into releasing a product too quickly or without adequate testing: carrying out the tests properly always came first.

6.11. I have seen a letter dated 23 November 1993 from Dr Terry Snape to myself regarding batches of a type of Factor VII, 8SM where '*…the reported histidine content of these three batches, which marginally exceeds the upper limit of specification for the product*' and so BPL were seeking a variation to their 8SM licence and *'(i)n the interim, batches will be presented to NIBSC for your review on the basis histidine content as found. We do not believe that this minimal shift in histidine content represents a compromise in product safety*' [MHRA0000012_003]. This would not have been an example of any undue influence either, not least because histidine was a minor component and I do not recall that we tested for it ourselves so it would make little difference.

6.12. In or around November 1995, I can recall once being '"*in dispute"* with *BPL on a batch of 8Y, No FHB 4443, where our potency estimates after repeat assays average 70% of the labelled value…*'. There was a clear discrepancy between our results and BPL's. On 15 November 1995, I described this in a letter to Mrs Glenda Silvester at the MCA where I stated, *'[w]hilst I have no wish to hold up supply of clinically essential material I do not feel I can sign a batch release certificate at present on the basis of the data we have*' [WITN6408010].

6.13. Despite some of these approaches, I believe that NIBSC as an organisation acted with complete impartiality and, as the Board's 'Modes of Operation' stated, did fulfil its objectives to:

> *l) provide impartial advice consistent with the Board's statutory role in the UK and NIBSC's status as a WHO International Laboratory;*
>
> *m) avoid any abuse of the Board's monopoly position (in the development of control tests and standards) while fostering the protection and exploitation of innovations by NBSB staff;*
>
> *n) maintain the confidentiality of information and materials as appropriate;*
>
> *o) pass on to the appropriate authority any information deemed significant to the protection of public health* [WITN6408011] (p.2).

Early provision of samples

6.14. I have been shown a letter dated, 15 January 1986, which was sent to me by Marie W Tatt, Regulatory Affairs Manager of Cutter Pharmaceutical, where they requested that tests be conducted, in advance of a product licence application, on samples of Koate-HS Antihaemophilic Factor prepared by a wet heat treatment process [BAYP0000014_038] and another letter dated, 17 August 1983, which was sent to me by E. R. James, Quality Control Manager of Revlon Health Care UK, where they requested tests be conducted on samples of Factorate prepared by a heat treatment process prior to clinical trials [MHRA0000079_015]. It was uncommon for pharmaceutical companies to send products ahead of their product licence applications to NIBSC, but we welcomed it when it did happen. This practice was offered by some manufacturers who had established good relationships with NIBSC.

6.15. The benefits of such practice were that it gave NIBSC the chance to familiarise themselves with the new product and report any issues to the Licensing Authority and gave the assessors of the licence submission access to an independent assessment of the product from NIBSC. I think that it benefitted manufacturers too because those who had extensive experience of batch release by NIBSC realised that this procedure was operated fairly and efficiently, and so attached value to approval by NIBSC of batches submitted before licensing.

Section 7: Knowledge of and response to risk of infection associated with blood products

7.1. At NIBSC, we were informed about the risks of infection associated with blood and blood products by reading scientific journals, attending scientific congresses, and in particular in the UK, attending meetings of, and having discussions with, Haemophilia Centre Directors. There was an increase in the number of meetings associated with infectivity of blood products as the infection evolved over time.

7.2. I have been shown a report of a Haemophilia Centre Directors meeting I attended on 9 October 1981 where it was recorded that I said '*…that the US*

commercial products are fractionated by a wide variety of methods and this could affect the degree of contamination of each of the brands' [SBTS0000400_015] (p.6). This comment was mainly made in relation to the purity of the products because the purer the products, the less likely they were to harbour infectious viruses. Purity is simply a measure of how much the Factor VIII or Factor IX is contaminated by other proteins – in the early products the clotting factors were less than 1% of the total protein, but this percentage increased as methods were developed to reduce the proportion of contaminating protein. Some of these methods would also, coincidentally, remove some infectious viruses, though they were not designed to do so.

7.3. Information about the range of commercial fractionation methods was obtained from published papers and presentations at scientific congresses. I believe such information had to be submitted to the Licensing Authority as part of the submissions to obtain a product licence, and as such, could be obtained from the MCA. Information about the size of the donor pools was contained in the protocols submitted with the samples intended for batch release.

7.4. Included in those protocols was information about the donated blood itself. For example, in the case of products from the USA, individual donations had to meet the FDA requirements for blood and plasma donations. In the case of products manufactured in the UK, only donations from the BTS were used and the testing procedures used and the criteria for donor exclusion were those operated by the BTS. This was the only information about the degree of risk assessment that I recall.

7.5. I thought then, and think now, that more information could have been supplied by US manufacturers on the sources of their starting plasma.

Hepatitis

7.6. When I started at NIBSC, it was well known that transmission of hepatitis B was the major concern for blood transfusion and blood products. Subsequently, it was recognised that there was another virus, initially named 'non-A non-B', which subsequently became known as hepatitis C, could also transmit hepatitis. My knowledge in this area mainly came from meetings of, and discussions with,

Haemophilia Centre Directors in the UK, and from colleagues in the Division of Virology.

7.7. The risk of transmission of hepatitis B was quite low, because of its relative rarity in the population, the donor exclusion procedures, and the early development of a test for HBsAg. Transmission of hepatitis B was recognised as leading to severe illness, with potentially fatal consequences.

7.8. Transmission of non-A non-B hepatitis was more frequent, but initially thought to lead to only mild illness. Non-A non-B hepatitis initially led only to mild symptoms, but many years later, it was recognised that frequent infections could lead to severe liver disease.

7.9. It was generally recognised that blood and blood products from paid donors in the USA and elsewhere in Europe carried a higher risk of transmission of hepatitis than if sourced from unpaid donors in the UK, but this is my recollection and I am not sure where the evidence for this came from or when it emerged.

7.10. The main roles for NIBSC in responding to the risk of hepatitis transmission from blood and blood products, prior to the introduction of screening requirements and the development of viral inactivation methods, was the introduction and supply of a working standard for HBsAg for use by transfusion centres when the test became available, and the provision of advice on the assessment of viral inactivation methods when these started to be introduced by manufacturers.

HIV/AIDS

7.11. I became aware of the risk of contamination of blood and blood products with HIV by reading scientific journals and attending scientific congresses. I became aware of the risk of transmission of HIV by attending the meetings of, and having discussions with, the UK Haemophilia Centre Directors.

7.12. As I recall, it fairly soon became evident, from clinical data reported by Haemophilia Centre Directors, that blood products prepared from UK-sourced plasma carried a much lower risk of HIV transmission than commercial products prepared from paid donors. This data would have been reported at meetings rather than recorded in documents, although I cannot recall the timescale.

7.13. I have been asked to look at the minutes of a Haemophilia Centre Directors meeting held on 13 September 1982 (which I attended in the afternoon) and where it was recorded that, *'…there was a remote possibility that commercial blood products had been involved'* [CBLA0001619] (p.10). While I do not remember any specific discussions NIBSC had following this meeting, there was a recognition that HIV could be potentially transmitted by Factor VIII concentrates. Given the knowledge at the time, there was little NIBSC could do in responding to the concerns that there was a risk of transmitting HIV through blood and blood products. One thing I do remember is that the Director, Joseph Smith, was concerned about the risks to NIBSC staff of handling products which were potentially infectious, and since the HIV virus was known to be heat-sensitive, he suggested that we heat all samples in an oven before testing. This did not work: it resulted in caramelisation and insolubility of most products.

7.14. I have been shown correspondence and enclosures discussing how blood products made from plasma collected before donor selection requirements were introduced in the USA, might be dumped in the UK: [DHSC0001394; DHSC0002229_006 and DHSC0002229_019]. I was not a party to this correspondence nor to the discussions regarding the matter. I have no knowledge or recollection of the issues discussed therein or of any discussions about the issue at NIBSC although discussions may have taken place at a higher level.

7.15. While I am generally unfamiliar with the '*Background Papers*' relating to AIDS that were circulated in or around May 1983 [DHSC0002229_019], I have read these documents and agree with their content.

7.16. I have seen correspondence dated 23 May 1983 entitled 'FVIII and AIDS' from Dr Fowler to Dr Walford discussing how manufacturers would be able to identify which batches of plasma were collected after 24 March 1983 (when a stricter approach to verifying the safety of blood was adopted in the USA). This stated that, '*[t]he 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' [DHSC0002229_006] (p.1).

7.17. To the best of my recollection and understanding, it is correct to say that the protocol as to what was submitted by manufacturers as part of the batch release process was to be agreed by Dr Duncan Thomas and the manufacturer but to a certain extent Dr Thomas could insist on what information should be supplied in the protocol. Manufacturers had to comply with NIBSC requirements. While the Licensing Authority were kept informed of all developments in relation to this topic, to my understanding, NIBSC did have the power to advise the Licensing Authority to reject any batches that did not comply with the requirements set on in Dr Fowler's minute [DHSC0002229_006].

7.18. While I believe US manufacturers were required to submit information about the date which the plasma used in their blood products was collected, I cannot be sure as I am relying on memory.

7.19. I had not seen the incomplete note from Dr Winstanley to Dr Walford dated 10 May 1983 contemporaneously. I have since been shown it and it states, '*It is made a condition of product licences in this field that the licence holder exercises proper quality control, which involves accounting for the source and quality of the blood, its processing and final product examination*' [DHSC0002227_035] (p.2). This is simply stating the basic requirements for manufacturers obtaining a product licence, with particular reference to the source and quality of the blood or plasma donations. Compliance with such conditions would be scrutinised by the Licensing Authority.

7.20. I have been shown the minutes of a DHSS meeting about AIDS held on 3 June 1984. I did not attend this meeting and probably would not have been aware of it at the time. There is recorded some discussion of the '*control of imports*' where legal restrictions in relation to imports of Factor VIII manufactured from plasma donated prior to 23 March 1983 would present '*significant practical difficulties*' and so it was planned that the Medicines Division would have formal discussions with the relevant manufacturers in order to achieve control [DHSC0002229_030] (p.1). Although I was not involved in these discussions nor aware of them, the practical difficulties referred to would have been related

to supply issues, as at this time, restrictions on importation of products would have led to a shortage of supply of these essential medicines.

7.21. I have been shown the minutes of a CSM (B) meeting on 13 July 1983 [ARCH0001710] and the agenda [DHSC0001209] and papers [DHSC0002229_059]. I can confirm that I had no involvement in the meeting whatsoever and, as far as I can recall, I was not informed of the outcome of the meeting.

7.22. My view at the time on whether imports of commercial concentrates should be prevented or restricted in light of the risk of AIDS was that the benefit / risk ratio of these products was unclear. There was insufficient information as to the extent of AIDS transmission and these products were essential life-saving products (lack of availability of products could cause severe disability and even death in patients), so I did not have strong views either way. It is probable that I would have discussed my views with my boss, Dr Duncan Thomas. At the time, I was unaware of other views within or outside of NIBSC relating to this matter.

7.23. The decisions regarding the response to the risks of infecting patients with AIDS as a result of blood products were difficult and at the time, I thought such decisions were best taken by the doctors treating haemophilia patients, in conjunction with the Licensing Authority.

7.24. The suggested agenda for that meeting prepared for by Dr Joseph Smith and referenced in paragraph 7.21 says, *'…brief possible conclusions are indicated – doubtless these will be changed radically'* [DHSC0001209]. It was unusual but not unknown for meeting agendas to include possible conclusions on the face of it. I do not think it was typical of the way Dr Joseph Smith worked or the manner in which he chaired and conducted meetings. While I do not have any thoughts on preparing the agenda in this manner, I imagine Dr Joseph Smith would have had his reasons for doing so.

A meeting to discuss the infection hazards of blood products

7.25. On 9 February 1984, a meeting took place at NIBSC to discuss the infectious hazards of blood products. The meeting was attended by figures from the UK and USA, including state and commercial fractionators, those involved in regulating blood products, civil servants, medics and scientists. I attended [MHRA0000076_018] (p.2) and my role in the meeting was to take notes, as indicated by a minute prepared by Dr Penny Carr [CGRA0000610] (p.2).

7.26. The meeting was called to examine infectious hazards of blood products in relation to hepatitis and AIDS, and in particular to hear from all manufacturers of products used in the UK about their efforts to mitigate these risks. As I recall, there were a number of meetings which took place discussing this topic, however, I think this was the only one in which all the manufacturers actually took part.

7.27. The meeting was 38 years ago and so I do not have any recollections of the meeting that go beyond the various records but looking at those records now ([MHRA0000076_018; CGRA0000610; PRSE0003071; WITN4461081] (pp.19-20)) there are no matters which I find surprising.

7.28. During this meeting, there was discussion of whether and when batches of factor concentrate should be recalled. The minutes recorded:

> *The general feeling of the meeting was that if the diagnosis of AIDS in a donor is definite, then products prepared from pools to which the donor had contributed should be withdrawn. If a donor is found to have symptoms and signs, such as lymphadenopathy, which were associated with incipient AIDS, but were neither diagnostic nor specific for the condition, the recall of material to which the subject had previously contributed plasma was not justified. It was recognised that the scientific rationale for this course of action left much to be desired, but that no other action could be taken which would not imperil the supply of Factor VIII* [PRSE0003071] (p.10).

7.29. The context of this was that the symptoms found in the donor were not diagnostic or specific for AIDS. The scientific rationale would be to assume that the donor might develop AIDS and hence the batch should be withdrawn. The course of action recommended, not to withdraw the batch on supply grounds,

could therefore have been regarded as leaving 'much to be desired' on scientific grounds.

7.30. My view at the time the course of action was taken was that this was a difficult but pragmatic decision, bearing in mind that these were essential and life-saving products for treatment of haemophilia.

7.31. The only possible alternative would have been to recall the batches. This would have been discussed and rejected for reasons indicated above.

7.32. I have seen Dr Penny Carr's note of the meeting in which she recorded that:

> *The four U.S. market withdrawals were discussed and we explained that we are all still making decisions on a case-by-case basis. The decisions were not being made based on scientific information but simply because of emotional and political considerations* [CGRA0000610] (p.6).

7.33. It is important to note Dr Penny Carr's comment that, '*decisions were not being made based on scientific information*' related to the four US withdrawals (of which I would have had no involvement). It was not (as suggested in the rule 9 letter I received) a comment on the overall discussion and conclusions. Had it been, I would have disagreed with the suggestion of 'emotional and political' considerations playing a role. Decisions on batch recall were made on a case-by-case basis, taking into account patients' safety and supply issues.

7.34. In comparing the accounts given in the draft minutes [PRSE0003071] (p.10) and Dr Penny Carr's minute about the discussion on pool sizes [CGRA0000610] (p.6), it was an accurate description that Dr Penny Carr and others (presumably the US fractionators) sought to persuade the rest of the meeting that small pool sizes would not provide greater safety. I agreed with the conclusions.

7.35. Dr Penny Carr also noted that Dr Joseph Smith summed up the discussion on laboratory test procedures with *'…practically no discussion at all'* [CGRA0000610] (p.7). I have no recollection of what Dr Joseph Smith actually said and whether this was a correct summary. It should be emphasised that this was Dr Carr's view, which may not have been entirely accurate. My surmise is that, as there were no laboratory tests which were diagnostic for AIDS at this time, there was nothing much to discuss.

7.36. I have no further comments that are relevant to the Inquiry's Terms of Reference on this meeting other than it was a very useful meeting.

NIBSC and the response to risk of infection

7.37. NIBSC's role in responding to the threat posed by AIDS infection through the use of blood products, from the period of the first indication of a potential risk to the introduction of heat-treated products, was twofold. First, NIBSC held meetings such as the one described in paragraph 7.25 above, in which manufacturers, Regulatory Authorities and scientists could present and discuss their latest information in an atmosphere of freedom and collaboration. Secondly, they provided scientific advice on viral inactivation methods and their assessment, both to manufacturers and the Licensing Authority.

7.38. I have been shown the minutes of a NIBSC Liaison Group on the Virological Aspects of the Safety of Blood Products meeting held on 2 May 1986 where it was discussed that all licensed immunoglobulins were to be prepared from plasma derived from screened donors by the end of June 1986 [DHSC0002345_017] (I also exhibit a summary of the same meeting in case it assists: [CBLA0002308]). This meeting was held to share information and where appropriate, scientific and technical resources among the plasma fractionation laboratories and NIBSC covering all aspects of virological safety. The initial focus was on LAV/HTLV-III (later known as HIV). Although I was at the meeting, I had no involvement in these discussions as immunoglobulins were handled by the Division of Immunology at NIBSC, which is where the scientific expertise lay. Nor can I comment on why June 1986 was selected although it should be noted that immunoglobulins were generally regarded as safe products with regard to transmission of HIV.

7.39. I have been shown a draft paper prepared by Dr Duncan Thomas in or around May 1986 [MHRA0028426]. Although I was not involved in the production of this paper, I am unsure if the date of May 1986 is correct. The paper mentions that there were only two possible cases of AIDS in the UK, whereas in the meeting of February 1984, there were two definite cases in the UK, and by May 1986 there would have been many more.

7.40. I have no knowledge of to whom the paper was circulated to and what actions, if any were taken. The only action which could have been taken earlier was by the Government investing in the upgrade of the factory at BPL. Screening blood donors earlier would not have been possible as the screening tests for HIV were not available at the time – as soon as they became available, they were introduced by the BTS.

7.41. I have been shown a letter dated 24 October 1986 from Dr Rotblat, the Senior Medical Officer within the DHSS, notifying Dr Duncan Thomas that seroconversions had occurred in Birmingham linked to Armour's Factorate product [MHRA0000078_002]. Deciding or taking any course of action on this matter would have been a matter for the Licensing Authority and not NIBSC.

7.42. I have been shown a letter from DHSS to Immuno Ltd dated 5 August 1987 where it sets out requirements for licence holders: '*…licence holders for blood products should be required to supply quality assurance and performance evaluation information on the screening procedures currently carried out for antibodies to HIV and for HBS antigen*' [MHRA0033319_041] and listing the required information. I believe these requirements were not enforced sooner than August 1987 because, in the case of anti-HIV tests, these tests had only recently become available. In the case of HBsAg, considerable experience had been gained by both manufacturers and control authorities and there was no reason to suspect that results were unreliable – it was just part of a general tightening up of scrutiny of the methodology and performance of the viral marker tests.

Section 8: Reduction of risk of infection associated with blood products

Viral inactivation and heat treatment

8.1. The process by which applications for heat-treated products (or products subjected to any other form of viral inactivation) were scrutinised and how those methods developed over time were a matter for the MCA / CSM and I do not know whether such applications were treated as new or abridged licence applications. I have seen a draft document entitled, 'Control Authority Batch

Release' produced in May 1993 which discusses the Council Directive 89/381/EEC in force at the time. The document relates to products which '*…derived from human blood or plasma*' and outlines the batch release process '*by a State laboratory or a designated laboratory*' [WITN6408012] (p.1). While the document does not highlight how the methods developed over time, it does highlight the procedure applicable in the early 90s in comparison to the method I have outlined in Section 3: Batch release procedure.

8.2. Neither I nor NIBSC had an official role in the scrutiny of such applications, however, some manufacturers did submit samples to NIBSC on an informal basis (as discussed at paragraph 5.23 above).

8.3. Batch release testing was performed on heat-treated products once they had acquired a product licence. This method did not apply to samples being supplied on a named patient basis unless such samples were submitted voluntarily by the manufacturer (discussed from paragraph 5.23 above).

8.4. The viral inactivation of blood products was a developing area of knowledge and manufacturers would have made their data available at scientific meetings and also informally to NIBSC at informal meetings and in telephone conversations. Manufacturers would have also had to provide information on viral inactivation to the Licensing Authority as part of their product licence applications.

8.5. I think that the Licensing Authority and the bodies that assisted it in the licensing process must have been reliant to a large extent on studies and information provided by manufacturers, since manufacturers were the only ones able to carry out and evaluate such studies (although, as I have said, I was not involved in this). I am sure the experienced assessors in the Licensing Authority would have been able to identify situations where the information supplied was inadequate.

8.6. In a SNBTS Briefing Paper on the Development of Heat Treatment of Coagulation Factors that I have seen, Dr Peter R Foster expressed his opinion on the obstacles in developing the heat treatment method, one of which was the '*inaccurate and laborious analytical methods for the measurement of factor VIII activity*' [PRSE0002291] (p.16). He referenced this as coming from an

article that Thomas Burton Loram Kirkwood and I co-authored entitled 'Standardization of Factor VIII I. Calibration of British Standards for Factor VIII Clotting Activity', published in November 1980 [SHPL0000769]. The phrase 'inaccurate and laborious' is an opinion of Dr Foster's, with which I do not agree, and is not expressed in the article referenced. The article describes differences among laboratories when assaying the same sample, but we analysed the reasons for this and proposed solutions. The assays were not inaccurate in themselves, and, far from being an obstacle to the development of heat treated products, they were essential in order to determine the extent of losses of Factor VIII activity after heat treatment. The term 'laborious' is a description from someone who was probably unfamiliar with the actual performance of such assays – people who were well practised in the assays would have not regarded them as particularly laborious.

8.7. The methods used to assess Factor VIII activity in heat-treated products were the same as those used for non-heat-treated products. There was some concern that heat treatment might induce changes in the Factor VIII molecule which could affect the various assay methods in different ways, but this proved unfounded, except with regard to one product.

8.8. By and large there was good agreement between the various methods used for assay of Factor VIII activity, with the exception of a difference between the results of 1-stage and 2-stage methods for some products. The assay methodology did not have any impact on the development of heat treatment.

8.9. I have been shown the minutes of a CSM(B) meeting I attended on 5 March 1986. I was sometimes invited to attend CSM(B) meetings (or parts of the meetings) to offer my expertise but I was not a routine attendee. In the minutes it was noted that, in relation to the concerns about potential transmission of HTLV-III by heat-treated Factor VIII, *'…there was insufficient evidence for action to be taken on any specific product'* [DHSC0001801] (p.3). The main concern about the safety of heat-treated products upon their introduction was whether or not the heat treatment was actually successful in eliminating HIV infectivity. Another concern was the possibility that heat treatment might introduce neoantigens, i.e. altered Factor VIII molecules, which could give rise to antibodies to Factor VIII in recipients. Clinical evidence of transmission of

HIV would have been required to take action on a specific product and then the batch concerned could have been withdrawn. I have no recollection of whether action was taken in relation to specific products. This would have been a matter for the Licensing Authority.

8.10. At the time, there were two possible cases of HTLV-III transmission in recipients of Armour's product and those people were being monitored. The surveillance would have been of their clinical symptoms, the point being that heat treatment might have killed the virus, but the 'dead' antigen might produce antibodies in recipients without the onset of clinical disease. I have no knowledge of whether or not the patients were told of their condition as this would have been a matter for the doctors treating them.

8.11. I have been shown a Factor VIII sample testing report entitled 'Examination of Samples and Protocols' [MHRA0000066]. The tests being performed by NIBSC on blood products for HTLV-III / LAV antibodies in 1986 were carried out by the Divisions of Virology and / or Retrovirology, and I have no detailed knowledge of the methods used.

8.12. I have been shown the June 1986 edition Lancet article co-authored by me titled, 'Factor VIII degradation products in heated concentrates' [SBTS0000330_101] and the September 1986 edition *Lancet* article authored by Morfini et al., which refers to my June 1986 article [SHPL0000075_017] (p.4). Given the pressing need for these products, the early findings relating to the possible protein degradation in heat-treated concentrates were uncertain and did not deter the use of heat-treated products in patients. To the best of my knowledge, I am sure that BPL, PFL and PFC were aware of the issue of protein degradation but I have no knowledge of whether this influenced their research and development of heat-treated concentrates.

8.13. I have been shown the report of a National Blood Transfusion Service ('NBTS') / NIBSC Technical and Scientific Working Group on Viral Contamination of Blood Products meeting I attended on 30 March 1988. The report refers to Dr Schild explaining that the reason the meeting was called was because of the '*...confusion that existed over the variety of different methods manufacturers were employing to remove or inactivate contaminating viruses*'

[SBTS0000371_040] (p.1). I think the use of the word 'confusion' is misleading. What Dr Schild was referring to was the wide variety of different methods used for virus inactivation, which was a consequence of the different manufacturing processes used.

8.14. The report also records in the general discussion that '*...several points were raised concerning the legal implications of producing a "less safe" product for patients who were already HIV-positive*' [SBTS0000371_040] (p.8). Although I have no recollection of what was discussed, Professor Bloom had referred to the undesirability of continuing to expose such patients to further doses of virus. He thought, however, that they could be treated with products which were reasonably safe, but for which full viral safety had yet to be demonstrated.

8.15. I have been shown the minutes of a BTS / NIBSC Working Group on Plasma Fractions meeting which I attended on 6 September 1988 [JPAC0000043_048] where the application of viral inactivation / removal steps during manufacture was discussed. Advice by NIBSC on the approach taken to validate the viral inactivation / removal during the licensing process was given by the Division of Virology under Dr Philip Minor. Although there were no recommendations made on the actual methodology of virus inactivation, it was recommended that an overall reduction of nine logs was desirable, with one step showing a reduction of at least five logs.

8.16. Licensing bodies, including NIBSC, had to rely on the information provided by manufacturers about viral inactivation/removal to a large extent, since manufacturers were the only ones able to carry out and evaluate such studies. As I have said above, I am sure the experienced assessors in the Licensing Authority, as well as scientists at NIBSC, would have been able to identify situations where the information supplied was inadequate.

8.17. Regarding the licensing of heat-treated products, at the time, there was a recognition of the urgent need for these products to reduce or eliminate the risk of HIV transmission.

8.18. Any changes in the level of scrutiny applied to the licence applications for heat-treated products, or the level of risk which was considered acceptable in relation to such products was a matter for the Licensing Authority, but to my knowledge,

the same level of scrutiny was applied to heat-treated products as to other products. The approach to balancing issues of safety with regard to other considerations in respect of licence applications for heat-treated products was also a matter for the Licensing Authority.

8.19. I have been shown a letter from the Co-ordinator of The Haemophilia Society to all Centre Directors and Transfusion Centre Directors dated 14 November 1984 [BART0002307], a letter from A. L. Bloom to Dr Alison Smithies, the Principal Medical Officer, dated 21 November 1984 [DHSC0001211] and a letter from M.E Duncan to Mr Sloggem of the Supplies Division dated 28 November 1984 [DHSC0002251_015] all discussing the beginning of using heat-treated products. The transition to using heat-treated products was a matter for the Licensing Authority, not NIBSC, nor were NIBSC involved in giving information to patients who had received non-heated blood products.

8.20. I also have no knowledge on the point in time from which the use of non-heated blood products should have ceased. I also have no knowledge of information that should have been given to patients who had received non-heat-treated blood products because NIBSC were not involved in giving information to patients.

Plasma pool testing

8.21. To my knowledge, NIBSC was the first National Control Laboratory in Europe to recommend and implement plasma pool screening. I did not play any role personally in introducing screening of plasma pools in the UK but I did fax a letter to Dr Andre Rejman at the Department of Health on 24 February 1993 attaching a document which was '*prepared in support of our case for plasma pool testing*' and which said, '*Nonetheless, testing of pools is justified at present because the screening of donors has only recently been introduced and it is therefore prudent to check on implementation of the use of screened plasma for fractionation. More sensitive tests may become available in due course*' [WITN6408013] (p.3). From my recollection, I do not think it could have been

introduced any earlier than it was, because of the lack of availability of testing methods for the infective virus.[1]

8.22. There was close co-operation between NIBSC and the BTS in relation to plasma pool screening via the BTS / NIBSC Liaison Committee and the various Working Groups which had been established in regard to the plasma pool screening.

8.23. I have been shown the report of a BTS / NIBSC committee meeting discussing the tests for viral contamination in blood products which I attended on 28 June 1988 [NHBT0007581]. At the time it was considered that '[*t*]*he main protection against virus contamination rests in the measures taken to select donors and screen the individual donations*' [NHBT0007581] (p.1). The meaning of this statement was that donor selection and tests of individual donations were the best way of minimising viral contamination in the plasma pools, rather than tests on the plasma pools.

8.24. The use of bulk plasma pools continued despite being aware of the inherent risks for two reasons. Firstly, the use of plasma pools was the only practicable way of manufacturing fractionated products. Secondly, by this time, virus inactivation methods had been introduced during the manufacture of blood products.

8.25. The size of the bulk plasma pool was to be identified during manufacture and a sample of it was to be sent to NIBSC for additional tests for HIV and hepatitis. This was because the size of the pool was relevant to the sensitivity of the tests. Samples were sent to NIBSC as a 'belt and braces' approach to ensuring that

[1] There were (obviously) lots of different tests that became available over the years (i.e. tests of blood, tests of plasma pools, tests of blood products, tests of virus inactivation methods and tests for HIV and Hepatitis C etc). I cannot recall when these were all introduced but just by way of some limited background on the theme of testing, I have exhibited the Minutes of the Second Meeting of the NIBSC AIDS Working Party on 23 January 1986 which I attended along with my NIBSC colleagues [MHRA0000074, pp.1-3]. This shows our team testing the commercial ELISA test kits using panels of reference sera and freeze-dried reference sera. Attempts were made at this stage to detect infection particles of what was then called HTLV-III/LAV (later HIV). I have also exhibited 'Programme of current and proposed future work on AIDS and human immunodeficiency virus (HIV) at NIBSC' which was undertaken by NIBSC as part of its role as a WHO Collaborating Centre on AIDS [WITN6408014]. The document is undated on its face but appears to be from 1986. It shows that work was ongoing at this time to develop and evaluate improved approaches for safety testing of blood products and the evaluation of manufacturing procedures in producing safe products.

plasma pools were negative for viral markers. I do not recall how many, if any, cases there were of plasma pools testing negative by manufacturers and positive by NIBSC.

8.26. The national working standard for testing plasma pools was that for HBsAg, and as such was the responsibility of the Division of Virology under Dr Philip Minor so I cannot comment on the reasons for any delay in producing that standard or its impact.

8.27. After BPL and PFC completed virus marker testing for HIV on their pooled blood products, NIBSC were sent samples from each product batch to complete further testing as part of the batch release procedure [PRSE0002556] (p.21).The HIV testing procedure undertaken by NIBSC on these samples, including what tests were used and the steps taken if a sample was found to be positive were carried out by the Division of Retrovirology and I have no knowledge of the technical procedures used (although I have offered some information uncovered in the course of preparing this statement at paragraph 8.36 below).

8.28. Before NIBSC completed their own testing, information such as the results of BPL's or PFC's virus marker test results would have been provided to NIBSC as part of the protocol submitted for the batch release procedure. I do not think that NIBSC's tests ever differed from those of the manufacturer, but if they did, the manufacturer and Licensing Authority would have been informed, and the batch would not have been released. Otherwise, manufacturers would know that NIBSC tests results were satisfactory by the fact that the batch was released.

8.29. NIBSC applied the same testing for HIV markers on plasma pools and final products for all manufacturers with a product licence. I do not believe NIBSC carried out testing for anyone else.

8.30. I have been shown the minutes of a BTS / NIBSC Plasma Fractions Committee meeting I attended on 12 September 1991 where the use of unconfirmed HCV positive plasma donations was discussed and it was concluded that:

> *...a consistent and defensible position was to recommend that these unconfirmed positive donations not be used for fractionation for reasons*

> *of both operational and legal significance: the scientific arguments were seen as relatively marginal in the absence of more data on this group of donations* [NHBT0007614] (p.2).

8.31. The scientific arguments were the fact that the confirmatory tests were negative on these donations which meant that they were probably non-infectious, but one could not be absolutely sure. The scientific arguments were seen as relatively marginal at the time for two reasons. First, the fact that the confirmatory tests were negative meant that the infectious load from these donations, if any, was very low. Secondly, the virus inactivation procedures in place would have been able to remove this low load of infectious virus during manufacture.

8.32. My understanding of the operational matters was that I think they would have involved the safety of the manufacturing staff with respect to handling potentially HIV positive plasma donations. Legally, I imagine the manufacturers would have been open to criticism if they had included donations which were potentially HIV positive, despite the lack of confirmation and the presence of viral inactivation procedures. There were also the practical issues that the number of such donations was low, and the withholding of these donations by the BTS had minimal impact on the supply of plasma for fractionation.

8.33. As I mentioned earlier (paragraph 4.18 above), I have been shown a paper which I co-authored entitled, 'Testing of Blood Products & Plasma Pools for Viral Markers – NIBSC Experience From 1986-1993'. We concluded:

> *In the [sic] view of the above results, and the concerns that the European public has about safety of blood products, we feel that control authority testing for viral markers should be mandatory as part of the European batch release procedure for blood products* [DHSC0006465_037] (p.2).

8.34. I have also been shown a Vox Sanguinis article entitled, 'Testing Plasma Pools for Markers of Viral Contamination: The UK Experience' which I co-authored in 1996. We wrote:

> *Plasma pools from which licensed blood products used in the UK are derived, which may contain as many as 20,000 donations, are tested for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV) and human immunodeficiency virus 1 and 2 (anti –HIV-1 and 2) to ensure that there has been no breakdown in donor screening as a*

result of administrative or human error [RLIT0000145] (p.1).

8.35. We also observed that '*For HBsAg, the 'sensitivity' of assays, i.e. the ability of a kit to detect low concentrations of antigen, has improved considerably in recent years*' [RLIT0000145] (p.2).

8.36. Although I have no recollection of this now, Table 1 of that article shows the test kits in use at NIBSC at that time:

Table 1. Test kits in use at NIBSC

Viral Marker	Screening test	Confirmatory/supplementary tests
HBsAg	Wellcozyme HBsAg (VK21) Murex HBsAg (GE14/15/16)	Wellcozyme HBsAg confirmatory kit (VK25) Murex HBsAg confirmatory kit (GE17)
Anti-HCV	Sanofi Pasteur Monolisa anti-HCV (new antigens 72307)	Chiron RIBA 3.0
Anti-HIV-1/2	Abbott HIV 1/HIV 2 (3rd generation) Plus or Wellcozyme EIA (VK54/55)	(1) Wellcozyme or Abbott EIA (depending on assay used in initial screen) (2) Serodia (Fujirebio) HIV-1/HIV-2 particle agglutination test (3) Cambridge Biotech HIV-1 Western blot kit (4) Sanofi-Pasteur HIV-2 Western blot kit

Other kits are suitable for the assay of plasma pools and blood products but have not been evaluated for use at NIBSC. NIBSC may use alternative assay kits after appropriate evaluation.

8.37. Even having re-read these two articles, in regard to the extent to which the accuracy of plasma pool screening was impacted by the availability or sensitivity of testing kits, I have no knowledge on the availability of different kits testing for the same marker and the impact of those kits on the accuracy of the tests as this was outside my area of expertise. I left such matters to the virologists.

8.38. Regarding sensitivity, clearly there would be an impact of the pool size on the results. We also wrote, *'It is possible that the treatment of pools during the production process, e.g. by freeze/thawing or the presence of inhibitory factors, may have reduced the sensitivity of the PCR tests'* [RLIT0000145] (p.5).

8.39. At the time, combined testing by manufacturers and NIBSC would have identified all plasma pools which were positive by the test methods used, but because of the nature and sensitivity of the tests, it could not be guaranteed that all plasma pools were completely free of an infectious virus. Negative

screening tests did not guarantee that all plasma pools were completely free of infectious viruses, but it meant that the virus load, if any, was very small, and this would easily be dealt with by the virus inactivation methods used.

8.40. Plasma pool testing was valuable in avoiding the use of potentially infectious starting material, but was subject to limitations of sensitivity, as indicated above in paragraph 8.38. By comparison, final product testing was less useful because of the nature of the tests used and the composition of the products. For instance, tests for antibodies to HIV and hepatitis C would be negative on most products because of the absence of, or very low levels of, IgG. The only way to test for potentially infective virus in final products was by the use of PCR testing, which came later.

8.41. I wrote a letter dated 24 May 1993 to Dr J. Purves at the MCA stating my comments on a letter Dr Terry Snape had sent on 5 May 1993 [MHRA0000112_001] '*concerning the retrospective finding that a single HCV positive donation was one of over 23,000 donations in a plasma pool used to manufacture a number of products at BPL…*' [MHRA0000117_001] (p.1). Within my response, I stated,

> *(i) it is clear that the products do not meet the EC Guidelines on the screening of blood donations for the manufacturer of blood products, ie the requirement that from 1 January 1993 all products should be made exclusively from donations tested and found negative for anti-HCV.*
>
> …
>
> *The use of products derived from this pool could be considered as historically analogous to the pre-1993 situation before hepatitis C screening became mandatory* [MHRA0000117_001] (pp.1-2).

Retrospective identification

8.42. The issue of retrospective identification rarely arose. I have been asked about the following times when it did and the discussions that ensued.

8.43. I have been referred to the minutes of a BTS / NIBSC Plasma Fractions Committee meeting that I chaired in September 1993 and I can see that batch recall for hepatitis C in plasma donations was discussed [NHBT0007457] (pp.4 - 5). In situations where retesting of plasma donations had identified anti-HCV in donations previously found to be negative and issued for fractionation, the

general view was that although the compromised batches did not constitute a health hazard, there was reluctance to authorise their release.

8.44. Following one such instance of retrospective identification in May 1993, the position taken was that there was *'...no scientific reason for withholding the products question on safety grounds or for recalling those already released'* [MHRA0000007_004] (p.1).

8.45. I have also been shown the draft minutes of a meeting held by the MCA on 10 June 1993 *'... to discuss BPL blood products compromised by hepatitis C Positive donation'*. This was the issue that I mentioned which gave rise to my correspondence with Dr Purves at paragraph 8.41 above. The meeting was attended by representatives from the MCA, NIBSC and the CSM(B). The draft minutes showed that my NIBSC colleague *'Dr [Philip] Minor held "the strong opinion that retrospective identification of a contaminated donation should automatically necessitate withdrawal of product but the general view of the Meeting was that screening had been introduced to control the initial viral load and not necessarily to guarantee absolute safety. This is ultimately achieved by subsequent viral inactivation procedures in the manufacturing process...the inactivation methods used by BPL would more than adequately cope with this level of contamination'* [MHRA0000007_004] (p.1).

8.46. At the time, it was considered that viral inactivation procedures in place were sufficient to deal with the load of infectious virus represented by one or two contaminated donations in a large plasma pool (over 20,000 donations – the minutes show one in 21,000 or 23,000). Evidence for this was that no transmission of hepatitis C had been observed from virus inactivated products prepared from plasma pools before hepatitis C screening had been introduced: the level of hepatitis C virus in such pools would certainly have been much higher.

8.47. While I am sure it was difficult to balance the many factors that may have affected the decision to withdraw, product withdrawal itself could be a safety issue for patients because of the shortage or lack of availability in alternative products. Among the factors that had to be balanced were the unknown risk of infection against the known risk presented by a lack of available products.

8.48. At the time, the European Commission ('EC') Guidelines on the screening of blood donations for the manufacture of blood products were in force (namely the 'CPMP' Guidelines) and from 1 January 1993, all blood products were required to have been made '*...exclusively from donations tested and found negative for anti-HCV*' [MHRA0000117_001] (p.1). As the blood products by BPL were in breach of these Guidelines, BPL requested for an exemption [MHRA0000121; MHRA0000007_010; MHRA0000112_001; MHRA0000123 and MHRA0000007_012].

8.49. I have been shown a letter from J. Craske, Consultant Virologist at the Public Health Laboratory Service dated 12 May 1993, to Dr. E. M. Love, a Consultant Haematologist at the NBTS regarding a report on the positive results on two specimens which were tested for the hepatitis C antibody [MHRA0000007_015]. I had not seen this letter before and, as I have no scientific knowledge of this area, I cannot comment on its contents.

8.50. I have been shown a letter I sent to Dr John Purves, MCA, on 18 May 1993 where the safety of Factor VIII, 8SM (as well as other products) were discussed. I can see that despite noting that the release of FVIII and IgG products would contravene the CPMP Guideline, '*...the weight of evidence suggests that these products are clinically safe*' [MHRA0000116]. The ultimate decision would have been made by the MCA and would probably have relied on robust virus inactivation procedures in place to ensure the products' safety.

8.51. In the 1992 CSM(B) Position Paper on Screening of Blood Donations and Blood Products for Infectious Agents, it was proposed that the Licensing Authority decide for each product licence application whether it would need to be informed of cases of retrospective identification where no recall was made [MHRA0000104] (p.10). At the BTS / NIBSC Plasma Fractions Committee Meeting in September 1993, it was noted that *'Both BPL and PFC wish to be able to make the decision themselves re release of a product...based on agreed written guidelines on viral safety...'* [NHBT0007457] (p.5).

8.52. The scope for decision making by manufacturers on release or recall following retrospective identification, within the operative viral safety guidelines, and whether this differed between UK public fractionators and commercial

manufacturers was a matter for discussion between the manufacturers, both public and commercial, and the Licensing Authority.

8.53. The decision whether any manufacturers' decisions regarding product release or recall could be reviewed and / or approved by NIBSC, the MCA or other relevant bodies would have rested between the manufacturer and the Licensing Authority. I think that the Licensing Authority would have had the ultimate say. NIBSC would have been kept informed. These situations were rare.

8.54. I have no knowledge on the position the Licensing Authority adopted regarding notification by manufacturers in the event that no recall was made.

8.55. NIBSC were not involved in informing patients who had been given, or might be given, a blood product containing a contaminated donation. This would have been a matter for the doctors treating them.

Section 9: Clinical trials

9.1. NIBSC played no role in organising, participating in or monitoring clinical trials (and neither did I). Nor did we have any involvement in scrutinising applications made under the Medicines (Exemptions from Licences) (Clinical Trials) Order.

Section 10: Other issues

10.1. Looking back at the events of the 1970s, 1980s and 1990s, I believe the system for licensing blood products for use in the UK was robust and thorough, including the scrutiny of product licence applications by the Licensing Authority as well as the operation of the batch release process by NIBSC.

10.2. I do not think there were any specific weaknesses, except perhaps the existence of loopholes allowing the use of unlicensed products. From informal discussions with manufacturers, the system in the UK was regarded as the most stringent in the world, and NIBSC batch release certificates were highly valued.

10.3. In regard to how the named patient process was used during this period, I recognise the thinking behind the process, namely to allow the use of new products which had not yet reached the product licence stage, for the clinical

benefit of patients. However I think it was overused, particularly when it continued to be used after a product licence had been granted.

10.4. NIBSC made a significant contribution to the system for licensing blood products for use in the UK, both in the operation of the batch release procedure and the provision of scientific advice. '*NIBSC is also the first such laboratory to achieve international accreditation for its control testing quality system*' [DHSC0043012_057] (p.3). The only area where perhaps it could have been more effective was in the provision of information and test samples by manufacturers to NIBSC in conjunction with product licence applications, i.e. before the licences were granted.

10.5. Other parts of the licensing regime also made an effective contribution to the system for licensing blood products for use in the UK i.e. the Licensing Authority and it is difficult to think of how this could have been more effective. After I became Head of Division, I did get to know the Licensing Authority team and I was impressed by their knowledge and thoroughness.

10.6. I have no knowledge of the exact timelines for the introduction of virus marking testing and licensing of virus inactivated products. However my impression is that, once the hazards of HIV and hepatitis C infection became known, the Government responded in a timely and effective manner by the rapid introduction of tests for HIV and hepatitis C by the Blood Transfusion Service when they became available, and the licensing of virus-inactivated products. However, where the Government could have acted earlier was in the provision of investment to expand the manufacturing facilities at BPL, in order to bring forward the date by which the UK could become self-sufficient in blood products, thereby avoiding reliance on expensive and potentially infectious imports.

10.7. While no doubt more learning will arise from this Inquiry, I think many of the lessons regarding the potential transmission of viruses to haemophiliacs have been well and truly learnt. This includes the application of screening tests to blood and plasma donations, robust viral inactivation techniques, together with the availability of recombinant products which taken altogether ensures that the

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products which haemophiliacs now receive are as safe as possible with regard to virus transmission.

10.8. Given the state of knowledge about HIV and hepatitis C, the lack of availability of tests for infectious virus, and the supply situation, particularly with regard to the use of American products derived from paid donor plasma, I think that the infection of haemophiliacs by HIV and hepatitis C was a tragedy for which, in my experience at least, no one organisation or individual is to blame. The only action which might have reduced the impact of virus infection would have been earlier investment by the Government in expansion of the factory at BPL, which would have led to less reliance on imported commercial products.

Statement of Truth

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

Signed GRO-C

Dated 9th August 2022