Witness Name: Sir Michael Rawlins
Statement No.: WITN6406001
Exhibits: WITN6406002-WITN6406036
Dated: 24-03-2022

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF SIR MICHAEL RAWLINS

I, Sir Michael Rawlins, will say as follows: -

Section 1: Contents

Section 1: Introduction

1.1. My full name and title is Professor Sir Michael David Rawlins GBE, Kt, MD, FRCP (London), FRCP (Ed), FMedSci. I have provided my date of birth and home address to the Infected Blood Inquiry ('the Inquiry').

1.2. I offer this draft statement in response to a Rule 9 Request made by the Infected Blood Inquiry dated 27 July 2021. I have adopted the subtitles contained in the Rule 9 Request, adding some further subtitles where I feel it assists.

1.3. I can confirm that I have not been involved in any other inquiries, investigations, civil or criminal litigation in relation to human immunodeficiency virus, and / or hepatitis B virus, and / or variant Creutzfeldt-Jacob disease, and / or blood products. I have been reminded by the documents I have seen that I did provide an affidavit in a High Court case involving the product licence and clinical trial certificates for an anti-depressant called Bolvidon but I do not think that this will assist the Inquiry. The affidavit concerned issues relevant to the assessment of the haematological adverse reactions of the drug Mianserin, its risks and benefits, as well as the restrictions on its use which were being proposed by the Licensing Authority.

Section 2: Opening Comments

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

2.2. I should state at the outset that, although I have no direct personal experience of caring for patients with haemophilia, I am very conscious of the suffering experienced by patients and their families as a result of the administration of infected blood.

2.3. In preparing my response I have depended heavily on a large number of documents forwarded to me by the Government Legal Department. I am also aware that it is possible that other relevant documents may emerge during the

course of the inquiry and I would be more than happy to examine these too. In providing my response I have also depended on my own recollections. As I am sure the Inquiry will appreciate, however, many of the most relevant events occurred 30 to 40 years ago and, as a consequence, my recollections are incomplete. Moreover, I have myself retained no documents relating to my time as a member, vice-chair or chair of the CSM.

Section 3: Professional and Employment History

Professional Qualifications

3.1. The following table outlines my professional qualifications:

Table 1 – My Qualifications

Date	Qualification and Institution
1962	BSc (First Class Honours) University of London
1965	MB BS (Honours) University of London
1968	Member Royal College of Physicians of London
1973	MD University of London
1977	Fellow Royal College of Physicians of London
1987	Fellow Royal College of Physicians of Edinburgh
1989	Fellow Faculty of Pharmaceutical Medicine
1998	Fellow Academy of Medical Sciences

3.2. The following table outlines my employment history:

Table 2 – Employment History

Date	Position	Institution
1966	House physician	St Thomas' Hospital, London

Date	Position	Institution
1967	House surgeon	Queen Elizabeth Hospital, Portsmouth
1967	Senior house officer (Neurology)	St Thomas' Hospital, London
1967	Senior house officer	Brompton Hospital, London
1968-1970	Lecturer in Medicine	St Thomas' Hospital Medical School, London
1970-1972	Senior registrar (clinical pharmacology)	Royal Postgraduate Medical School, London
1972-1973	MRC Travelling Fellowship	Karolinska Institute, Stockholm, Sweden
1973-2006	Ruth and Lionel Jacobson Professor of Clinical Pharmacology	University of Newcastle upon Tyne
1977-2006	Honorary Consultant, Clinical Pharmacology and General Medicine	Freeman Hospital, Newcastle upon Tyne

3.3. The following table outlines the positions I have held that are or may be relevant to the Inquiry:

Table 3 – Positions Held

Date	Position	Committee, Council or Agency
1979-1980	Member	Toxicity and Clinical Trials Subcommittee, Committee on Safety of Medicines (CSM)
1980-1992	Member	Safety, Efficacy and Adverse Reactions (SEAR) Subcommittee
1980-1992	Member	Adverse Reaction Group of SEAR (ARGOS)
1980-1986	Member	CSM
1987-1992	Vice-chair	CSM
1993-1998	Chair	CSM

Date	Position	Committee, Council or Agency
c.1996	Member	Royal College of Physicians' Committee on Ethical Issues in Medicine
1998-2008	Chair	Advisory Council on the Misuse of Drugs
1999-2013	Chair	National Institute for Clinical Excellence (now the National Institute for Health and Care Excellence)
2015-2020	Chair	Medicines and Healthcare products Regulatory Agency (MHRA)

3.4. In addition to the positions above, I was also the chair of the Newcastle District Drug and Therapeutics Committee in and around 1984. I am afraid that I cannot recall the exact dates of my appointment.

3.5. Please note that I continued in my role as Professor of Clinical Pharmacology in the Department of Pharmacological Science at the University of Newcastle throughout my time as a member, vice-chair and the chair of the CSM as the latter were not full-time positions.

3.6. I have offered more detail on the CSM from paragraph 4.1 but, first, have set out the details of those roles I held after leaving the CSM and which touch on possible areas of interest to the Inquiry. I suspect, though, that these are less likely to be of relevance:

Advisory Council on the Misuse of Drugs

3.7. In 1998, I was appointed chair of the Advisory Council on the Misuse of Drugs. This body was established under the Misuse of Drugs Act 1971 to advise Home Office ministers on various aspects of the control drugs of abuse. It played no role in the regulation of biological substances and does not therefore appear to me to be of any relevance to the Inquiry.

National Institute for Clinical Excellence

3.8. I chaired the National Institute for Clinical Excellence (now the National Institute for Health and Care Excellence) from 1999 to 2013. NICE is primarily responsible for producing evidence-based guidance and advice for healthcare

practitioners, public health practitioners and social care practitioners. It has no role in the licensing of either medicines or medical devices. Although it has published guidelines on various aspects of the management of haemophilia and AIDS, to the best of my knowledge, none have concerned the use of blood products.

3.9. My role as the chair of NICE was to chair board meetings, help develop strategy and provide informal advice to the CEO and members of the Senior Management Team. I also acted as an ambassador for NICE, nationally and internationally, explaining what we did, why we did it, and how we did it. I do not anticipate that this role will be of relevance to the Inquiry.

Medicines and Healthcare products Regulatory Agency (MHRA)

3.10. I was appointed non-executive chair of the MHRA in November 2014, reappointed in 2017 and demitted office in 2020 when my two three-year terms of appointment had expired. My responsibilities include chairing meetings of the Board, contributing to the development of the Agency's strategy, holding the executives to account, monitoring the Agency's 'key performance indicators' and meeting with relevant outside organisations to discuss the Agency's work.

Section 4: Licensing process in general, including the role of the CSM

4.1. The broad principles of the licensing process during the 1970s and 1980s were similar for biological materials and small chemicals.

The Licensing Authority

4.2. The 'Licensing Authority' was established by the Medicines Act 1968 and comprised the Secretaries of State for Health and Agriculture with their Scottish, Welsh and Northern Ireland counterparts acting jointly. The Medicines Act provided that medicines (including blood products) had to be licensed before

being allowed onto the UK market (although please see paragraph 13.7 below and Section 18: about 'named patient basis' prescription of unlicensed products).

4.3. The Licensing Authority was the term used to describe the ministers with ultimate responsibility for granting, renewing, varying, suspending or revoking product licences. Because I was not part of the Licensing Authority myself, my knowledge of the ministers' activities is limited but I think it is correct to say that they did not have regular meetings in the same way as the CSM did and instead would deal with matters on an ad hoc basis and primarily by way of Ministerial Submissions. I also understand that much of the ministers' work was delegated to the Medicines Division (see **[MHRA0004773** (page 8)**]**).

4.4. As far as I can recall, all discussions with the Licensing Authority were conducted through the Secretariat and staff of the Medicines Division (and later with the Medicines Control Agency). There was no direct interaction between the Licensing Authority and the CSM.

The Medicines Division

4.5. The Medicines Division was part of the Department of Health and had the ultimate responsibility for advising the Licensing Authority on the exercise of its powers. The Medicines Division included medical staff, pharmaceutical staff as well as administrative staff. Among their other responsibilities, the Medicines Division secretariat acted as the Secretariat for the CSM, prepared papers for meetings of the CSM and its subcommittees, ensured their timely distribution to committee and subcommittee members, and prepared the minutes of committee and subcommittee meetings. The Secretariat provided professional assessors who would assess and advise the CSM and its subcommittees on the licence applications that were received. There would usually be a pharmaceutical assessor and / or a medical assessor who would consider and assess the product licence application and provide us with a report. In July 1977, the Department of Health and Social Security's Medicines Division published 'The Control of Medicines in the United Kingdom' **[MHRA0004773** (page 9)**]** which describes this process saying:

> *New applications for product licences and clinical trial certificates are assessed jointly by a doctor and a pharmacist. A summary of the evaluation is submitted to the appropriate Section 4 committee to assist members to formulate their advice to the licensing authority. The Division provides both the professional and the administrative secretariat of these Committees.*

4.6. The staff of the Medicines Division were then responsible for taking action on the CSM's advice.

4.7. As already indicated, the Medicines Division of the Department of Health provided the Secretariat for the CSM and its subcommittees, and was the sole means of communication between the Committee and the Licensing Authority. The CSM did not deal with the ministers directly but passed on our recommendations through the Secretariat.

4.8. In respect of adverse reactions monitoring, 'The Control of Medicines in the United Kingdom' **[MHRA0004773** (page 9)**]** recorded:

> *The Division provides staff, who work under the direction of the Committee on Safety of Medicines and its Adverse Reactions Sub-Committee in particular, to monitor adverse reactions to medicinal products. Four doctors are engaged on this work full-time, assisted by 80 part-time doctors distributed around the country, who follow up selected reports and can undertake special inquiries.*

The Medicines Control Agency

4.9. In April 1989, the Medicines Control Agency ('MCA') was established. The functions of the Health Ministers under the Medicines Act were discharged on their behalf by the MCA acting as the executive arm of government which regulated the pharmaceutical sector and implemented policy. As already discussed, prior to its establishment, its role was carried out by the Medicines Division.

4.10. The MCA's primary objective was to safeguard public health by ensuring that all the medicines on the UK market met appropriate standards of safety, quality and efficacy. It was composed of medical, pharmaceutical, dental, scientific,

legal and administrative staff. Its main functions were to carry out the work of the Licensing Authority, to monitor adverse drug reactions, to act as the enforcement authority and to follow up reports of defective batches of medicines and issue any necessary warnings. It did this through the work of the CSM and other committees.

The Medicines Commission

4.11. The Medicines Commission was established in 1969 by the Medicines Act 1968. Its functions and roles are fully described in the 'The Control of Medicines in the United Kingdom' at paragraphs 10-11 **[MHRA0004773]**. In essence, the Medicines Commission comprised a body of experts who advised ministers on topics relating to the Medicines Act and medicines in general. Among its other responsibilities, it was responsible for recommending the constitution and functions of Medicines Act committees and recommending who should serve on them.

4.12. I had little direct contact with the Commission apart from the fact that companies whose applications had been rejected by the CSM were permitted to make an appeal to the Commission either in writing or in person. As chair of the CSM I was invited to attend meetings when companies were making appeals against the CSM's advice. In the late 1980s and early 1990s, the appellate process could take two years or longer while the applicant reviewed the original data and assembled new information **[WITN6406002].**

Section 5: Committee on Safety of Medicines

5.1. The Committee on Safety of Medicines ('CSM') was a committee of the Medicines Commission and was established in 1970 pursuant to section 4 of the Medicines Act 1968. It replaced the Committee on Safety of Drugs which had been set up in 1963 following the Thalidomide disaster. Its Terms of Reference were:

> *To give advice with respect to safety, quality and efficacy in relation to human use of any substance or article (not being an instrument,*

apparatus or appliance) to which any provision of the Medicines Act 1968 is applicable.

To promote the collection and investigation of information relating to adverse reactions for the purpose of enabling such advice to be given.[1]

5.2. The CSM's role, broadly, was to advise the Licensing Authority on the quality, safety and efficacy of new and existing medicines used to treat or prevent human disease. Its work was solely advisory. As I describe further below, the CSM's subcommittees would analyse the detail of the applications (and there was some overlap between membership of subcommittees and the CSM) before the CSM would hold meetings to consider the applications and make a recommendation to the Licensing Authority.

5.3. The CSM comprised independent experts from throughout the UK who covered various specialities in the medical, scientific and pharmaceutical fields. The members were appointed by the UK Health Ministers on the advice of the chair of the CSM. The CSM would receive applications for product licences which would be examined and then it would make recommendations as to whether a licence should be granted, withheld or varied. I commented in a presentation in 1990 (discussed further below, in particular at paragraph 7.20) that the CSM's view was 'invariably accepted' by the Licensing Authority **[WITN6406004]** and this remains my impression from the time I was on the CSM.

5.4. In collaboration with the Medicines Control Agency, the CSM also oversaw the Yellow Card system (described from paragraph 13.5 below) and publication of 'Current Problems'. Current Problems was a news bulletin published three or four times per year which provided information on the adverse effect of medicines. It was distributed to doctors, dentists, coroners and pharmacists (see **[WITN6406005]**). When I was chair of the CSM, I was also on the Editorial Board of Current Problems though I cannot recall if I took this role on before my promotion to being chair.

[1] As quoted in the CSM's Annual Report for 1990: **[WITN6406003].**

Structural changes to the CSM Subcommittees and my own career on the CSM

5.5. I first became involved in the CSM in 1979 at which time there were six subcommittees **[MHRA0004773** (page 7)**]**:

a) Toxicity Clinical Trials and Therapeutic Efficacy which considered the medical and biological data on licensing applications;

b) Biologicals which considered licence applications for immunological and blood products, some enzymes, hormones and antibiotics;

c) Adverse drug reactions which advised on the collection and evaluation of reports of adverse reactions to drugs;

d) Chemistry, Pharmacy and Standards which considered the pharmaceutical aspects of allopathic licence applications;

e) Standards of Herbal Products which considered the quality of herbal medicines; and

f) Anti-Microbial Substances which advised on the use of antibiotics and related substances in humans, animals and for food preservation or other purposes.

5.6. I was invited to join the Toxicity and Clinical Trials Subcommittee. This subcommittee advised the CSM on the safety and efficacy of new and existing medicines. It did not consider biological products (such as Factor VIII) which were the responsibility of the CSM's Biological and Vaccines Subcommittee ('Biologicals Subcommittee' – this is often referred to as the CSM(B) in the documents).

5.7. I was invited to join the CSM itself in 1980 at around the same time as the decision was taken to 'slim down' the subcommittee structure. The Toxicity and Clinical Trials Subcommittee was merged with the Adverse Drug Reactions subcommittee to form the Safety, Efficacy and Adverse Reactions subcommittee (SEAR) to which I was also appointed. In addition, a small

number of the members of SEAR met monthly to review 'yellow card' reports of suspected adverse drug reactions. This subgroup was known as the Adverse Reaction Group of SEAR (or ARGOS) which again I was invited to join (an offer which I accepted).

5.8. The revised subcommittee structure also included the Biologicals Subcommittee as well as the Chemistry, Pharmacy and Standards subcommittee. I do not recall what happened to either the Standards of Herbal Products subcommittee, or the Anti-Microbial subcommittees and have no memory of either being in existence during the time I was a member, vice-chair or chair of the CSM.

5.9. I continued as a CSM committee member (1980-1986) before becoming the vice-chair (1987-1992) and then the chair (1993-1998).

5.10. Sometime during the 1990s, further changes were made to the subcommittee structure with the establishment of the Pharmacovigilance Subcommittee. By 1995, there were four subcommittees:

a) Safety and Efficacy Subcommittee;

b) Biological Subcommittee;

c) Chemistry, Pharmacy and Standards Subcommittee; and

d) Pharmacovigilance Subcommittee (see **[WITN6406006]**).

5.11. When I left the CSM in 1998, there was no longer a subcommittee on Safety and Efficacy; this was subsumed into the main Committee. There were only three remaining subcommittees (see for example **[WITN6406007]**). I ceased all involvement with the CSM at the end of 1998.

Changes to the CSM working practices during my career

5.12. During the 1990s, timescales on the work carried out by the CSM were introduced by new regulatory systems, in particular a change in the European system for marketing authorisations (product licences) and new time scales under which the EC centralised and mutual recognition procedures were

required to operate. This meant that there was pressure on the CSM and its workload increased. We therefore changed the operation of the CSM by enlarging the CSM's membership and pairing its members so that there would be, for example, two psychiatrists, two paediatricians etc, who would attend alternate meetings (see **[MHRA0014544** (page 2)**]**). These changes that took place in early 1996 are described in a copy of Agency Press from March 1996 **[WITN6406008]**. (This contains an article written by Leslie Whitbread, the Secretary to the CSM, where he recorded how from January 1996 the CSM increased its monthly meetings to fortnightly and had taken on more members raising the total to 30 members of whom 18-20 would be present at each meeting under the pairing system including a core membership of ten members who would attend every meeting.) We also increased the number of external expert assessors and these external experts might be drafted in to attend meetings.

5.13. Other than these changes and those described at paragraph 5.10 above, I do not recall any further changes to the structure of the licensing regime.

CSM interactions with other bodies

NIBSC

5.14. The National Institute for Biological Standards and Control (NIBSC) was established under the Biological Standards Act 1975 to secure high standards of safety, quality and efficacy, as well as consistency of biological substances used in medicines. It would devise potency yardsticks and carry out batch tests of biological products among other work.

5.15. I have no recollection of any interactions between either the CSM or its subcommittees and NIBSC. I understand now that there would have been liaison between NIBSC and the Biologicals Subcommittee but this was not a subcommittee on which I served. I can see from the documents that there would also have been interaction between the CSM and NIBSC, not least because of the batch release procedure which I discuss below, but I have no

recollection of it. Although I feel it is likely that I must have been aware of NIBSC when I was on the CSM (I have seen that references to NIBSC feature in CSM minutes), I have no recollection of this now and it was only when I became chair of the MHRA (in 2015) that I felt that I became aware of the important work NIBSC does.

European Medicines Agency and the Committee for Proprietary Medicinal Products

5.16. As far as I recollect, during my chairmanship of the CSM the European Medicines Agency ('EMA') / European Medicines Evaluation Agency ('EMEA') / Committee for Proprietary Medicinal Products ('CPMP') was concerned with developing guidelines for the use of individual Member States' drug regulatory bodies. The European licensing system later included a centralised system, which provided marketing authorisation (i.e. product licences) in order to market products in all EU Member States, and a decentralised system, in which the marketing authorisation of one national authority would be recognised by all other Member States. The centralised system was administered by the EMA which used experts from nominated Member States to conduct the detailed scientific work. Meanwhile, all Member States could input into licensing decisions through the CPMP who would then make a recommendation to the European Commission. The CPMP would also arbitrate in cases where there was a differing opinion under the centralised or decentralised systems. Pharmacovigilance (the monitoring of a medicinal product on the market), inspection and enforcement activities remained the responsibility of individual Member States.

5.17. As far as I recall, the CSM had little involvement with either of these two bodies because our focus was on UK licensing. The CSM would be consulted by UK CPMP delegates before discussing issues at the CPMP but if there was not time before a CPMP meeting, one or two CSM experts would usually attend the CPMP meeting (**[MHRA0014544** (page 3)**]**). I note from the documents I have been shown (**[MHRA0014826** (page 2)**]**) that the CSM would consider applications to the CPMP and would comment on CPMP draft guidelines but I have little recollection of this now. During the 1990s, it became increasingly

apparent to me that the EU was moving in the direction of harmonising the regulation of medicines across the Member States.

Committee on the Review of Medicines

5.18. The Committee on the Review of Medicines was set up in 1975 to advise ministers on the general review of safety, quality and efficacy of products already on the market **[MHRA0004773** (page 7)**].** This can be contrasted with the CSM which was interested in new products coming on the market. When the Medicines Act came into force there were many hundreds (possibly thousands) of products already on the market. These (or rather their manufacturers) were granted Product Licences of Right ('PLR') which could then be converted to full Product Licences if considered to be satisfactory in relation to quality, safety and efficacy by the Committee on the Review of Medicines ('CRM').

5.19. The CRM had four subcommittees:

a) Anti-rheumatic agents;

b) Analgesics;

c) Psychotropics; and

d) Immunologicals.

5.20. As far as I remember there was no direct interaction between the CRM and the CSM except in those instances where there appeared to be significant new safety issues with a particular PLR. I can see from the document setting out the Control of Medicines in the United Kingdom **[MHRA0004773** (page 8)**]** that the CSM and CRM agreed on mutual access to one another's subcommittees. While I do not personally recall this, it appears from this document that the members of the Biologicals Subcommittee were also appointed to the CRM's Immunologicals subcommittee.

Section 6: Product Licence Applications

6.1. In this statement, I have focussed on applications for product licences although the CSM did also consider manufacturers licences and clinical trial applications.

6.2. After the introduction of the licensing regime in 1971, medicines in the UK could not be imported, marketed or manufactured, except in accordance with a product licence (see **[MHRA0004773** (page 12)**]**).

6.3. In order to apply for a product licence, a product manufacturer would need to make an application which would be referred to the appropriate subcommittee for advice on safety, quality and efficacy. From April 1989, licence fees were introduced **[MHRA0014776** (page 2)**].** Significant information was required to support a licence application and (while I have little recollection of this now) I can see from the documents that this included the following (and see for example **[CBLA0000272]**):

a) Name of product;

b) Activities for which the licence is required;

c) Whether previous applications had been made in respect of the product and if so, their details;

d) Scientific evidence;

e) Product particulars, pharmaceutical form (i.e. tablets, capsules, injections etc) and intended use (i.e. whether for administration to patients or for use as an ingredient in another medicinal product);

f) Active constituents and the way such ingredients would be presented on the leaflet, label or descriptive material;

g) Uses, including recommended clinical use, proposed route of administration and directions for use to be included on the product literature;

h) Recommended dosage and dosage schedule;

i) Contra-indications, warnings and precautions to be included on the data sheet, container label, package label and leaflets;

j) Method of intended retail sale and supply;

k) Physical characteristics such as colour, odour, taste, gravity, viscosity, consistency, particle size, bulk density, crystal form, size, shape, superficial markings for identification; hardness, disintegration and delayed release characteristics;

l) Manufacturing details such as:

(1) The manufacturing or assembly operations relating to the product (dosage form);

(2) Address of places of manufacture and assembly;

(3) Storage arrangements;

m) Details about quality control;

n) Proposed types of containers;

o) Labelling and proposed expiry dates;

p) Importation details if applicable; and

q) Previous applications that had been granted, revoked or refused internationally.

6.4. These applications were vast. I note that in the minutes of the Annual Meeting between the Association of the British Pharmaceutical Industry ('ABPI') and the CSM on 8 March 1990 **[MHRA0014776** (page 2)**]**, it was recorded that the number of volumes submitted per product licence had reduced from 170 in 1988 to 58.9 in 1989 which the CSM saw as a marked improvement. This dropped further to 52 in 1990 **[MHRA0014742** (page 1)**]**. This gives you an idea of the huge amount of material that would be submitted with each product licence application and would need to be considered.

6.5. The way that the CSM would assess licence applications was as follows:

a) The application would first be considered by the professional assessors at the Secretariat who would write a report for the relevant CSM subcommittee. You can see an example of one such report at **[MHRA0033319_016]**. This example was for a variation application for Kryobulin Heat Treated Factor VIII which was assessed by both Mr Sloggem (a pharmaceutical assessor) and Dr Rotblat (a medical assessor). This application was received on 5 January 1987 and was due to be considered by the Biologicals Subcommittee at their meeting in July 1987. As was the case with this example, the report would provide a summary and an assessment of the application and the assessors would offer a recommendation.

b) The relevant subcommittee would consider the application and then would make a recommendation to the CSM.

c) The CSM would then consider the application at one of its meetings and would look at the CSM subcommittee's report to decide whether to advise the Licensing Authority that it would be appropriate to grant a product licence. These were large meetings that would last one or two days and would consider many applications.

6.6. I cannot recall this process changing over time.

6.7. It is important to state that the CSM did not simply rubber-stamp the decisions of its subcommittees. It would consider each application for itself and would often ask questions of the subcommittee or manufacturer or amend the recommendations. For example, you can see that in the SEAR minutes from our meeting of 10 October 1986 (which I attended), the Chairman updated members that the main committee had agreed to grant a product licence for Hytrin Tablets made by Abbott Laboratories but had amended the SEAR recommendations and issued two conditions **[WITN6406009]** . This reflects my view of how the committees worked: the CSM respected and was assisted by the work of its subcommittees but did not blindly follow their recommendations.

Applications for variations

6.8. An application for a variation to an existing product licence would require the applicant to provide evidence supporting the changes requested. This might be, for example, an extension to the product's indications, or a change in the dosage schedule, supported by appropriate data. The manufacturer would complete an application for a variation (see **[WITN6406010]** by way of example) on which they would be asked to specify the present particulars, the proposed variation and reasons for that variation with supporting evidence.

6.9. It is important to note that there were no material differences in the level of scrutiny applied by the CSM to applications for new product licences or applications for variations, amendments or abridged product licences. All applications were considered with the same care and attention.

6.10. Applications for variations would sometimes be invited, for example, in 1986 after the CSM considered the manufacture of blood products from plasma derived from unscreened donors, the CSM recommended:

> *All blood products should be prepared from plasma individually tested for HBsAg and anti-HIV. Companies producing blood products should apply for variations to their product licences to cover this point as soon as possible.* **[DHSC0002303_030]**.

Abridged product licence applications

6.11. An abridged product licence application might involve, for example, a change in the source of the product or a change in the excipients (excipients are the inactive substances which act as the vehicle for the drug or active substance). Evidence to show comparability with the original product would be expected. Straightforward applications for variations of product licences, or abridged licence applications, could and would be dealt with by the staff of the Medicines Division / Medicines Control Agency and only be referred to the CSM if the relevant professional assessor(s) were unsure or minded to reject.

6.12. I have seen a validation sheet for an abridged application by the Blood Products Laboratory from late 1989 which gives another example of why an abridged

application was sought for a Factor VIII product **[WITN6406011]**. This shows BPL seeking an abridged application for 'Dried Factor VIII Fraction Type by Injection Nominal'. The Notes and Background recorded that the first full granted licence containing the active constituent human anti-haemophilic Factor VIII was over ten years old and that BPL had been manufacturing this product since 1985. They sought to fast-track their licence because of the impending end of their Crown immunity.

Time considering applications

6.13. The time that it took the CSM to assess applications varied; generally speaking, unsuccessful applications took longer. The work was time-consuming and demanding. In 1987, the mean assessment time was 33.8 weeks and by 1989 this had dropped to 31.2 weeks (page 4 **[WITN6406004]**). While this period was longer than we would have liked, there were good reasons for it:

> *First, each individual assessment (pharmaceutical, scientific, clinical) of a product takes approximately four weeks and, if undertaken rigorously, needs to be performed consecutively but with close collaboration between the assessors, when added to the time taken for administrative validation (2 weeks), and for consideration by the CSM and its relevant subcommittees (4 to 6 weeks), the minimum overall assessment time is unlikely to be less than 20 to 22 weeks. Second, applications are assessed, and considered by the Committee, in strict order of submission. Since applications are often spaced unevenly, a backlog can easily arise. Third, […] unsuccessful applications take, on average, about 4 weeks longer to assess than successful ones. This is because unsuccessful ones are often deficient, resulting in informal or formal contacts with the company in an attempt to resolve them. Finally, there is a mechanism for 'fast-tracking' the assessment of applications perceived to make available new products of major public health importance. This was used twice, for NAS applications, during the period under review with an average assessment time of 10 weeks. Applications involving the European Licensing system may also influence the overall handling times.* (Pages 8-9 **[WITN6406004]**).

6.14. I note that in the Annual Meeting between the ABPI and the CSM on 8 March 1990, the minutes recorded that each meeting of the CSM considered on average 16 product licence applications **[MHRA0014776** (page 2)**]**. The minutes say that in 1989, 200 product licence applications were considered with a 54% refusal rate at first consideration.

6.15. The minutes from the meeting the following year (1991) reflected that SEAR would consider applications before they went to the main CSM and at that stage, negotiations would take place with manufacturers allowing potential problems to be resolved at that early stage **[MHRA0014742** (page 2)**]**. Professor Asscher, then the CSM chair, estimated that this resolved over 50% of the problems that would lead to product licence applications being rejected by the CSM.

6.16. By June 1996, the CSM was releasing its assessment reports to applicants with refusal letters. There were also 'clarification' meetings held between the manufacturers and the Biologicals Subcommittee to discuss biotech quality issues before the main CSM meeting **[MHRA0014544** (page 2)**]**. This was all part of our drive to be as transparent about our processes as possible.

Section 7: Safety, efficacy and quality of blood products during the licensing process

7.1. Section 19(1) of the Medicines Act 1968 (which remained in force throughout my time on the CSM) set out the factors that were relevant to the determination of an application for a licence:

> (1) *Subject to the following provisions of this Part of this Act, in dealing with an application for a product licence the licensing authority shall in particular take into consideration—*
>
> (a) *the safety of medicinal products of each description to which the application relates;*
>
> (b) *the efficacy of medicinal products of each such description for the purposes for which the products are proposed to be administered; and*
>
> (c) *the quality of medicinal products of each such description, according to the specification and the method or proposed method of manufacture of the products, and the provisions proposed for securing that the products as sold or supplied will be of that quality.*

7.2. Safety, efficacy and quality were therefore at the heart of our work. Very broadly, 'safety' in this context would look at the issue of contamination. This might be assessed by batch testing and screening and of course, later, post-release surveillance in the form of the yellow card reports. Batch testing would confirm potency but could not test efficacy. 'Efficacy' meant looking at how effective a product was and to assess this, it would involve considering the clinical trials. 'Quality' assessment was carried out by the pharmacists who would look at the molecular breakdown of the product to assess how pure the product was, whether it contained the correct chemicals and how stable it was.

7.3. We did not consider whether there was another product on the market that was or might be equally or more efficacious for the same purpose (and indeed, such considerations were prohibited by s19(2) of the Medicines Act 1968). We could take into account, however, that a safer product was just as or more effective. We did not consider any other criteria.

7.4. I vaguely recall that it took a while before international standards for potency were universally used by pharmaceutical companies but I cannot recall when these standards were adopted.

Scrutiny of blood donations

7.5. Even before I joined the CSM, it would consider the source of donated blood used in blood products. Our interest and scrutiny of this issue grew as the terrible situation of infected blood emerged. I cannot now remember the details of what changed and when.

7.6. In February 1976, when Bayer was granted a licence for Koate, for example, the licence was granted subject to the conditions that satisfactory information be provided about the number of donations in each pool **[BAYP0000001_110].**

7.7. From 1989, manufacturers of blood products were asked to submit samples of plasma pools to NIBSC as part of the batch release process **[MHRA0034935_077]** which had, prior to that, been sought on an informal basis. I think this was later added to product licences as a formal condition.

7.8. On 21 February 1990, the minutes of the CSM meeting record that there was discussion of the provision of plasma pool samples for the control testing of blood products **[CABO0000308_009]** (paragraph 10). The CSM had noted and endorsed a recommendation of the Biologicals Subcommittee that:

> *10.l In view of the limitations of testing for HBsAg and antibodies to HIV in finished products and the greater sensitivity of tests on the plasma pool, manufacturers should be required to submit formally to NIBSC samples of plasma pools in addition to other samples and protocols required for batch release.*
>
> *10.2 Product licence holders should be asked to confirm that all plasma pools used in the preparation of a given product have been tested and found to be free of HBsAg and antibodies to HIV and the licence amended accordingly.*

Clinical Studies

7.9. We would be assisted by and give careful consideration to clinical trials and other such information provided by the pharmaceutical companies when scrutinising applications for product licences. On safety and clinical trials using human subjects, in 1990, I made the following observation in a presentation called a 'Survey of United Kingdom Product Licence Applications containing "New Active Substances"':

> *For agents shown to be effective in an otherwise lethal condition, relatively small numbers of subjects will be required to demonstrate safety and efficacy. At the other end of the spectrum very much larger numbers of patients will be needed to be studied to reassure the manufacturer, and the Committee, of the safety of products intended for common conditions, those with a more benign natural history, and those for which alternative treatments are available.*
>
> *The number of subjects exposed to most NAS's, before marketing, can only provide provisional reassurance about safety in larger, and more heterogeneous population. The data presented in this paper underlines the importance of post-marketing safety surveillance.* (Pages 9-10 **[WITN6406004]**).

7.10. The following year, 1991, at the Annual Meeting between the ABPI and the CSM, the minutes record that I reported:

> *recurring problems which the CSM has noted during the year: pre-clinical issues included incomplete mutagenicity studies and unsatisfactory pharmacokinetic validation of toxicology studies; clinical issues concerned inappropriate dosage regimes and inadequate global safety analyses. [I] emphasised, however, that these issues were always raised with the companies concerned…*

I feel this demonstrates that the CSM was well-placed to scrutinise and challenge clinical trials and studies as well as spot issues with the documents, data sheets and analyses we were presented within applications.

Licences in other jurisdictions

7.11. We would be informed when a licence had been granted in another jurisdiction and would give this some weight but it would not be a determining factor: we would still carefully scrutinise the application afresh. It would often be helpful to see details of licensing in other jurisdictions as it could mean that there was more information available about the product's safety and efficacy as it would have probably been used by more people.

7.12. Where there was a product licence in existence in another EU Member State, we would give this 'due consideration' and where we wished to refuse such a licence, the matter would be referred to the CPMP (see for example **[WITN6406012]**).

Conditions of product licences

7.13. I have been reminded that under s19(3) of the Medicines Act 1968, where an application indicated that the purposes for which the licence was required related (wholly or partly) to medicinal products which have been or were to be imported, the licensing authority could make a licence provisional on undertakings and declarations given by or on behalf of the manufacturer.

7.14. I note that in the minutes of the Annual Meeting between the ABPI and CSM on 8 March 1990 **[MHRA0014776]**, it was recorded that 'a number of licences had been granted conditionally. Many of these had only minor alterations, others with major alterations, but with all the conditions being fulfilled without dissent'.

In the presentation that I gave at that meeting, we observed that of the 46 conditional licences granted to new active substances, the 'minor conditions all required modification to the product's Data Sheet but the major conditions involved either restrictions to the licensed indications (n = 15), the satisfactory completion of mutagenicity studies (n = 4), or both (n = 2)' and that the manufacturers had been able to meet the conditions (pages 3-4 **[WITN6406004]**).

7.15. I do not now recall the particular conditions which were imposed for product licences for blood products but I have seen various references to conditions in the documents. Conditions that I have seen referred to, among others, included: an undertaking to permit inspection of the manufacturer's premises by, or on behalf of, the Licensing Authority (see for example **[WITN6406013]**); the provision of further information about aspects of the manufacturing process and / or assay process **[WITN6406013],** expressing potency in International units **[WITN6406014];** changes to data sheets **[WITN6406015]**, changes to a product's name and labels; assurances about the sensitivity of blood screening test kits and specifications about product preparation **[WITN6406016]**.

Batch release

7.16. There were special arrangements needed for the control of biologicals – including blood products – because their purity or potency could not always be adequately tested by chemical means. Licence holders could be directed to submit full details of the control tests applied and sometimes samples for confirmatory testing of each batch of a product before it was released for sale. Where this took place, Batch Release Certificates were issued on the advice of NIBSC (see **[MHRA0004773** (page 15)**]**). This process, known as 'batch release' became more common in later years as I explain in more detail from paragraph 13.1 below.

Rejected applications and appeals

7.17. Where the CSM did not feel that it could recommend that the licensing authority should grant a product licence, or it intended to advise that an existing licence be revoked, varied or suspended, the applicant or licence holder had to be

given the opportunity to appear before the CSM or make written representations. If, on hearing those representations, the CSM still advised the licensing authority against granting the licence, the licensing authority had to inform the applicant or licence holder who could then make representations to the Medicines Commission at a further hearing or in writing (see further **[MHRA0004773]** at page 13).

7.18. The appeal process was often used by manufacturers who had unsuccessfully applied for a product licence. I note that by March 1990, of the 71 applications rejected by the licensing authority, 24 had been granted on appeal following the submission of additional data or reanalyses of previously submitted data (page 6 **[WITN6406004]**). In 1993, David Jefferys and I published 'United Kingdom Product Licence applications involving new active substances, 1987-1989, their fate after appeals' in the British Journal of Clinical Pharmacology **[WITN6406002]**[2]. This article recorded that fifty-one applications were subject to appellate procedures and of these, forty-four (86%) succeeded on appeal. Of the product licence applications considered between 1987 and 1989, 57% either did not reach the market (23%) or were subject to substantial restrictions on dosage or indications (34%). Considering this evidence, we concluded, 'Drug regulation, in the United Kingdom, thus plays a significant role in promoting public health rather than merely delaying the entry of new products to the market'.

A snapshot of the CSM's work 1990/1991

7.19. I have been shown a copy of the minutes of the ABPI and CSM on 24 July 1991 which I also attended **[MHRA0014742]**. These minutes offer a helpful snapshot of the work of the CSM at that time (a period when I was the vice-chair). They show that the CSM held eleven meetings in 1990 (the same as in 1989) and considered 232 product licence applications (an increase from 200 in 1989). Of these, 74 (32%) were approved (compared to 92 (46%) in 1989).

[2] This article was based on work that we conducted and first recorded in 'Analysis of Product Licence Applications for New Active Substances (1987-89)' **[WITN6406017]**. I have included more detail about earlier work on this subject and article at paragraph 7.20.

7.20. At the Annual Meeting between the ABPI and CSM on 8 March 1990, I gave a presentation with Dr Jefferys (the Principal Medical Officer and a Medical Assessor) giving the detailed figures of the numbers and scientific aspects of product licence applications considered over 1997-1989 **[MHRA0014776].** The presentation was called a 'Survey of United Kingdom Product Licence Applications containing New Active Substances' **[WITN6406004]**. The substance of this presentation was later published in the British Medical Journal (Rawlins, M.D. & Jefferys, D.B. (1991). Study of United Kingdom product licence applications containing new active substances, 1987-9, *Br. med* J, **302**, 223-225) and then updated in a further article in 1993 which I mention at paragraph 7.18 above **[WITN6406002]**. Broadly speaking, New Active Substances were chemical, biological or radiopharmaceutical substances not previously authorised as a medicinal product (including blood products). In this original presentation, we observed that 56/118 applications were rejected on grounds of inadequate evidence of efficacy. Of those, four applications were in the therapeutic group 'Nutrition and blood' and two of these were successful (page 11 **[WITN6406004]**). We stated that '[I]n a few instances this was due either to uncertainty about a product's long-term efficacy (6 applications) or the failure to demonstrate efficacy throughout a dosage interval (3 applications). In the majority of cases, however, the Committee and Secretariat, was unconvinced of the overall efficacy of products for the indications claimed.' (Pages 6-7 **[WITN6406004]**).

7.21. Table 3 shows that there were 14 applications rejected on the grounds of safety alone (page 12 **[WITN6406004]**). We observed:

> *Concerns about clinical safety at initial assessment are, perhaps, less surprising. Such issues involve risk-benefit decisions that are generally resolved by judgmental analysis. Differences in such risk-benefit assessments, between commercial innovators and the CSM, are at the heart of drug regulation. It is disappointing though, that 48% of applications should provide deficient preclinical safety data concerning general toxicity testing, mutagenicity screening and carcinogenicity studies. Although in some instances these involved differences in data interpretation between the Committee and Secretariat, and the companies' experts, the majority of instances were about inadequacies in both the design and conduct of studies. Since detailed guidelines for the conduct of preclinical studies, harmonised throughout the EEC,*

> *are generally available the reasons for these inadequacies are unclear. Part of the explanation arises from the submission of applications, by some companies, that are overtly premature: in such instances the manufacturer may be seeking from the Committee and the MCA, a detailed list of deficiencies which it can rectify before an appeal.*

7.22. This presentation also showed that for each application for a new active substance, the CSM would keep a prospective record of its therapeutic group, the date of receipt of the application by the Medicines Control Agency, the date it was considered by the CSM and whether the CSM advised its grant (with or without conditions). If a licence application was initially rejected (provisionally), we would record the reasons. Furthermore, we kept a record for each application of how many healthy volunteers were exposed to the substance during premarketing studies, the number of patients treated with the product during clinical trials and the total number of treated patients available for an assessment of safety **[WITN6406004]**. I have not seen copies of these records in the course of preparing this statement and do not know whether they were retained or still exist.

7.23. As I have mentioned, I updated the presentation at the meeting the following year and in 1993, David Jefferys and I published 'United Kingdom Product Licence applications involving new active substances, 1987-1989, their fate after appeals' **[WITN6406002]** which drew together the information about appeals from the three-year period. In that time, the CSM had considered a total of 118 applications for new active substances of which 91 (77%) were eventually granted product licences. The proportion of successful applications seemed to decrease between 1987 and 1989 and there was also an increase in the number of unsuccessful applications for which no appeal was pursued.

Procedure for processing emergency product licence applications

7.24. I have no recollection as to whether emergency product licence applications were made (or granted) for any blood products. Nor do I recall the procedure for processing emergency product licence applications.

Section 8: Challenges faced by the CSM in the 1980s and 1990s regarding licensing of blood products

8.1. I have been asked about the main challenges faced by the CSM in the 1980s and 1990s regarding the licensing of blood products when I served as a member, vice-chair and chair. I have been referred to the minutes of the Annual Meeting between the Association of the British Pharmaceutical Industry ('ABPI') and CSM on 8 March 1990 **[MHRA0014776]** ('the 1990 minutes') and on 24 July 1991 **[MHRA0014742]** ('the 1991 minutes'), both of which I attended. These have been supplied by the Inquiry to assist me in recalling what the main challenges faced by the CSM in the 1980s and 1990s regarding the licensing of blood products. In fact, neither of these sets of minutes expressly refers to the licensing of blood products which illustrates that blood products were just one part of our large portfolio of products. It is important to recognise that blood products only made up a part of what we did on the CSM and I recall that there were significant issues and challenges that arose involving other products during the 1980s and 1990s. In the early 1990s for example, these included issues involving oral contraceptives (especially regarding a possible link to breast cancer), the effects of bovine spongiform encephalitis and difficulties regarding hypoglycaemic reactions following the introduction of human insulin **[MHRA0014776** (page 2)**]**.

8.2. The 1990 minutes show the then-chair of the CSM, Professor Asscher, giving an account of the CSM's activities during his period of tenure. He highlighted that the CSM had encouraged improved communication on three fronts: first resolving issues before hearings and thereby reducing the number of hearings; secondly increasing the use of conditional approvals of product licence applications rather than refusals and, finally, advising companies which applications were 'good and what were bad'. He recorded that no licences had been revoked in three years, pre-hearings had been halved, the number of product licences granted increased dramatically and the proportion of refusals reduced considerably. Communication was a big issue and the minutes note

that only one licence was issued unconditionally without any referral back while a number of licences were granted conditionally.

8.3. The 1991 minutes show that I referred to certain problems which the CSM had noted during the year (as already cited at paragraph 7.10 above): 'pre-clinical issues included incomplete mutagenicity studies and unsatisfactory pharmacokinetic validation of toxicology studies; clinical issues concerned inappropriate dosage regimes and inadequate global safety analyses'.

8.4. I think that this background about other products and concerns exercising the CSM is crucial to understand the work that we were carrying out. Beyond this, however, I am afraid I cannot shed any light on the challenges faced by the CSM in the 1980s and 1990s regarding the licensing of blood products. Nor can I now comment on how successful the CSM was at meeting those challenges.

Section 9: Advice of the CSM Main Committee regarding Alpha's Antihaemophilic Factor (Human) Wet-Paste (Bulk Cryoprecipitate), dated 24 March 1983

9.1. I have been provided with a copy of **[DHSC0003946_060]**. This is a copy of the advice provided by the CSM on 24 March 1983 following an application for a licence for a blood product made by Alpha Therapeutic (UK) Ltd called Antihaemophilic Factor (Human) Wet-Paste (Bulk Cryoprecipitate). I have no recollection, now, of this application or our discussion and decision.

9.2. The advice which the CSM gave was that we were unable to advise the grant of a product licence for the preparation because of a number of concerns:

a) The bulk cryoprecipitate should be prepared by Alpha Therapeutic only from human source plasma that derived from their own licensed plasmapheresis centres;

b) Evidence should be provided showing that the cryoprecipitate was at least the equivalent quality to that used in Alpha's US-licensed Factor VIII;

c) Inadequate information was presented on the control of the material during transport to the UK;

d) An undertaking should be given that donor lists should be available to the manufacturer of the finished dosage form;

e) Were a licence to be granted, batch release procedure should apply and include the provision of protocols and samples of bulks as required; and

f) There were inadequate details on the manufacturing process.

9.3. At the end of the document, we recorded some remarks which asked the Licensing Authority to consider the legal implications of licensing this bulk blood product as an ingredient rather than finished product, 'especially in view of the great difficulties foreseen for the manufacturer of the finished dosage form in exercising full control going back to the source material'. We also advised that special attention be given to inspecting Alpha's US premises and we noted that there was no evidence of efficacy provided because the product was only intended as an ingredient. It is probably relevant to say that at the time we were considering this application, our knowledge had grown about the risk of AIDS.

9.4. I do not recall whether the CSM expected all plasma to come from licensed plasmapheresis centres and if it did, over what time period this was the case or the steps taken to reduce the risk of infected donations. Although I have no recollection of this and was not present, I note that the minutes of a meeting at NIBSC from February 1984 recorded Dr Ashworth from Cutter telling NIBSC that '[a]ll plasmapheresis stations in the United States are licensed by the FDA, as is the centre in Belize' **[PRSE0003071]**. I note too that the CPMP Note for Guidance on Plasma-Derived Medicinal Products from 1997 said that information on the collection and control of source material should include information on starting materials updated annually and a system should be in place to enable the path taken by each donation to be traced from the blood

collection establishment through to finished products and vice versa (paragraph 2.3.1) **[WITN6406018]**. It stated that:

> *Information should be provided on the countries where donations are collected and the organisations responsible for collection. An exhaustive list of names and address of blood/plasma collection establishments including any subcontractors and any separate sites for testing of individual donations should be provided. Collection establishments should be inspected and approved by a competent authority.*

Section 10: Contaminated blood products

10.1. I have been given a copy of the minutes of the meeting between the ABPI, the CSM and the MCA in June 1996 which I attended **[MHRA0014544]**. I am quoted as saying:

> *…most drug 'safety issues' are usually known to the manufacturer for some time, and that when a major issue arises, the normal channel for action would be from the licensing authority, to the Sub-Committee on Pharmacovigilance and then to the CSM, but this would obviously depend on individual circumstances.*

10.2. I think that this procedure applied to licensed products (including but not limited to blood products) and unlicensed products if the Medicines Control Agency was aware that an unlicensed product was being used on a 'named patient' basis. It would, I believe, have applied from the start of the initial establishment of the CSM and throughout my period on the CSM.

10.3. I recall for example a process of this nature happening when the licence for Practolol (a selective beta-blocker) was revoked following reports of an association with an 'oculomucocutaneous syndrome' (a condition involving the skin, eyes and peritoneum).

10.4. Where an issue arose regarding a contaminated blood product, the treating doctor would report it to the Medicines Division or the MCA by letter or by way of a Yellow Card report. The Medicines Division / MCA would refer the matter to the relevant subcommittee(s) who would then report to the main Committee. The timescale, if I recall correctly, would have been one to three months. After

due consideration by the subcommittee and the CSM, the outcome might range from 'no action' to 'immediate suspension' of the licence.

10.5. When the CSM learnt of contaminated blood products, our role was to assess the risk and advise on steps to minimise the risks.

10.6. My comment about drug safety issues 'being known to the manufacturer for some time' would have been a general statement and not one referring specifically to blood products. Manufacturers of blood products were aware of the possibility of risk of transmission of disease but this was not what I meant in this sentence.

Recalls, licence suspensions and revocations

10.7. I do not recognise the term 'stop orders'. I can see, however, from the report of Dr Fowler for a CSM Meeting in or around 1981 considering Speywood's product Humanate, that the term 'stop order' seems to have been used, at least in this report, to mean a requirement for a licence holder to supply samples and protocols of tests on each batch of a product and not to sell or supply material from a batch until they had received a certificate of clearance from the licensing authority (paragraph 1.4 **[MHRA0036365_018]**). It therefore seems to me to be a term that was used to describe the batch release procedure.

10.8. The 'recall' of a product would be most likely to occur if a batch was found to be contaminated by a known or suspected toxic ingredient. Following the identification of a safety issue, I would expect that the manufacturers themselves would consider surrendering their product licence and withdrawing material already issued as I describe at paragraph 11.6 below. If that did not happen, a licence might be 'suspended', with immediate effect if the CSM considered that it was too dangerous to continue to be prescribed. Otherwise the licence would be 'revoked' by a process that allowed the product licence holder to appeal against the decision before it was implemented.

Section 11: 1993 BPL blood products compromised by hepatitis C donations

11.1. I have been provided with some documents that relate to Bio Products Laboratory (BPL) blood products being compromised by hepatitis C donations in 1993 (**[MHRA0000007_004]; [MHRA0000121]; [MHRA0000117_001]; [MHRA0000112_001]; [MHRA0000123]; [MHRA0000122_002]; [MHRA0000007_014]; [MHRA0000007_015]** and **[MHRA0000007_010]**). I was not involved in these meetings or copied into any of the correspondence about this incident. I do not recall whether I knew about it at the time.

11.2. I am very surprised by the conclusions of the meeting on 10 June 1993 which was attended by representatives from the MCA, NIBSC and the Biologicals Subcommittee. That meeting concluded that '[t]here is no scientific reason for withholding the products in question on safety grounds or for recalling those already released'. This appeared to be an internal MCA meeting and I am unable to say whether the conclusions of this meeting were communicated to the CSM, the clinicians or patients potentially affected. I also have no recollection of the MCA or NIBSC having any role in exempting fractionators from safety guidelines as appears to have happened (or at least been considered) here. I was not aware that they had such a power or discretion.

11.3. Finally, during my time with the CSM, no account was ever taken of the cost of a product. In fact, on one occasion in around January 1998, I was summoned to meet one of the Health Ministers, Baroness Jay, and asked whether the CSM might make decisions on cost-effectiveness of products. I said that I would not advise it because I felt that separation between cost and the matters that the CSM needed to consider was crucial. Section 20(2) of the Medicines Act 1968, which dealt with the grant or refusal of licences, specifically said that the licensing authority shall not refuse to grant a licence on grounds relating to price and should not insert provisions into the licence as to price. This emphasises how important it was to retain this separation. It was never pursued. While that was in the context of granting licences, the same was true for any decisions to be taken on existing licences: cost was not a factor.

11.4. It is worth adding, however, that supply could be a relevant concern because if there was no supply, that might of itself be a safety issue but this would be dependent on the circumstances.

11.5. It can be seen from these documents, in particular **MHRA0000007_004** at page 2 (and **MHRA0000121** at pages 1-2), that it looks as though fractionators may have had some degree of freedom to make decisions for themselves relating to safety matters, notwithstanding that a safety concern had been identified in relation to a particular blood product:

> *2. There is no requirement for BPL to have a dispensation from the official guideline since these give clear guidance on the action to be taken by a Company in the event of a donor being found retrospectively to be infected (i.e. a re-assessment of the batch documentation and re-control of finished products should always be carried out; the need for withdrawal of the given batch should be carefully considered, taking into consideration criteria such as the disease, the type of seroconversion, and the nature of the product and its manufacturing method.)*
>
> *3. BPL should feel empowered to make the decision for themselves in the event of a reoccurrence of this situation by proper interpretation of the CPMP Guidelines.*

11.6. It is correct that the manufacturers bore some responsibility for the safety of their products and indeed, they were often best placed to act most quickly in recalling products if that was necessary (they knew to whom they had been sold and could issue a recall swiftly and directly) whereas anything that went back to the MCA or the CSM would require input and expert consideration followed by discussion which would inevitably take time. That is not to say that these bodies had no responsibilities or power but it was incumbent on everyone involved in the licensing and manufacturing of products to act swiftly to ensure they were as safe as possible at that time. In this instance, I can see that BPL took the decision not to release what R.C.D. Walker, the Chief Executive of BPL, called 'a compromised product'. I do not know what would have happened had a different decision been made but it is fair to say that the decision would not have been left to the manufacturer alone if there were concerns about safety. Had BPL taken a different decision, this could have led to action being

taken by the MCA, CSM or others such as whether maintaining the status quo was appropriate, or whether the licence should be revoked.

Section 12: Recombinant

12.1. I have been referred to **[MHRA0026440_003]**. This was an undated recommendation of the SEAR (not the CSM itself) at which a product, Recombinant Clotting Factor, was considered. Factor VIII was its active constituent. The document records that the SEAR recommended a product licence be granted to Baxter for Recombinant on the condition that satisfactory responses were provided to the CPMP. The two conditions were:

a) Liver function data for the study in previously untreated patients should be provided; and

b) The summary of product characteristics should be amended, in particular:

> *2.1 The statement that preclinical studies have shown that Recombinate is safe and effective should be deleted, from the sections on Undesirable Effects and Pharmacological Properties.*
>
> *2.2 The statement in the indications section, that Recombinate may be considered as a primary treatment option in patients not previously exposed to human blood derivatives should be deleted.*

12.2. I have been shown further documentation which suggests to me that this document would have been written in or before July 1992 when the application for Recombinant's product licence was considered by the Biologicals Subcommittee (pages 220 to 264 **[WITN6406019]**). It seems to be a CPMP Biotech application for Recombinate with the Netherlands as rapporteur (page 259) but I have to say that I cannot now recall what a CPMP Biotech application was and whether the main CSM would have seen it.

12.3. This further documentation shows that the Biologicals Subcommittee also considered the application and made recommendations. I can see that the

Dutch Rapporteur had raised pharmaceutical questions about the product (page 230-231), the UK Secretariat had added further questions (page 244) and that, finally, one of the assessors, E.N. Gate (245) had recommended in June 1992 that if those pharmaceutical questions could be resolved, the product should be granted a licence (page 245).

12.4. While I cannot comment on the reasons behind the recommendation of SEAR, I note that it was the medical assessor who first recommended that:

> *The statement that preclinical studies have shown that Recombinate is safe and effective should be removed from the sections on Undesirable Effects and Pharmacological properties.* (page 262)

12.5. The assessor considered four clinical studies of which he considered two to be pivotal. On efficacy, the assessor observed that few of those patients in the long term study reported formally on efficacy (paragraph 2.2, page 260) but that it '*appeared that Recombinate was very effective'* (page 261). On safety, he noted that there were '[o]nly a few minor adverse events' (paragraph 2.3.1, page 261) and there was a tendency for liver function to fluctuate:

> *as practically all the patients had long standing hepatic impairment. One patient appears to have become HBsAg positive during treatment. However he had some markers of liver disease (HBcAb) at baseline.*
>
> *[…]*
>
> *There has been concern about the possibility of an increased incidence of inhibitors in patients receiving Recombinate or highly purified plasma derived Factor VIII.*
>
> *[…]*
>
> *Patients receiving Recombinate have been carefully monitored for inhibitors and this aspect was the primary endpoint sought in the pup study.*
>
> *No new inhibitors have developed in previously treated patients.*
>
> *7 pups have developed inhibitors, including 3 of high titre. This is an incidence of 16% and is comparable to the baseline incidence in new patients.*
>
> *The company will continue to monitor the situation.*
>
> *[…]*
>
> *There has been a tendency for a fall in T4 count.*

12.6. Although I can speak for neither the medical assessor nor the SEAR, nor do I have any memory of this, it seems likely that these findings from the clinical trials raised enough question marks that it seemed a little too stark to publicise that 'Recombinate is safe and effective' at this stage and that is why they recommended its amendment.

12.7. I cannot say either whether this decision could properly be characterised as an exemption from safety guidelines but I think it unlikely based on the documentation and the explanation I have given above. I have no recollection of what information about this was given to clinicians or patients. I have no knowledge of whether information was or should have been passed on to the clinicians and / or patients about the identified risk and by what means that would have been done.

Section 13: Adverse Reaction Reporting

13.1. As 'The Control of Medicines in the United Kingdom' states, it was a core belief when it came to regulation of the marketing of medicinal products that controls before marketing could never be sufficient **[MHRA0004773** (page 16)**].** Clinical trials were useful where patients were carefully observed to establish pharmacological actions and efficacy of a drug and to identify major safety problems that studies on laboratory animals had not detected. But great importance was – and I believe still is – attached to the monitoring of possible adverse reactions to medicinal products.

13.2. In 1986, I wrote an editorial in the Quarterly Journal of Medicine called 'Spontaneous Reporting of Adverse Drug Reactions' (QJM, New Series 59, No. 230, pp. 531-534, June 1986) **[WITN6406020]**. The strength of these schemes is that a large population is kept under observation by potential reporters, most commonly doctors, but as I noted in the article, there are shortcomings:

a) They rely on doctors reporting suspected rather than proven adverse reactions;

b) They are inherently more likely to detect adverse reactions which occur soon after the start of treatment;

c) Some reactions such as those with a long latency may remain unrecognised;

d) Only a small proportion of even serious adverse drug reactions were reported to the CSM;

e) Reporting rates tend to decline with time after a product has been marketed.

13.3. But while spontaneous reporting schemes rarely provide estimates of the absolute incidence of a particular adverse reaction, they still continue to make important contributions to clinical science and drug safety, for example:

a) Identifying and characterising new drug hazards and classifying clinical features of reactions discovered by other means;

b) Identifying risk factors pre-disposing to adverse drug reactions such as age;

c) Estimating the relative toxicities of individual drugs where there was a group of drugs with similar therapeutic properties being used for similar clinical indications.

13.4. In the article, I described that many drug regulatory authorities in developed countries had established spontaneous adverse reaction reporting schemes and the UK's Yellow Card system was 'one of the oldest and the most successful of these national schemes'. It was an alerting mechanism suggesting a possible association between a drug and an adverse reaction. I understand that it remains in operation to this day.

Yellow Cards

13.5. The Yellow Card scheme is a spontaneous adverse reporting scheme set up in 1964 following the Thalidomide disaster. Confidential reports about individual patients could be made on a voluntary basis by members of the professions,

usually on a specially designated 'Yellow Card'[3]. These Yellow Cards were issued to all doctors, dentists and coroners. Doctors, dentists and coroners were requested to report any suspected adverse reactions using the reporting forms on which they could set out the relevant patient information (name, sex, age, date of birth and weight), drug information and exposure (name of drug, route of administration, daily dose, date drug started and ended and indication for therapy) and suspected adverse reaction/s. There was room for additional notes to provide information about relevant past medical history, test results, biopsies and so on. Guidelines on the types of adverse reactions that should be reported were published in the British National Formulary, Monthly Index of Medical Specialities, the Data Sheet Compendium and Current Problems (see for example Current Problems No 31 published in June 1991 in which we issued advice about adverse drug reaction reporting **[WITN6406021]** page 4**)**.

13.6. During my time on the CSM, we did a lot of work to increase Yellow Card reporting, from introducing Yellow Cards into NHS prescription pads and the British National Formulary in 1986, to making an education video about the CSM's work and the importance of adverse reporting and organising an 'ADR Roadshow' in East Anglia in 1988 **[MHRA0014826** (page 8)**]**. We also conducted pilot studies such as the one starting in April 1988 to assess the involvement of hospital pharmacies in adverse reactions reporting **[MHRA0014826** (page 9)**]** and attitudinal studies such as the one conducted in 1991 in the Northern Region **[WITN6406022]**. It was something to which the CSM and the SEAR Sub-Committee gave a great deal of consideration (see for example the SEAR Recommendation from 1991 following a meeting at which it had considered declining Yellow Card reporting **[WITN6406023]**).

---

3 Manufacturers, hospitals and other users could also report defective products. These would usually relate to batches or groups of batches. If necessary, the affected batch or batches could be recalled, for example if a batch was mislabelled, contaminated, contained incorrect ingredients or strength or when it was considered that the administration of the product would constitute a serious health hazard. The arrangements for recall would be undertaken by the manufacturer, the wholesalers or the Department of Health (again, see **[MHRA00004773** (page17)**]**).

13.7. Another example of a pilot we ran is contained in the minutes of the annual meeting of the ABPI and CSM on 8 March 1990 at which it was recorded that:

> *Both sides agreed that the primary role of the hospital pharmacist in reporting adverse drug reactions is to encourage doctors to complete yellow cards. Professor Rawlins previously supported this view but he commented that he now feels that in certain circumstances hospital pharmacists should be allowed to report adverse drug reactions direct to the CSM. To that end, a pilot scheme is being introduced in the Northern Region in which pharmacists will be encouraged to sign forms on behalf of doctors in hospitals as part of the team. The yellow card will be specially marked and readily identifiable. Professor Jones expressed concern that pharmacists would sign off clinical decision and opinions. Professor Breckenridge confirmed that although a pilot scheme had worked well in Liverpool, it had been less successful elsewhere. It remained to be seen what success the Newcastle pilot scheme achieved.* **[MHRA0014776** (page 6), para IV]

13.8. The outcome of the pilot was highly satisfactory and led to including pharmacists' reports in the yellow card database.

13.9. Adverse reactions to Factor VIII, such as hepatitis, would certainly have been 'reportable' under the Yellow Card scheme.

13.10. As I recall, the Yellow Card Reports would be sent to the Medicines Division / Medicines Control Agency. The Yellow Cards were sent first to the three Regional Monitoring Centres in Cardiff, Newcastle and Birmingham before being communicated to ARGOS and the CSM as appropriate. The CSM maintained a Register of Adverse Reactions which recorded these reports and they would then be investigated. Other data was derived from the pharmaceutical industry, the Registrar General and coroners which would also be added to the Register.

13.11. To give some context, the CSM received 1,415 adverse reaction reports in 1964 **[WITN6406024** , (page 16)**]** which increased to 15,527 in 1986 **[MHRA0020159],** 19,246 in 1989 **[MHRA0014793]** and about 16,000 in 1990 **[MHRA0014742** (page 3)**].** The CSM's Annual Report for 1990 also shows these figures in its list of the numbers of reports of suspected adverse reactions from 1980 to 1990 **[WITN6406003]**. It also gives a breakdown for 1989 and

1990 of how many of these were in the form of Yellow Cards (7811 and 5723 respectively) and how many came in other reports (such as BNF slips (yellow cards interwoven into the British National Formulary), data sheet slips, industry reports and others).

13.12. Once received, the Yellow Card would be stamped with a unique registration number and the information coded onto a computer entry form. From around 1990 we used a new computer system called 'ADROIT' – Adverse Reactions On-Line Information Tracking – to support the monitoring of adverse reactions using the latest information technology **[MHRA0014826** (page 9)**].**

13.13. The original and coded forms were then sent to a Senior Medical Officer for scrutiny. The medical officer would check that the information entered on the computer was accurate, decide if any further information was needed from the reporting practitioner and would assess the association between the drug and the suspected reaction. At the time that 'The Control of Medicines in the United Kingdom' was written in 1977, there were 80 part-time doctors engaged to investigate reports of individual reactions at the request of the CSM or the Secretariat.

13.14. The computer system would provide signals of possible new adverse reactions or an increase in frequency of known adverse reactions. Print-outs of information on the latest reports on all drugs would be scrutinised by medical staff at two weekly meetings. A print-out of adverse reactions received for those drugs that were under intensive monitoring (discussed from paragraph 12.24 below) would be scrutinised monthly by the medical staff and the CSM SEAR sub-committee (ARGOS).

13.15. There was not a fixed number of reports that would signify a possible drug hazard. One single report might be sufficient to conclude there was an unacceptable risk. Adverse reactions reports needed to be judged by such considerations as the seriousness of the adverse reaction itself, their potential to cause a fatality or irreversible damage to a patient, the drug's use and therapeutic benefits and the types of patients who seemed to be suffering from adverse effects.

13.16. When I was on the ARGOS, we would go through the Yellow Card reports and we would use what we termed 'the rule of three'. This was an arbitrary number that we picked which we felt could be regarded as a 'signal' but that is not to say that if we saw one sole report that alarmed us, we would wait until we had two more.[4]

Investigations

13.17. Once a possible adverse reaction problem with a drug had been identified, a medical officer would be responsible for investigating. They would assess the evidence to see if there was good evidence of an association between the drug and the reaction. They would examine and analyse the original reports to characterise the reaction, identify any possible risk factors and consider evidence that the reaction was possibly or probably associated with the drug in question. They would gather information on drug use so they could assess the likely frequency of a reaction in the patient population. This might include obtaining prescription data and the Intercontinental Medical Statistics figures on drug use figures by age and sex. They would then calculate reporting rates to make an estimate of the incidence of reactions. They would look at medical literature, reports from overseas, the WHO Adverse Reaction Database, information from other drug regulatory authorities and others involved in conducting post-marketing surveillance studies. They would look at other drugs in the same therapeutic class and compare the adverse reaction profiles of drugs used for the same therapeutic purposes.

13.18. All of this work would feed into a risk / benefit analysis of the drug under investigation and a report of the findings would be presented to the Sub-

[4] In around 2000, Professor Steven Evans joined the MCA as a statistical assessor (Professor Evans is currently a member of the Inquiry's Expert Group on statistics). Professor Evans developed a novel approach to signal detection now known as 'Proportional Reporting Ratio' ('PRR'). This would compare the ratio of the number of reports of a particular adverse event to a particular product (e.g. abnormal liver function test) to the total number reports of adverse events to the same product. This ratio is then compared to the ratio of the total number of reports of the same adverse event (e.g. abnormal liver function tests) in the database as a whole. This technique is now used globally by drug regulatory agencies.

Committees of the CSM for their views. Their recommendations would then be passed to the main CSM for consideration.

Consequences

13.19. The CSM would advise the Licensing Authority of its conclusions and make recommendations on what action was required to improve patient safety. Warnings could be issued to doctors warning them of the drug's adverse reactions along with a recommendation (for example not to prescribe to a particular age group, to change the dosage or to take certain precautions). These sorts of recommendations might then be made as variations to the drug's product licence and amendments made to the data sheet with copies sent to all doctors. If a major safety hazard was identified, the CSM may advise that the product's licence should be revoked or suspended.

13.20. In most cases, the pharmaceutical company would voluntarily vary its licence and might well take action before the Licensing Authority did, in which case formal licensing action might not be needed. If that did not happen, formal regulatory action could be taken pursuant to s28 of the Medicines Act.

Dissemination of adverse reaction information

13.21. As stated in 'The Control of Medicines in the United Kingdom' (**[MHRA0004773** (page 17)**]**), there were six chief ways that the CSM warned of adverse effects and encouraged cooperation by providing feedback of information:

a) Leaflets in the 'Adverse Reactions' series were issued to all doctors, dentists and pharmacists when it was necessary to give an urgent warning about dangerous adverse reactions.

b) Where there was a major drug hazard which required immediate communication to doctors and others, the CSM chair would write to all doctors, dentists and pharmacists. These 'Dear Dr' letters would be sent as a matter of urgency to ensure that those treating patients could act quickly to safeguard their patients. It must be remembered that this was in the days before the internet or email was widely used so this was considered the fastest and most effective route to spread these important

updates. I note that the 'Control of Medicines in the United Kingdom' says that this would be used for 'less urgent warnings' but in fact, in my experience and to the best of my recollection, we used this process for the more urgent warnings as it would take less time to write the letters than to print and circulate leaflets.

c) I mentioned 'Current Problems' at paragraph 4.4 above. This regular bulletin was the method by which the CSM would inform doctors, dentists and pharmacists of possible adverse drug reactions. It had been introduced to bring information on possible early warnings of problems to the attention of professionals. It would describe suspected adverse reactions, warn of drug hazards and make recommendations to improve drug safety. As I have explained, I was on the Editorial Board when I was chair of the CSM (see for example **[WITN6406005]**). We would determine what would be published in Current Problems in three ways:

(1) When Yellow Card Scheme reports reached a certain level;

(2) To highlight important reports in published literature; and / or

(3) To act on the results of the intensive monitoring (the inverted black triangle) scheme[5] **[MHRA0014742** (page 6)**]**.

In the 1991 minutes of the Annual Meeting of the British Pharmaceutical Industry and the CSM, I note that some manufacturers raised concerns about not having been consulted or informed before information on their products was published in Current Problems **[MHRA0014742** (page 6) **]**. The minutes state 'Interaction between companies and the CSM were normally good'. This perhaps demonstrates that our primary aim was to share information with professionals and issue warnings quickly rather than engaging in lengthy correspondence with the manufacturers themselves if it appeared that issues were emerging.

[5] This is discussed further from paragraph 13.25 .

d) We made computer print-outs of the Register of Adverse Reactions reported for specific drugs, known as 'drug analysis prints', available to all doctors. These would list suspected reactions reported for particular drugs along with an explanatory note advising doctors how to interpret the information. They would be provided to medical libraries and post-graduate centres;

e) Doctors or dentists submitting Yellow Card reports would receive a copy of the relevant part of the drug analysis prints and the explanatory note; and

f) The CSM would publish adverse reaction information from the Yellow Cards in scientific journals such as the regular British Medical Journal 'CSM Updates'.

13.22. The scheme described above also applied to unlicensed drugs which would be viewed by the Secretariat of the Medicines Division/Medicines Control Agency and reported to the CSM as considered necessary. While obviously the CSM could not recommend revocation or amendment to the product licences of such drugs, we could nonetheless disseminate the news of the adverse reaction reports as described above at paragraph 12.21.

Yellow Card Scheme and Blood Products

13.23. I recently saw a table provided by the MHRA which enumerated, annually, the total numbers of yellow card reporting and those relating to certain blood products. I understand that the data was extracted from the Yellow Card database in February 2021.

13.24. Between 1 January 1970 and 31 December 1995 this data showed there were 310,042 UK spontaneous suspected adverse drug reaction (ADR) reports. Of these, 144 reports concerned a selection of blood products that have been of

interest to the Inquiry[6] which included 79 suspected cases of HIV/AIDS or hepatitis **[WITN6406025]**.

The Black Triangle Scheme

13.25. In 1976, the Black Triangle Scheme was launched to place new products under special surveillance. It was known as the 'Special Reporting (Black Triangle) Scheme'. New products (drugs / medicines etc) were identified with an inverted black triangle symbol (▼) in the British National Formulary ('BNF'), the monthly index of medical specialities ('MIMS'), Data Sheet Compendium and product advertising material. This distinguished them from established products.

13.26. Where a product was marked with a black triangle, all suspected adverse reactions were to be reported (for example by way of a Yellow Card Report). This applied even where the reactions seemed minor or were well-recognised and even where the practitioner was unsure if there was a causal relationship.

13.27. New products were (and continue to be) marked in this way because when they come on the market, there is relatively limited information from clinical trials about their safety. Only when large numbers of patients have taken the medicine are rare or long latency adverse effects identified. It is therefore crucial that effective surveillance takes place after marketing to ensure the identification of rare adverse effects and to ensure appropriate action is taken.

13.28. The triangle was initially reviewed after four years and removed unless there was a specific concern but this was later reduced to two years unless the CSM had a concern about its safety **[WITN6406026** (page 5)**]**. Although the review was to be automatic (at least from 1988 onwards) I have seen the licence for Antihaemophilic Factor (Human) Method Four-Heat Treated Hemofil HT which was granted in February 1985 and which stated:

> *3. Special reporting instructions apply to this product [...] You should mark this product with a black triangle in the data sheet. You may apply to the Licensing Authority after four years for this to be removed.*

[6] 8Y; Anti-haemophilic Factor (Human); F9; Factorate; Feiba; Gammagard; Hemofil; Humanate; Hyalase; Hyate C; Immune Serum Globulin; Koate; Kryobulin; Profilate; Prothromplex; Monoclate P.

[MHRA0000087(page7)**]**

13.29. In 1988, the CSM reviewed and revised the Black Triangle Scheme to make it a more effective alerting mechanism **[MHRA0014826** (page 9 paragraphs 31-32)]. Our concern was that it was appearing on too many drugs for it to serve as an effective alerting mechanism **[WITN6406026** (page 4)**].** As a result, drugs were to be selected for the scheme on an individual basis and the triangle was to appear on all prescribing information and advertising. We also published an article reminding all doctors, dentists and pharmacists of the significance of the black triangle symbol and a poster list of all the products then carrying the symbol in the 24th edition of Current Problems **[WITN6406027]** and it was regularly re-issued thereafter (see for example **[WITN6406021]**). The aim of this was to allow it to be kept to hand in surgeries, wards and outpatient clinics to remind doctors and others of those drugs requiring special reporting.

13.30. It is apparent from the minutes from the ABPI and CSM annual meeting on 8 March 1990 **[MHRA0014776** (page 5)**]**, that the CSM was disappointed that the black triangle was displayed so unprominently in some advertisements and that '[l]arge numbers of doctors apparently do not understand what the inverted black triangle means'. At the meeting, the ABPI accepted a suggestion that the triangle should always be against the proper name of the product in the body of the advertisement and of a size that gave prominence to it, relative to the size of the advertisement. It felt that MIMS and BNF clearly explained its meaning so no additional words were needed next to the triangle itself. The minutes stated, probably fairly, 'it is difficult to quantify its effectiveness'. Its effectiveness was dependent on patients reporting even minor side-effects to their doctors and the doctors knowing that this was a new product and making an adverse reaction report. I do not now recall the scheme's effectiveness – and I suspect it was difficult to assess even at the time because of the many unknown unknowns. I do not recall what training about the scheme was given to clinicians. That said, the minutes of the ABPI and CSM annual meeting held on 24 July 1991 suggested that the scheme was useful with examples given of a warning with an age limit being issued for one product, early publication of advice in Current Problems on two products, discussions with the British

Diabetic Association on problems relating to human insulin and the establishment of a working party on the use of beta agonists in asthma treatment, which I led **[MHRA0014742** (page 2)**]**.

13.31. Blood products were among those which were marked with the triangle (see by way of example 'Factor VIII Fraction (Monoclate P)' features on the list from June 1991 **[WITN6406021])**. I cannot recall anything about the scheme with regards to blood products specifically.

Section 14: Batch Release Procedure

14.1. To be clear from the outset, I have virtually no independent recollection of the 'batch release' scheme and am heavily reliant on what I have read in the documents.

14.2. I have seen from the documents I have been provided (such as **[BAYP0000001_110]** dated 2 February 1976), that the batch release procedure was in operation before I started work on the CSM Sub-Committee in 1979. The requirements of the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1976 gave the Licensing Authority the power to require the submission of protocols and samples from each batch of a product for examination (see for example, Guidance Notes on the Application of the Medicines Act 1968 to Biological Medicinal Products **[MHRA0033773** (page 8)**]**). The Regulations also allowed the Licensing Authority to direct that a batch must not be sold or supplied or offered for sale or supply until it had been issued a certificate by the Licensing Authority (which, as covered at paragraph 10.7 above, I think was referred to as a 'stop order').

14.3. Batch release procedure was where, after a product had been licensed (and often as a condition of its licence), a sample would be taken from a batch of a product and checked by NIBSC to ensure that the composition of the batch matched the manufacturer's specifications as well as the licensing conditions such as labelling requirements. In particular, NIBSC was concerned with checking potency. Once it was confirmed that the sample met the specification,

the batch of that product would be issued with a Batch Release Certificate and could be released onto the market and sold.

14.4. The CSM could include a condition on a licence that the product must be subject to the batch release procedure but other than this, as far as I recall, the CSM played no further role in the batch release procedure. It has been suggested to me that NIBSC would give advice to the CSM about product licence applications and this may well be correct (though I do not now recall it).

14.5. The batch release procedure would continue until the manufacturer had satisfied the Licensing Authority regarding its capacity and ability to ensure that the product met the specification and conditions of the product licence and that batch consistency could be maintained. For some hazardous substances, the batch release procedure would be applied permanently.

14.6. I cannot say what information was typically required from manufacturers to be submitted when complying with the batch release procedure as this was not something that the CSM or I dealt with directly; it would have been a matter for NIBSC and the Medicines Division / MCA). Equally, I cannot say if it evolved over time.

14.7. I do not know but think it unlikely that the batch release procedure would apply to blood products which were to be used on a 'named patient basis' or any other bases which sat outside the formal licensing process. I say this because prescribing on a 'named-patient basis' involves a prescriber requesting supplies of an unlicensed product for a particular (i.e. 'named') patient. It would have been impossible for the CSM to have either overseen, or restricted, 'named patient prescribing' which was permitted under section 9 of the Medicines Act 1968. The Act was in force in various forms from its implementation on 25 October 1968 throughout my career.

14.8. I do not now recall the circumstances in which agreement to participate in the batch release procedure would be stipulated as a condition for granting a product licence. It seems to have been commonly applied to biological products (including blood products) prior to 1986 (and I have seen for example at letter

from 1983 **[DHSC0002227_035** (page 2)**]** which suggests that '"batch release" condition' was imposed on 'all blood products' in or by 1983, but I cannot comment if this was actually correct). Nonetheless, it is clear that from 1986 following a recommendation of the CSM from around June 1986[7], all blood products were subject to the batch release procedure **[DHSC0002303_030]**. I do not know or recall the circumstances in which, once batch release was imposed as a condition, the batch release procedure would thereafter be used for a particular product.

Section 15: Relationships with pharmaceutical companies

Pharmaceutical companies and the CSM

15.1. Interactions between individual pharmaceutical companies (also referred to as 'manufacturers') and the CSM were almost entirely conducted by the Secretariat of the Medicines Division / MCA. The only occasions when there would be direct interaction between members of the CSM would be at the annual meetings between the CSM, the staff of the Medicines Division / MCA and the ABPI and during oral hearings (when a manufacturer would appeal against adverse advice or decisions of the CSM).

15.2. I am unsure about the 'rules' relating to CSM members' financial or other interests with pharmaceutical companies during my time as a member. I would hope that members would have been required to inform the CSM of any potential conflicts of interest and I note that there are instances in the CSM minutes where members declared interests. I can confirm, however, that during my tenure of office with the CSM and MHRA I had no dealings with individual pharmaceutical companies and had no investments in pharmaceutical (or devices) companies.

[7] I have not seen a copy of the minutes of this meeting and am unaware whether the minutes still exist.

15.3. I cannot comment on why CSM members were permitted to have interests in pharmaceutical companies.

15.4. I do not recall any occasion when pharmaceutical companies attempted to influence the decisions of CSM members apart from appropriately attending, and contributing to, oral hearings.

Pharmaceutical companies and clinicians

15.5. I do not now know or recall the 'rules, regulations or guidance' in place concerning relationships between clinicians and pharmaceutical companies. It is important to appreciate that companies need to collaborate with clinicians during the development of drugs in order to assess the product's effectiveness and safety. Such clinical trials are now regulated by the MHRA.

15.6. I have been shown the CSM Minutes from 22 January 1981, a meeting I attended **[MHRA0036365_001].** At the meeting was a hearing in respect of Humanate, a Speywood product **[MHRA0036365_018]**. The minutes record that the 'representatives' of the Company were a spokesman, Mr D Williams, and Dr Peter Jones, the Director of the Haemophilia Centre at the Royal Victoria Hospital in Newcastle. Although I cannot recall how often clinicians appeared in support of pharmaceutical companies at oral hearings of the CSM, it was not uncommon. They were usually present to give expert advice to the CSM on behalf of the company.

15.7. The background recorded in the minutes explains that in February 1980, Speywood obtained a variation to their product licence for an anti-haemophilic globulin (Factor VIII) called Koate. This permitted them to sell remaining stocks of Koate for up to a year and then to import an anti-haemophilic globulin (Factor VIII) manufactured by Cutter (but purchased from Parlier Medical Supply Company) to relabel the product and sell under the new brand name Humanate. I am afraid, however, that I do not recall whether or how frequently such 'variations' to a Product Licence occurred or whether such 'variations' were routinely referred to the CSM or only if the professional secretariat had concerns.

Royal College of Physicians' College Working Party on the Ethics of the Relationship between Physicians and the Pharmaceutical Industry

15.8. On 18 October 1984, I attended the Royal College of Physicians' College Working Party on the Ethics of the Relationship between Physicians and the Pharmaceutical Industry by invitation **[RCPH0000299].** The Working Party's remit seems to have been to draw up some guidance for physicians following concerns about the relationships between doctors and the pharmaceutical industry. At the meeting there was discussion about hospitality and gifts being given by the pharmaceutical industry to those in the medical profession.

15.9. I have no recollection of the meeting nor have I retained any documents relating to it. My comments at the meeting were recorded and although I cannot remember this, I believe that they would have been a fair reflection of my views and input:

> *6a….Dr Rawlins said that the fundamental ethical issue was very much based on the fact that doctors spent very large sums of public money each year, and that the public could reasonably expect doctors to prescribe drugs with deference to their efficacy, safety and economy. The public might sometimes feel that prescriptions were based on drug company advertising and there was much public concern on this matter. The result might be the emergence of Drug Watch Committees. Physicians had a special responsibility in relation to prescribing: many doctors regard physicians as teachers. Knowledge of how to use drugs was derived from physicians either by prescribing, mimicry (doctors tend to use drugs they saw physicians using), and they also exerted influence as authors and editors of articles. Sometimes there was pressure on the physician to refer to a drug in a favourable light, and attempts at persuasion were made. Dr Rawlins said it was evident on occasions that pressure was used by colleagues who had been doing research on behalf of a company, and he felt strongly that consultancies and their financial details should be declared. He felt that money should not go to one person but to a department.*
>
> *[…]*
>
> *b. Dr Rawlins wanted the GMC to be involved, giving doctors positive advice concerning their relationships with the Industry; he felt that bad publicity was too drastic a deterrent, and he thought that a watchdog committee would be a welcome concept, especially as far as the pharmaceutical industry was concerned. Doctors did not always*

> *recognise when they were being manipulated and therefore it might be unfair to pillory them.*
>
> *c. Dr Rawlins would like to see hospitality totally divorced from promotion;… The usual practice was for company representatives to find out if consultants used a drug before issuing invitations and to participate on these terms was unethical. If this independence was observed, Sir Kenneth wondered what was the point of the drug company being involved at all. Dr Rawlins said that the company was buying goodwill. In reply to the President's question Dr Rawlins said he would prohibit stalls advertising drugs at meetings.*

15.10. My concerns – and those of others – about the relationships between pharmaceutical companies would have been general and not just in respect of blood products. Similarly, any concerns about the suppression of unfavourable results would have been general and not specific to blood products.

15.11. Where it is recorded that I said, 'it was evident on occasions that pressure was used by colleagues who had been doing research on behalf of a company, and [I] felt strongly that consultancies and their financial details should be declared', this would have been a reference to my colleagues in Newcastle – I do not think I meant any reference to those doctors who were members of the CSM.

15.12. My reference to 'stalls' (paragraph 6c) advertising drugs at scientific meetings would have been related to all drug promotion not just blood products. I believe it would have been a reasonably common occurrence and I felt it was inappropriate for pharmaceutical companies to advertise their products at scientific meetings where the focus should be on independent discussion looking at efficacy and safety. Those attending might have felt inhibited by the presence of pharmaceutical companies and the discussion might not have been as frank as it would otherwise have been.

15.13. Following this meeting, in March 1986, the RCP's Working Party published the 'Report on the Relationship Between Physicians and the Pharmaceutical Industry' **[RCPH0000105].** It is almost 36 years since this report was published and I cannot now recall whether and what 'inducements' were made to clinicians to prescribe blood products or unlicensed products. I am sure that promotion of pharmaceutical products was effective in persuading clinicians to

prescribe them, otherwise companies would not have gone to the trouble and expense. Again, though, this relates to all drugs and not just blood products.

Section 16: Knowledge of and response to risk of infection associated with blood products

Hepatitis

16.1. At Newcastle, my clinical practice was devoted to clinical pharmacology and general internal medicine. I therefore had no practical experience of treating patients with haemophilia and no experience of managing patients with hepatitis. I was aware of the broad outlines of both haemophilia and hepatitis but was not an expert in either condition.

16.2. I had no association with either the CSM or its sub-committees in the mid-1970s when anti-haemophilic treatments were first licensed. I only became aware of the association between the use of blood products and hepatitis in the 1980s as a member of the CSM and through my work as the chair of Newcastle's District Drug and Therapeutics Committee and on an Ad Hoc Group to Consider the Use of Heat-Treated Factor VIII Concentrate in 1984 (see **[BPLL0002848_003]**). I presume, but cannot be certain, that most treating clinicians became aware of the problem at around the same time.

16.3. I cannot recall the information that was provided by pharmaceutical companies about the risk of hepatitis associated with blood products to the CSM and / or to the Licensing Authority and / or to treating clinicians. I understand that it was mentioned as a risk on warning labels and data sheets which were submitted with product applications (see for example **[ARMO0000002]** page 60) and it was something that would be discussed at CSM meetings (see for example the meeting on 25 July 1991 **[MHRA0034575_063** page 5**]**) so it was clearly on the CSM's radar.

16.4. Beyond what I have set out elsewhere in this statement, I cannot recall more detail about the response of the CSM to concerns about transmission of

hepatitis B and non-A non-B hepatitis in blood products, save to say that of course it was something that we took very seriously and about which we were very concerned.

Hemofil: 1985

16.5. On 18 March 1985, I was copied into a letter from Dr Peter Jones to Mr Peter Hopley **[TYWE0000014].** I think it is likely that the reason I was copied into this letter was because at the time I was the chair of Newcastle's District Drug and Therapeutics Committee (rather than in relation to my role on the CSM).

16.6. Despite the contents of this letter, as I recall from a subsequent meeting of the Hospitals' Division of Medicine, I verbally advised that, notwithstanding the additional costs, we should use heat-treated Factor VIII rather than expose patients to the risks associated with non-heated material. Some of my colleagues in the Medicines Division stated that since some patients had already been infected, the heat-treated material should only be offered to patients uninfected with hepatitis B or HIV. The argument was curtailed by a statement from the District General Manager, Chris Spry, that he was not prepared for *any* patient in his area to be given material known to be contaminated, irrespective as to whether they had been infected or not. He would therefore authorise the additional costs.

16.7. I have no idea, however, what information would have been communicated to patients, either in Newcastle or in the rest of the UK, who received blood products with a high incidence of Non-A Non-B hepatitis.

16.8. The letter referred to a Travenol Factor VIII product. In 1984, the CSM considered a licensing application for Travenol's Factor VIII product Hemofil T. In the Addendum to the Interim Report **[SHPL0000283_005** (page 118)**]**, appended to 'Appendix IV, An Attempt to Reduce the Risk of Hepatitis with Heat Treated Factor VIII Concentrate – Interim Report from February 1984', there appears to be an update to a study from 26 July '1874' (this date is clearly wrong). It states that there was:

> *...an incidence of non-A, non-B hepatitis of 55%. This compares favourably with the 64% calculated from the last assessment in February...It should be noted that no clinical signs or symptoms of hepatitis have been seen with the exception of one patient who developed post-surgical jaundice. No case of seroconversion for hepatitis B has occurred although only 6 of the 20 patients were vaccinated against hepatitis B.*

16.9. I note that when the CSM considered Hemofil in September 1983, we advised that we could not recommend a product licence be granted on grounds relating to safety, quality and efficacy because, among other concerns, 'inadequate evidence of safety and efficacy was provided...justification should be provided for the inclusion and choice of heat treatment [and] the heat treated product was inadequately characterised' **[WITN6406036** (page 32)**]**. We remarked to the manufacturer that 'Evidence of the long-term safety in haemophilic patients of treated products such as this is regarded as an important pre-requisite of licensing.' We also deprecated to the Licensing Authority the '[p]romotional letters making unjustified claims on improved safety margins in respect of infection and AIDS'. This shows that the CSM was not simply granting produce licences without critically analysing them and was not afraid to report back to manufacturers and the licensing authority with concerns.

16.10. A licence for Antihaemophilic Factor (Human) Method Four-Heat Treated Hemofil HT was granted in February 1985 **[MHRA0000087, page 7].** This imposed special reporting instructions under the black triangle scheme for four years.

Blood Products and Testing of Hepatitis C: July 1991

16.11. At the CSM meeting on 24 July 1991, a paper entitled 'Blood Products and Testing of Hepatitis C' was considered **[MHRA0034575_063]**. The CSM made the following recommendations (which I note refer to anti-HIV rather than hepatitis):

> *7.1 All UK licensed products manufactured from human plasma should be produced from donors tested and found negative for anti-HIV by suitable validated tests, from a date to be agreed.*

7.2 The Companies should provide samples of plasma pools, intermediate and final product, to NIBSC as part of the batch release procedure.

7. 3 There should be no recall of untested products produced before the implementation date.

7.4 The decision should be referred to the CPMP so that a harmonised policy can be agreed throughout the EEC.

16.12. I have not seen a copy of the original paper and I cannot now recall the information which was taken into account by the CSM in formulating these recommendations. Nor can I say why these recommendations were implemented at this time (if indeed they were); what level of compliance there was from pharmaceutical companies or why there should be no recall of untested products before the implementation date. It is difficult for me to comment now on whether these decisions related to hepatitis testing and, if so, whether they should have been made sooner. I cannot recall whether there was discussion of the information that should be provided to patients by clinicians or labelling regarding possible risks associated with untested products, nor can I say what happened once this issue was referred to the CPMP.

AIDS

16.13. I am uncertain when I first became aware of the association between AIDS and blood products but it was probably in the early to mid-1980s. I am equally uncertain as to when pharmaceutical companies provided information about the risks of HIV and AIDS in blood products to the CSM, the Licensing Authority and / or to treating clinicians.

16.14. Again, beyond what I have set out elsewhere in this statement, I cannot recall more detail about the response of the CSM to concerns about transmission of HIV and AIDS in blood products, but as with hepatitis, it was something that we took very seriously and about which we were very concerned.

16.15. I have seen the CSM minutes from 21 and 22 July 1983 at which the paper 'Summary of Main Points from a Consideration of AIDS and Licensed Blood Products' was considered **[DHSC0006259_007]**.

16.16. It is important to remember that at this point, our understanding of AIDS was much less developed than it is now. The Biologicals Subcommittee recorded in their recommendations that, 'There is need for research work on AIDS in the UK, especially in relation to the possible new introduction of this disease into the virgin soil of the United Kingdom'.

16.17. I was present at this meeting in July 1983. I have also seen a copy of the paper (described as 'tabled paper 4'). It is a summary of a discussion that took place at the Biologicals Subcommittee on 13 July 1983 during which they were advised by various expert advisors: Professor Bloom; Dr Craske; Dr Galbraith; Dr Gunson and Dr Mortimer.

16.18. The CSM's conclusions endorsed those of the Biologicals Subcommittee. The Biologicals Subcommittee and CSM were unsure of the aetiology of AIDS but an infectious agent 'seems likely'. They also recorded the following conclusions:

> *(2) Patients who repeatedly receive blood clotting-factor concentrates appear to be at risk, but the evidence so far available suggests that this risk is small. The risk appears to be greatest in the case of products derived from the blood of homosexuals and IV drug abusers resident in areas of high incidence (eg, New York and California), and in those who repeatedly receive concentrates in high dosage. Balanced against the risks of AIDS (and of other infections transmitted by blood products) are the benefits of their use; in the case of haemophilia they are life-saving.*
>
> *(3) The possibility was considered of withdrawing clotting factor concentrate from the market and replacing them with cryo-precipitate. It was concluded that this is not feasible in the UK on grounds of supply.*
>
> *(4) The possibility was considered of withdrawing US preparations from the UK. It was concluded that this is not at present feasible on grounds of supply. Moreover, the perceived level of risk does not at present justify serious consideration of such a solution. Efforts are however being made to secure UK independence of foreign suppliers of clotting factor concentrates. This should reduce markedly, although not eliminate, the risks to recipients of these products, and the Sub-Committee strongly supports this aim. The Sub-Committee was also informed that the UK Haemophilia Centre Directors have adopted a policy for use of US Factor VIII in order to minimise risks as far as possible.*

> *(5) It is advisable that all clotting-factor concentrates derived from US plasma sources and intended for use in the UK be prepared only from material manufactured from plasma collected after new regulations were introduced by the FDA on March 23rd 1983. These regulations, were introduced specifically to minimise the likelihood of collecting blood from affected donors. This step is recommended notwithstanding the possibility that its practical value may be relatively small. It cannot, however, be taken until supplies of post-March 23rd material can be assured. It is recommended that close contact is maintained between the Licensing Authority and Supplies Division with the aim of introducing this step immediately it becomes feasible. […]*

16.19. They went on to note that efforts were being made to develop and introduce products treated to inactivate the viruses but that none were presently available in the UK.

16.20. I cannot, from memory recall the basis for these decisions as I do not have the relevant background papers (described as 'current information available on incidence and epidemiology, aetiology and related factors') or any notes of the discussion on which the CSM or Biologicals Subcommittee based their decisions. I have no recollection of the meeting or discussion and am again reliant on the documents. I have no recollection of the evidence available at the time which suggested that the risk to patients who received or repeatedly received blood clotting factor was small.

16.21. Although I cannot recall the factors that led to the conclusion that it was not feasible to withdraw factor concentrates and replace them with cryoprecipitates, I think that decisions such as this would depend on the nature of the risk and its frequency as well as the nature of the benefits. Decisions such as these (which apply to all medicines and not just blood products) were and are invariably based on a subjective judgement rather than on mathematical modelling. From what little I remember from the time, I think we would have been influenced by the serious concerns that withdrawing these products without suitable replacements would have endangered the lives and / or health of haemophiliac sufferers, reduced their life expectancy and very seriously worsened their standard of living. This would have been balanced against what was understood of the risk at the time. It is not possible to say what would have

been considered to be the necessary perceived level of risk for factor concentrates to be withdrawn from the market but I think it is correct to say that if we had known then what we know now about AIDS, urgent action would have been taken and it is possible that those products would have been immediately withdrawn (though it is fair to observe that there would have been consideration of other options too and it is simply not possible now to say what would have happened).

16.22. I do not recall or know to what extent the discussions referred to the need to inform patients of the risks – as they were understood at the time – relating to blood products they were receiving.

16.23. In the rule 9 letter I have been sent, it states that the FDA recommendation of 23 March 1983 'advised that all factor products, derived from US plasma, for use within the UK, be prepared only from material manufactured from plasma collected after that recommendation had been introduced'. Although I have no recollection of the FDA recommendation, I do not believe that this is a correct statement. The FDA would not have issued any recommendation directed at the UK, this being outside their jurisdiction. My understanding is that in March 1983, the FDA issued recommendations to expand medical screening of blood and plasma donors in the US (see for example, paragraph 30.11 of the Penrose Inquiry Report). As the paper's recommendations recorded, this was to 'minimise the likelihood of collecting blood from affected donors'. The recommendation that all factor concentrates from US sources 'intended for use in the UK be prepared only from material manufactured from plasma collected after new regulations were introduced by the FDA on March 23rd 1983' would have been a recommendation made by the CSM and Biologicals Subcommittee, not the FDA.

16.24. I have been asked 'Why was the practical value of this step deemed to be "relatively small"?'. As the conclusions record, it was not said that the practical value was deemed to be relatively small, but that it was a '**possibility** that its practical value **may** be relatively small' (emphasis added). This shows that the step was being recommended as a precaution out of an abundance of caution:

the CSM was conscious that it might prove of small practical value but it was nonetheless a step worth taking in order to minimise the risk. This shows that we did not have an accurate understanding of the risk posed by AIDS at that time. These decisions should not be assessed with the benefit of hindsight.

16.25. I have been shown an extract of a press release which appears to summarise the 'guidelines' **[HCDO0000392_089]**. It says:

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

16.26. I can see that this too (assuming it is an accurate summary) might explain the possibility that the practical value of using only plasma collected after the date that these recommendations were made may be relatively small. First, they are only recommendations so plasma centres and blood banks may not have applied them. Secondly, they are recommendations that would take some time to implement: education programmes, training and instruction for staff and establishing procedures could take months to implement; they would not happen overnight. And finally, the recommendations relied on paid donors to understand the information that they were given about AIDS, information which may not be palatable, and then to choose – often at ongoing financial cost to themselves and at risk of exposure or embarrassment – not to give blood. I cannot assess whether this in fact made any difference but I can understand why it might not have been considered likely to have a significant impact.

16.27. I cannot comment on the effect of the recommendation as I have no recollection of what effect it had.

16.28. I note the CSM's conclusion (7) said:

> *The Sub-Committee learnt that manufacturers were producing advertising material for use in the UK which appeared to make unjustified claims concerning the safety of heat-treated Factor VIII. It is advised that this should be stopped. It is feared that unlicensed material could be used on a named-patient basis, despite the fact that its safety and effectiveness had not been established or considered by the Licensing. Authority.*

16.29. I have no recollection of the unjustified claims that were made or by whom. I have been asked why the CSM 'advised' and '[w]hy was this not regarded as mandatory?'. The CSM was an advisory body. We had no powers other than to advise the Licensing Authority. I cannot recall what steps were taken to stop any such advertising.

16.30. I do not have any recollection of which, if any, unlicensed products were being used as described. That situation (where an unlicensed product is used on a named patient basis despite its safety and efficacy not having been established or considered by the Licensing Authority) could arise, even today, because clinicians have the freedom to prescribe any product on a named patient basis, even those which are unlicensed and untested.

16.31. I have no recollection of unlicensed products being advertised by pharmaceutical companies.

Elstree Product: December 1984

16.32. On 13 December 1984, Dr Peter Jones wrote a letter to five of his colleagues to which I was copied 'for information' **[PJON0000068_001]**. The letter states 'There is evidence that at least two batches of the Elstree product were compromised following donation by a donor with AIDS'. It described a policy by which '[w]e shall use up our present stock of NHS on patients already exposed to the relevant batch'. I do not recall seeing this letter though of course I may have at the time. I am not able to shed any light on the basis for Dr Jones's decision. As I have stated at paragraph 16.6 above, I was opposed to the continued use of non-heat-treated products (which would include this compromised stock), even on patients already treated with such products, and I hope that I would have communicated my views to Dr Jones but I cannot now

remember whether I did. Given there is another letter from Dr Jones to me written shortly after this on a similar subject (dated 25 January 1985), it looks as though we may have been in some sort of communication about the issue. I cannot say whether the product was withdrawn from use and if not, why not, nor do I know whether this decision was implemented and if so, how widely among other virologists, members of Reference Centres and / or Blood Transfusion Centres.

16.33. I see that in the letter Dr Jones said he believed that the risk of thromboembolic complications in commercial heat-treated Factor IX concentrate 'outweighs the risk of AIDS from Factor IX concentrate'. I do not recall any concerns about this and cannot say if it was a commonly held view. I would have deferred to his expertise on the matter. I do think, however, that it reflects how little was known about AIDS at this time and, unfortunately, the fact that in the early 1980s, its true ramifications were not fully understood.

16.34. On 25 January 1985, Dr Jones wrote to me directly about the current requirements for Factor IX units **[PJON0000010]**. He described two boys that he was treating with Factor IX concentrate for whom he did not yet have HTLV-III antibody results. He said that 'in view of their very high exposure already I think that they prove the exception to the rule' but I have no idea what he meant by this. I have no recollection of my own understanding of viral transmission in relation to Factor IX at that time. While I have no knowledge of what the two boys or their families were told about the potential risk of infection through the use of this product – and would not have been party to consultations, their treatment or to decisions on what to tell them – I think it is unlikely that the boys or their families would have been informed of the potential risk of infection. Those were the days of 'clinical paternalism' where clinicians often felt (for a variety of reasons) that patients or their families should not be unduly worried about this treatment.

CSM Meeting: 21 November 1985

16.35. At the CSM Meeting on 21 November 1985, among the routine work that we undertook considering applications, the CSM considered a paper entitled

'Screening for HTLV-III' and a letter from Dr Schild of NIBSC **[DHSC0105567].** We endorsed a recommendation made by the Biologicals Subcommittee to pass on to the Licensing Authority the following remark (paragraph 8.2):

> *The Committee is anxious that individual donations for all blood products should be screened for HTLV-III from the earliest possible date. Manufacturers should be requested to confirm that donations are being screened and to provide information about the nature of the screening tests used.*

16.36. This recommendation would then have been conveyed to the Medicines Division to undertake on behalf of the Licensing Authority.

16.37. The minutes also recorded 'it was also suggested that the Licensing Authority should consider the question of unlicensed blood products prepared in the UK under Crown privilege'.

16.38. I have been shown a letter from D.O. Hagger to Dr Harris (DCMO) dated 10 January 1986 which shows some detail of what followed the CSM's recommendation **[DHSC0001423]**. Mr Hagger recorded that at least one source of intramuscular, and one source of intravenous, immunoglobulin prepared from individually screened plasma donation was to be ready later in January with at least one more of each source by March / April 1986. Following discussion of 'the implications of the evidence available to them at this week's meeting', the Biologicals Subcommittee's provisional recommendation to the CSM was that 'no new licensing action should be taken to withdraw or restrict supplies of immunoglobulin preparations but that a very close watch on the situation should be kept'. The rationale for this was set out in the letter. The Biologicals Subcommittee also recommended that from 1 July for intravenous and 31 December for intramuscular, all products should be prepared from donors shown to be HTLV-III antibody negative, with immediate effect no preparations containing HTLV-III antibody in the plasma, pools, bulks or final products should be released for use and manufacturers should provide evidence of their capacity for their process to inactivate viruses. The manufacturers were to be told of these likely new requirements. This recommendation was endorsed by the CSM at its January meeting

[MHRA0036362_002]. Again, this recommendation would have been conveyed to the Medicines Division to undertake on behalf of the Licensing Authority. I do not recall (and am not sure that I would have known at the time) what was the nature of the manufacturers' response nor what sort of information was provided and whether it was regarded as sufficient reassurance about the degree of screening.

CSM Meeting: 30 January 1986

16.39. At the CSM Meeting on 30 January 1986, again among other matters, the CSM considered the paper 'The Safety of Immunoglobulin Preparations' and a report following contact with the producers of immunoglobulin preparations **[MHRA0036362_002].** We endorsed the recommendation of the Biologicals Subcommittee as follows:

> *The Committee recommended, on the evidence considered, that no new licensing action to withdraw or restrict supplies should be taken in respect of intravenous or intramuscular immunoglobulin preparations.*
>
> *However:*
>
> 7.1.1 *All immunoglobulin preparations should as soon as possible and not later than 1 July 1986 for intravenous and 31 December 1986 for intramuscular, be prepared only from donors shown to be HTLVIII antibody negative.*
>
> 7.1.2 *As from now, no preparations containing HTLVIII antibody in the plasma pools, bulks, or final product should be released for use.*
>
> 7.1.3 *Manufacturers should provide evidence of the capacity of their process to inactivate viruses by 1 July 1986 in respect of intravenous, and 31 December 1986 in respect of intramuscular immunoglobulin preparations.*
>
> 7.1.4 *The Committee considered that at present there was insufficient evidence to justify changing the indications for use of immunoglobulin.*
>
> *7.2 The Committee recommended that close surveillance should be maintained of the development of any new virological, epidemiological or clinical data.*

16.40. I cannot say whether these recommendations could reasonably have been arrived at sooner. The Medicines Division would raise matters such as this with the CSM if they had concerns and at that stage we would offer advice in the form of recommendations. I have no recollection of what information the CSM

had at this time regarding the ability of manufacturers to inactivate viruses but from the wording of the recommendation, it seems fair to presume at this time manufacturers had the ability to inactivate these particular viruses (such that they could provide evidence of this capacity) and, if not, that the Medicines Division would have either suspended or revoked their licences.

16.41. The CSM had made recommendations about HTLV-III screening in November 1985 (as described in paragraph 16.36 above). I do not know what happened about screening between November 1985 and January 1986. That would have been a matter for the Medicines Division to investigate and evaluate. I have been asked whether these recommendations applied to the prescription of unlicensed blood products on a named patient basis. The Licensing Authority and the CSM only dealt with licensed products (and those for which a licence was sought) so I think it is unlikely that any of the CSM recommendations could apply to unlicensed products prescribed on a named patient basis.

16.42. It is perhaps also worth adding that although the Department has not been able to locate the minutes for this meeting, I have seen a letter dated 25 June 1986 which records that at the CSM's last meeting, we had been considering the manufacture of blood products from plasma derived from unscreened donors **[DHSC0002303_030]**. We made the following recommendations:

> 1. *All blood products should be prepared from plasma individually tested for HBsAg and anti-HIV. Companies producing blood products should apply for variations to their product licences to cover this point as soon as possible.*
> 2. *Details of the method of testing for HBsAg and HIV antibody should be supplied.*
> 3. *All blood products will be subject to the batch release procedure.*

16.43. I am uncertain as to whether any earlier decisions or actions could, or would, have impacted on the number of individuals infected with AIDS.

Variant Creutzfeld-Jakob Disease (vCJD)

16.44. I have put together the following account in response to the questions I have been asked from my recollection and using the documents I have been shown,

but I am conscious that a fuller and perhaps more accurate account can be found in Volume 8 of the BSE Inquiry Report.

16.45. During the 1980s, I recall there were concerns in government about the risks of human transmission of BSE (vCJD) following the consumption of meat from cattle infected with BSE. Beyond this, I had very little knowledge or understanding of the possibility of transmission of BSE / vCJD associated with the use of blood and / or blood products.

16.46. I have seen that documents suggest that in October 1988, the CSM first considered the issue of bovine materials in pharmaceuticals (**[WITN6406028])** so I think it would have been around this time that BSE / vCJD (or nvCJD as it was originally called) first came to my attention in a professional capacity. I understand that at this time, '[t]he CSM recommended that no action be taken on oral or topical products but that no brain or lymphoid tissue should be used in parenteral products. All products should be sourced from outside the UK and should come from healthy herds which had not been fed material of animal origin'.

16.47. I recall that a Working Party on Bovine Spongiform Encephalopathy was set up, chaired by Sir Robert Southwood. In November 1988, this Working Group sought information from the CSM and there was some correspondence between Sir Robert and my predecessor Professor Asscher (see a briefing note on the role of the MCA in relation to the emergence of information relating to BSE **[WITN6406028]** ('the MCA Chronology')). The CSM endorsed the views of the Biologicals Subcommittee and SEAR that no immediate action should be taken against oral products in which bovine material had been used. Sir Richard approved the CSM recommendations in December 1988.

16.48. On 26 January 1989, Professor Asscher again wrote to Sir Richard saying that the CSM needed to consider the possible hazard from use of bovine material as an intermediate in the manufacture of products such as foetal calf serum which was extensively used in producing vaccinations.

16.49. In February 1989, the Working Party produced its report **[WITN6406029]**. It concluded that the risk of transmission of BSE to humans 'appears remote' but there was a 'possibility' that it could be 'transmitted orally [which] cannot be entirely ruled out' (paragraph 5.3.5). They did, however, note that '[w]ith the very long incubation period of spongiform encephalopathies in humans, it may be a decade or more before complete reassurance can be given' (paragraph 5.3.1). Considering other routes of transmission, the Working Group drew the attention of the Licensing Authority to the potential for the transfer of BSE in human and veterinary medicinal products (paragraph 10.5).

16.50. Some potentially contaminated materials such as cat-gut (used for stitches) could be readily removed from the market but there were very serious problems relating to vaccines and this is where the CSM became involved. Many injected vaccines (e.g. MMR) were manufactured using foetal calf serum. There was therefore a real possibility that their use could be associated with the subsequent development of vCJD. Moreover, although it was possible for foetal calf serum to be derived from countries with no vCJD in cattle, it would take three years for sufficient supplies to become available to inoculate the UK population of relevant children.

16.51. The MCA therefore convened a joint meeting of the CSM and its veterinary equivalent, the Human and Veterinary Medicines Briefing Group ('HVMB'). If my memory is correct, this was at the behest of the CMO. The HVMB consisted of members from the Department of Health and the Ministry of Agriculture, Fisheries and Food as well as other invited experts of which I was one **[WITN6406030]**. On 22 February 1989, the HVMB met to agree advice to give the CSM. The HVMB considered the Southwood Committee's opinion that 'cattle would prove to be a "dead end" host for the BSE causing agent and that it was unlikely that there would be any implications for human health.' The HVMB concluded that the slight theoretical risk of BSE being transferred to humans was more likely from products used parenterally such as vaccines rather than orally and it acknowledged that the implications for vaccination programmes could be very serious. The question of unlicensed products involving bovine ingredients was also raised but not subject to the Medicines

Act and instead controlled by the Supplies Technology Division. It appeared that they would follow the CSM's lead. It was agreed that a Working Group associated with the Biologicals Subcommittee would be set up.

16.52. The following day, 23 February 1989, the CSM Meeting was briefed about the HVMB meeting and recognised the need for research into BSE in relation to medicines' manufacture **[WITN6406031** (page 13)**]**. As the draft position paper showed:

> *The CSM agrees with the Southwood Working Party that the risk to man of infection via medicinal products is remote. As a purely precautionary measure, and for the sole aim of seeking to guard against what is no more than a theoretical risk to man, the CSM and the Veterinary Products Committee (VPC) have agreed joint advice for the manufacturers or human and veterinary medicines who use bovine, and other animal, materials either as an ingredient or in the production process. The advice will be issued by the Licensing Authority to the manufacturers early in March. They will also be asked for further details about any animal materials used in their products…*
>
> *The CSM stresses that it is very important to see any remote, and at this stage, theoretical risk which may be associated with the use of bovine or other animal materials in pharmaceutical products in the context both of the very tangible benefit to health that these products provide and, conversely, the actual and potentially serious risks that would arise if these products were not used at the appropriate time.* **[WITN6406031** (page 13)**]**[8]

16.53. In March 1989, letters and questionnaires were sent to licence holders seeking details of medicinal products using animal matter **[WITN6406031** (page 20)**]**.

16.54. The BSE Working Party was established and its first meeting took place on 6 September 1989 although it seems from the minutes that I was unable to attend **[WITN6406031** (pages 23, 25-31)**]**. The purpose of the working group was to advise the CSM on the implications of BSE with special regard to human medicinal products. It recommended that at that stage no licensing action was required in regard to products produced from bovine material and that the joint

[8] The final version of this statement **[WITN6406031** page 19**]** differed from this draft and in particular did not contain the second paragraph quoted. Nonetheless, this draft provides helpful background to the CSM's thinking. The CSM's consideration of the withdrawal of plasma derived products from the market because of the vCJD risk was something that was ongoing for many years (see for example the 1995 discussion in **[WITN6406032]**).

CSM / VPC guidelines (which can be found at **[WITN6406031** (page 44)**]** and which advised on the sourcing of animal material, tissues to be excluded and collection techniques) should apply to all bovine material sourced from the UK and other areas known to have BSE.

16.55. There were further meetings of the Working Party which reported back to the CSM (see for example 10 January 1990 **[WITN6406031** (pages 36 and 72-73)**]**).

16.56. Work on BSE and its possible implications continued with the situation being carefully monitored.[9] Close attention was paid to surveillance and measures being taken in other countries (see for example **[WITN6406031** (pages 154-155 and 160-196)**]**). The matter was considered by the CSM at intervals and we were kept abreast of developments (see for example the CSM meetings on 4 and 26 July 1990 **[WITN6406031** (pages 81-100)**]**, 22 September 1994 **[WITN6406034]**, 28 March 1996 **[WITN6406031** (pages 201-202)**]** among others).

16.57. In 1991, the CSM's guidelines were incorporated in the European guidelines produced by the CPMP on 'Minimising the Risks of Transmitting Agents causing Spongiform Encephalopathy via Medicinal Products' which came into force in 1992 **[WITN6406031** (page 203)].

16.58. On 1 April 1998, at one of the CSM's Working Group on TSE [Transmissible Spongiform Encephalopathies] and Variant CJD which I attended as an observer, there were presentations from both BPL and PFC **[MHRA0009404]**. It therefore appears to me that they were providing information about the risks of vCJD understood to be associated with blood products to the CSM (and the correspondence and questionnaires that I have mentioned at paragraph 16.52 above clearly opened the communication between pharmaceutical companies and the CSM Working Group). The MCA Chronology refers to the MCA having

[9] A summary of some of the work conducted before 1996 can be seen in the Position Paper: Pharmaceuticals and BSE **[WITN6406031** (pages 222-225)**]** and from 1997 in 'Action Taken Against the Theoretical Risk of Transmission of nvCJD by Blood and Blood Products' **[WITN6406033].**

already contacted companies holding licences for the manufacture of vaccines 'most of which were aware of the problems with BSE and some had already begun to take action' which suggests that there was communication with at least some of the pharmaceutical companies. I do not know what information was provided by the pharmaceutical companies to treating physicians.

16.59. On 30 April 1998, the Chairman of the TSE/nvCJD[10] Working Group, Professor Duff, attended the CSM meeting **[MHRA0034815_002]**. At that meeting, the CSM noted that 'there is currently no evidence that nvCJD can be transmitted by blood transfusion. However, given that the prion proteins associated with this disease can be detected in the lymphatic system it is possible that they are also present in white cells in the blood.' There was no test to detect the prion protein in individual donors and nor was such a test likely to be developed in the next two years (Professor Duff later said five years). It could not be validated that the manufacturing process could inactivate the putative agent of vCJD. We noted concerns about plasma pools and the need to maintain a secure supply of often-life-saving products. It was recorded that '[s]everal months will be required to secure a safe supply of blood from outside the UK'.

16.60. Following this discussion, the CSM revised the recommendations to include that 'manufactured blood products should not be sourced from UK plasma…the theoretical risk that nvCJD could be transmitted by blood products cannot be discounted'. BPL and PFC were to move to sourcing their products from plasma derived outside the UK but 'some rare and lifesaving specific immunoglobulins…may have to stay on the market for a longer period of time if replacement products could not easily be found.' Several 'months would be required to establish satisfactory sources of plasma, to clean equipment and to produce products from the new sources plasma.' From this discussion, it appears that the understanding of the CSM at the time (and accordingly, my view) was that the risks of vCJD infection from the use of commercial, imported blood and blood products (from countries that did not have a BSE problem) was

[10] New variant CJD (nvCJD) later became known as vCJD.

less than the risk presented by domestically produced blood and blood products.

16.61. In or before 1998, the CSM also recommended that blood products manufactured from a pool to which a donor with new variant CJD has contributed should be withdrawn which resulted in three withdrawals **[WITN6406035].** In 1998, we went on to recommend that 'the new variant CJD withdrawal policy should be extended to include donors who are strongly suspected of having new variant CJD by a reference centre'.

16.62. In or around May 1998, I commented on the precautionary approach that the CSM was taking:

> *No new evidence has been reported indicating that the nvCJD can be transmitted via blood products. However, while the risk remains only hypothetical, it cannot be fully discounted.* **[BART0002128_004].**

16.63. I also added the following which showed how the concerns about pooled plasma products were addressed:

> *It is important to note that the use of whole blood, platelets and fresh frozen plasma is not affected by this advice. These products are produced from single donations and patients would not be exposed to the same large number of donors as when the manufactured products are used.*

16.64. My involvement in this matter ended when I left the CSM in 1998.

16.65. I remember that some of the advice sought from the CSM boiled down to, basically, whether we would advise abandoning the use of routine childhood vaccinations, for around three years (though it looks from the minutes like this could have been up to five), and accept the substantial problems associated with mumps, measles and rubella (which would considerably increase morbidity and mortality), or whether we advised the continuation of the routine immunisation of children and risk the widespread occurrence of vCJD.

16.66. I can still remember, at the time, thinking that this was probably the most difficult decision I would ever have to make. In the end, but only after considerable

discussion, we recommended continuing routine immunisation. I feel that the approach we took was a sensible and cautious one which adequately balanced the risks that we understood at the time. It later emerged that we had given the correct advice because it was subsequently shown that there was no materno-foetal transmission of vCJD.

Section 17: Reduction of Risk

Viral inactivation in blood products

17.1. I cannot recall my early understanding of viral inactivation in blood products (if any) before these matters came before the CSM.

17.2. Applications for heat-treated products were considered by the CSM in the normal manner. One or more assessors from the staff of the Medicines Division would first evaluate the application. It would then be considered by the Biologicals Subcommittee. The views of the assessors and the Biologicals Subcommittee would then be submitted to the main Committee who would discuss it and make a recommendation (in the manner detailed in full from paragraph 6.3 above). I am afraid I cannot recall or add anything about how these methods of scrutiny developed over time.

17.3. I have no recollection of how knowledge was shared between the CSM and the Licensing Authority on the one hand, and pharmaceutical companies on the other, but I am sure that the Secretariat of the Medicines Division would have taken the lead on this.

17.4. The CSM would consider all evidence before it with care and this would of course include studies and information provided by manufacturers as I have explained at paragraph 7.9 above. The CSM and its Subcommittees comprised multi-disciplinary experts who would actively consider and assess the information and studies presented to us. We would by no means accept such evidence unchallenged and were readily able to identify inadequacies in the

design and conduct of studies (see for example paragraph 7.21 above) or information presented to us.

CSM Meeting: 22 November 1984

17.5. On 22 November 1984, the CSM meeting discussed heat-treatment of Factor VIII as part of our 'Any Other Business' discussion **[DHSC0003947_015]**. It was not raised in respect of any particular licence application. Dr Joseph Smith informed the CSM that heat-treatment of Factor VIII abolished detectable infectivity of the AIDS virus. The minutes record:

> *Therefore, companies should be encouraged to apply for variations of licences to permit widespread use of heat treated Factor VIII, so that the incidence of AIDS in haemophiliacs might be reduced.*
>
> *Professor Rawlins reminded the Committee that heat-treated Factor VIII is more expensive than the standard preparation. Widespread substitution of the heat-treated product may cause haemophilia centres to exceed their budgets.*
>
> *The Committee requested that the Licensing Authority propose to the Companies concerned that they make early applications for variations to use a dry heat treating process in the manufacture of their Factor VIII products.*

17.6. It is difficult to recall the CSM's exact intentions now but I think that the reason the CSM recommended encouraging companies to apply for variations rather than making heat-treatment a mandatory requirement was because there would have been a concern about such a mandate leading to a shortage of Factor VIII products. As the Inquiry knows, these products were life-saving and life-changing and the implications of their becoming suddenly unavailable would have been very serious. While, when judged with the benefit of hindsight, this may seem to have been the wrong approach, in late 1984, the full implications of the AIDS virus were still not widely understood.

17.7. The encouragement to make early applications for variations would have come from the Licensing Authority. I cannot now recall what form it would have taken nor how frequently it happened. I do not know now, if I did at the time, what the pharmaceutical companies' attitudes were to this encouragement.

17.8. My remark, summarised in the quotation above, about the expense of heat-treatment and the risk of haemophilia centres exceeding their budgets was, I think, probably just to remind the CSM about the ramifications of our decisions and the unintended consequences of making policy 'on the hoof' and without careful consideration of the issues involved. That is not to say that I felt we were doing that in this situation but my remark would probably just have been a note of caution. As I have confirmed at paragraph 11.3 above, financial considerations were not something to which the CSM gave any weight and I was not raising this point because of the costs implications but instead to remind everyone of the serious impacts that could flow from our decisions.

Dr Jones's evidence to the Lindsay Tribunal

17.9. I have been shown an extract of a transcript of Dr Peter Jones's evidence to the Lindsay Tribunal **[LIND0000312** (page 88)**].** Dr Jones said in evidence that in 1984 and 1985 while I was a Professor of Pharmacology at the Wolfson Unit in Newcastle-upon-Tyne, my remit was:

> *to look at our prescription of blood products. And it was Professor Rawlins and his team who looked at the provision of heat-treated concentrate with [Dr Jones] in 1984/1985, and gave clearance for us to start treating all our patients on heat-treated material.*

17.10. The Wolfson Unit in Newcastle was (and is) primarily a research centre. The notion that the Unit (or my team and I at the Unit) had any role in providing 'clearance' for treating patients is wholly incorrect. The Unit was a University building and had no role in deciding / advising on the use of medicines in the NHS. I was, though, at that time chairman of the Newcastle District Drug and Therapeutics Committee. I think that it may have been in that capacity, and on behalf of that Committee, that I may have informed Dr Peter Jones about the use of heat-treated Factor VIII. I have no idea as to whether Newcastle's use of heat-treated Factor VIII was earlier or later than other parts of the UK. To the best of my recollection, the Committee did not have any decision-making power on the provision of heat-treated Factor VIII or any strategy regarding its provision.

Recommendations of the Ad Hoc Group to Consider the Use of Heat-Treated Factor VIII Concentrate: 1984

17.11. I have been shown a letter I wrote to Peter Hopley, the District Pharmaceutical Officer at the Royal Victoria Infirmary, dated 23 November 1984 **[PJON0000062_001]**. I enclosed a copy of a report written by the Ad Hoc Group to Consider the Use of Heat-Treated Factor VIII Concentrate – of which I was the chair – from December 1984 **[BPLL0002848_003].** This gives a good insight into the likely state of my knowledge at that time.

17.12. I can see from my own letter that Mr Hopley had written to me on 22 November 1984 outlining the cost consequences of using heat-treated Factor VIII as soon as possible (but I have not seen his original correspondence). In the absence of a copy of his letter I am unable to indicate why we wrote as we did but my response (and the report) highlighted the desirability of using heat-treated Factor VIII concentrate.

17.13. The report itself had been written at the request of the District Administrator, Mr Spry (whom I have already mentioned at paragraph 16.6 above) and Dr C. B. Henderson, the Chairman of the Hospital Medical Committee. It sought to consider the necessity and implications of using heated Factor VIII concentrates in treating patients at the Royal Victoria Infirmary. The report acknowledged the increased costs of heat-treated Factor VIII. It offered advice to the Health Authority including:

a) There appeared to be little risk but substantial advantages to changing from commercial un-heat-treated Factor VIII to heat-treated Factor VIII;

b) On clinical grounds, use of cryoprecipitate and NHS Factor VIII should continue but from April 1985, NHS Factor VIII would be heat-treated;

c) 'In light of the available knowledge, we cannot identify groups of haemophiliac patients who would be likely to benefit from heat-treated commercial factor VIII, or who would be likely to be at special risk from conventional commercial factor VIII, apart from those without previous exposure to any factor VIII concentrate'.

17.14. Our advice did not take into account 'the economic consequences of changing to heat-treated commercial material. We believe that this decision must be for the Authority and its Officers'.

17.15. We offered further advice if the Authority could identify the funds needed to change to heat-treated product which included that the Health Authority should inform the Licensing Authority of its intention to use commercial heat-treated Factor VIII on a 'named-patient' basis.

17.16. As we wrote in the report, our understanding was that 'NHS factor VIII is substantially less likely to contain infective agents than that obtained from commercial sources which is ultimately derived from donors in North America' (page 1). Other than this, I have no recollection of why particular suppliers of Factor VIII were chosen and cannot comment on the decision-making process.

17.17. As I have summarised, the report recommended continuing to use un-heat-treated NHS Factor VIII until it was replaced with heat-treated Factor VIII from April 1985. This was a few months away and the risk of infection from NHS Factor VIII was believed to be substantially less than that of commercial Factor VIII. Even with the advantage of hindsight, it is difficult to see how the recommendations set out at paragraph 17.13 above could have been offered much earlier as the knowledge of AIDS transmission and viral inactivation were still developing at around that time and there were implications for the supply of Factor VIII. I presume that the advice to continue to use non-heat-treated Factor VIII was to avoid depriving haemophiliacs of what was regarded as 'essential' treatment.

17.18. I cannot comment on whether plans were put in place to inform clinicians and / or patients that there was a known risk of infection associated with the use of NHS Factor VIII (albeit a lower risk than attached to commercial equivalents); I do not know or recall, and I am not sure that I would have been party to, such discussions. If patients were not warned of the risk, I do not know why this was but, as I have already indicated, there was a paternalistic approach to patient information – at that time – that I would not now wish to defend.

17.19. I cannot comment on what steps were taken to ensure the quality, efficacy and safety of commercial heat-treated products to be used on a named-patient basis as this was entirely outside the remit of the CSM.

17.20. The report stated that 'in light of the available knowledge, we cannot identify groups of haemophiliac patients who would be likely to benefit from heat-treated commercial factor VIII, or who would be likely to be at special risk from conventional commercial factor VIII, apart from those without previous exposure to any factor VIII concentrate'. I think this reflects the view that the only priority group would be the previously untreated patients because within the cohort of those who had already received concentrates, you could not identify those who were at a particularly heightened risk than other patients. I do not now know what the term 'special risk' meant.

17.21. I recall that at some stage (as I have described in paragraph 16.6 above) there was consideration given to the possibility that patients who had already been exposed to infection could be given un-heat-treated Factor VIII but that this discussion was curtailed by Mr Spry who said that he was not prepared for *any* patient in his area to be given material known to be contaminated, irrespective as to whether they had been infected or not.

CSM Meeting: 26 March 1986

17.22. I have been shown the CSM minutes of 26 March 1986 at which I was present and during which the paper 'The Safety of Heat-Treated Factor VIII' was considered **[MHRA0036364_002]**. The paper had been written by Dr Rotblat and was dated 4 March 1986. **[BPLL0001351_018]**. It responded to concerns raised by Dr Peter Jones who felt that heat-treated Factor VIII was not safe. Dr Rotblat offered an analysis of the various cases of seroconversion for the HTLV-III antibody following treatment with heat-treated Factor VIII to which Dr Jones had referred.

17.23. On considering the paper, the CSM endorsed the recommendations of the Biologicals Subcommittee and recorded:

> *12.1 The Committee were glad to receive this data on the follow up of alleged transmission of HTLV-III by heat-treated Factor VIII. The Committee agreed that there was insufficient evidence for action to be taken on any specific product.*
>
> *12.2. Close surveillance should be maintained on the two possible cases of HTLV-III transmission in recipients of Armour material.*
>
> *12.3 The Committee advised that, if any of the data provided by manufacturers on viral inactivation suggested a danger, urgent consultation should be sought with appropriate members.*

17.24. I do not recall what scrutiny had been applied to heat-treated products (beyond the procedures I have outlined above) before they were permitted to be administered to patients. Nor do I remember why it was decided not to take action on any specific product.

17.25. Although I now have no recollection, I presume that the 'close surveillance' would be undertaken by those clinicians with direct responsibility for the patients who had received the Armour material and that they would be requested to inform the Medicines Division of any adverse outcomes.

17.26. I do not know (and might well not have known at the time) whether those patients were aware that they had potentially been infected or whether they (or others) to whom the Armour product had been administered had been advised of the risk. As I have already indicated, I fear that it would not have been the practice at the time for them to have been informed.

17.27. I do not know (or recall) what the threshold for 'sufficient evidence' would have been before action was taken in the mid-1980s. All of these matters often involved rather more complex and complicated discussions and consideration than the minutes and recommendations are ever able to reflect.

17.28. Where the CSM advised that if any data suggested a danger, urgent consultation should be sought with appropriate members (paragraph 12.3); I presume that this would have involved communicating with members of the CSM and Biologicals Subcommittee who had relevant expertise.

Correspondence between Dr Jones and Dr Isaacs: April 1986

17.29. I have been shown the letters from Dr Peter Jones to Dr A. J. Isaacs, a Principal Medical Officer, on 24 April 1986 **[PJON0000122_001]** and Dr Isaacs' reply on 2 May 1986 **[PJON0000119_001]**. I was copied into both letters.

17.30. Dr Jones wrote that there were 'still considerable misgivings amongst clinicians about the present policy with regard to blood products'. He asked if it was 'ethical to continue to use batched material which was in the pipeline before individual donor testing was introduced, without at least the informed consent of the recipient'. I do not recall being aware of the misgivings mentioned in this letter and nor do I recall being consulted for a view as to whether patients should be told about the risk of AIDS transmission either before or after individual donor testing was undertaken (though of course it is plain that patients should have been informed of the risk). Even with hindsight I am not sure what more the CSM or the Medicines Division could (or should) have done at that moment in time (something that even Dr Jones appears to recognise when he writes in relation to immunoglobulins, 'I do realise that there is little more that your Committee can probably do'). We were not, for example, in a position to advise doctors on their methods of treatment of patients or on obtaining informed consent; our role was a narrow advisory one as defined by statute.

17.31. Dr Jones went on to write:

> *...at the clinical end it is becoming increasingly difficult to prescribe to seronegative patients with confidence, especially in the climate of suspicion that all is not well at Elstree, and that some decisions that could affect our patients adversely are being made more for economic and political than for clinical reasons.*

I am not sure what Dr Jones meant by this and / or whether he was referring to issues at Elstree regarding the building works which is not something with which I had any involvement.

17.32. Dr Isaacs' response will, I am sure, have been entirely accurate. His failure though to comment on the statement that decisions were 'being made more for economic and political reasons than for clinical reasons' is entirely understandable given that Dr Isaacs was a civil servant.

CSM Meeting: 21 February 1990

17.33. I have been shown the CSM minutes from the meeting of 21 February 1990 at which I was present **[CABO0000308_009]**. At this meeting, the paper 'The Provision of Plasma Pool Samples for the Control Testing of Blood Products' **[MHRA0034935_077]** was considered. The CSM noted the paper and endorsed the Biological Subcommittee's recommendation that:

> *10.1 In view of the limitations of testing for HBsAg and antibodies to HIV in finished products and the greater sensitivity of tests on the plasma pool, manufacturers should be required to submit formally to NIBSC samples of plasma pools in addition to other samples and protocols required for batch release.*
>
> *10.2 Product licence holders should be asked to confirm that all plasma pools used in the preparation of a given product have been tested and found to be free of HBsAg and antibodies to HIV and the licence amended accordingly.*

17.34. A covering note on the report observed that since 1989, manufacturers of blood products were asked for samples of plasma pools as part of the batch release procedures undertaken by NIBSC. This was initially on an informal basis and was formalised as a result of the CSM's recommendation above. I cannot comment on the level of uptake of the informal request for plasma pool samples as this would have been dealt with by NIBSC and the Medicines Division or would have been for the Medicines Control Agency to assess, rather than being a matter for the CSM itself. For that same reason, I cannot comment on what steps would have been taken by the CSM if manufacturers rejected the recommendation as this would not have been a matter for the CSM.

17.35. I do not know whether the implementation of plasma pool samples being submitted to NIBSC could have happened earlier because I do not know what capacity NIBSC had to undertake this work and what steps they needed to take to ensure they could receive and process these additional samples.

17.36. As to the licensing of heat-treated blood products, I do not know whether this could have been achieved more quickly. It would have depended on the ability of manufacturers to make such products, make applications for licences (if they decided to do so) and then on the ability of the Medicines Division / Medicines

Control Agency to evaluate the submitted data, and possibly the ability of NIBSC to check the quality of samples of material. I am afraid that from this distance in time, I am not in a position to assess this with any accuracy.

High Purity Factor VIII: October 1992

17.37. I have been shown an annotated copy of a letter from Dr Jones to Dr Lewis from the AIDS Unit of the DHSS regarding High Purity Factor VIII dated 7 October 1992 **[DHSC0004773_017].** I would not have seen this letter when it was sent. Dr Jones states that, when high purity factor concentrates became available, the Regional Drug and Therapeutic Unit, which I headed, performed meta-analysis using public literature on HIV and the relationship between the use of high purity concentrates and progression of disease in HIV affected haemophiliacs. It stated that our conclusion was that there was sufficient evidence to recommend prescription of high purity concentrates in preference to intermediate purity concentrates. I think that this is correct but the day-to-day management of the Regional Drug and Therapeutics Unit was overseen by Professor James (Jim) Smith who later became the Chief Pharmaceutical Officer at the DHSC (2000-2005). I would have therefore have had no involvement in the meta-analysis described and cannot assist with how it was conducted. As far as I understand Dr Jones' letter, it would seem to me that as a consequence the Northern Region agreed to release the extra funds required for the purchase of high purity concentrates but I have no first-hand recollection of this.

Section 18: 'Named Patients' and the distribution of unlicensed products

18.1. As I have described at paragraph 14.7 above, prescribing on a 'named-patient basis' involved a prescriber – the treating clinician – requesting supplies of an unlicensed product to prescribe for the treatment of a particular (i.e. 'named') patient. Doctors have the clinical freedom to prescribe unlicensed products in this way and it was a system which was permitted under the Medicines Act and which remains in use today; it was and I believe still is, extremely common.

18.2. I have no idea – and would not have known at the time – what unlicensed blood products would have been made available on a named patient basis.

18.3. The CSM had no authority relating to blood products which were unlicensed but available on a named-patient basis. The CSM had no practical role in overseeing or restricting the use of blood products on a named patient basis and indeed, it would have been impossible for the CSM to have played any such role, given its remit and limited advisory role and powers. I have seen an article from 1997 published in *Haemophilia,* entitled 'Guidelines on Therapeutic products to treat haemophilia and other hereditary coagulation disorders' **[BART0000875]**. On page 10, it states the following which may be of assistance:

> *5.1.1.6* Named Patient Basis. *When an unlicensed drug is prescribed by a doctor outwith a CTC or CTX, usually to treat an individual patient, this is on a 'named patient basis'. The doctor will bear liability for the prescription and clinical use of the drug. The manufacture may be covered by the* Consumer Protection Act, 1987. *It is recommended, however, that appropriate indemnity is obtained from the manufacturer, or its agent, prior to clinical use. Hospital Trusts are now drawing up rules for unlicensed purposes. Clinicians should therefore seek permission from the appropriate authority in the Trust to ensure their protection through Crown Indemnity. Before using a drug on a 'named patient basis' the practitioner must satisfy him/herself that its use is reasonable and in the interest of the patient. In the event of an adverse reaction he/she may be called upon to justify his/her actions. The doctor should explain to the patient that the drug is unlicensed and that its use is experimental' he/she should be advised that the extent and severity of contra-indications and side-effects may still not be fully appreciated. The basis for prescribing may be appropriate when there is no licensed suitable alternative.*

18.4. I consider that the CSM's level of authority and practical role were sufficient but, again to be clear, the CSM did not have any role in overseeing unlicensed products.

18.5. I have been asked what action would be taken if the CSM or another relevant body or committee within the licensing structure had concerns about the safety, quality or efficacy of a product which was unlicensed but available on a named-patient basis. I have described in detail above the adverse reporting process and this covers the extent of my knowledge. The adverse reporting process

applied to licensed and unlicensed products alike. If the CSM, and / or the Medicines Division had been aware of the 'named patient' use of these products then it may have been appropriate for clinicians to have been made aware of the associated risks as I have described above, for example through a 'Dear Doctor' letter (from the chair of the CSM) and / or by an article in Current Problems.

Feiba: February 1982

18.6. I have been shown the CSM minutes of a meeting from 25 February 1982 at which I was in attendance **[MHRA0036366_001]** and advice regarding a product called Feiba that came from that meeting **[MHRA0036366_017].** For reasons that are not clear to me, there is no apparent mention of Feiba in the minutes themselves. In the advice document, the CSM stated we were unable to advise the grant of product licenc es for the preparations on grounds relating to quality and efficacy. We provisionally concluded that additional evidence and information should be provided.

18.7. I understand from a Pharmaceutical Examiner's Report dated 10 June 1985 (which the CSM would not have seen when considering the application in 1982), that Feiba had been available on a 'named patient' basis since around 1976 and continued to be available on that basis after the CSM's 1982 decision **[SHPL0000078_010]**.

18.8. Feiba could continue to be prescribed on a named patient basis because, as described above, section 9 of the Medicines Act 1968 provided exemptions which allowed a doctor to have a medicinal product specially prepared or specially imported for administration to a particular patient without the need for a product or manufacturer's licence. This is irrespective of the product's licensing status. Neither the CSM nor the Licensing Authority had any power to prevent it. Indeed, it would be highly unlikely that the CSM or Licensing Authority would even know if and when this was occurring. I do not know whether clinicians and / or patients would have been made aware of the fact that a blood product had not been granted a licence.

Gammagard: September 1995

18.9. I have been shown the CSM minutes of the meeting of 21 September 1995 which I chaired **[DHSC0016249** (page 8)**]**. During this meeting, Baxter's product Gammagard was discussed (paragraph 10). The minutes record that Dr Purves reminded the CSM:

> *...of the recent problems of viral contamination of blood products in Europe – Hepatitis C in Gammagard and irregularities in the testing of blood at donation centres in Germany. These problems had led the CPMP, in March 1994, to set up a Working Party to consider various aspects relating to the viral safety of blood products. The Working Party had identified 14 items that needed to be addressed systematically in Europe. The Committee noted that it would be kept informed of the progress of work.*

18.10. It was at the CSM meeting I attended on 20-21 October 1982 at which a hearing was held to consider licensing Gammagard, (which I am told was then called Immune Serum Globulin): **[DHSC0003944_014]** and **[DHSC0003944_016]**. I am told in the rule 9 letter that '[t]his product, which was found to have transmitted HCV to several patients, was sold on a named patient basis during the 1990s despite being refused a licence on the grounds of efficacy in 1982'.

18.11. For the same reasons as Feiba, explained at paragraph 18.8 above, Gammagard could continue to be prescribed on a named patient basis despite it not having been granted a product licence.

18.12. I cannot recall when the CSM first became aware of problems regarding viral contamination of this product; it seems likely that it was shortly before the meeting in September 1995 but that is only a supposition. I cannot recall how the CSM responded to this knowledge; I do not think that there would have been much, if anything, that we could do beyond our usual adverse reactions procedures as I have described above. I cannot comment on the controls on unlicensed products in the 1990s generally and left the CSM myself in 1998. It appears that the quotation I have given at paragraph 18.3 above from 1997 summarised the position.

Section 19: Reflections

19.1. I have been asked whether I consider that the CSM responded to the risks posed by infected blood products in a timely and appropriate manner. To the best of my recollection, I do. I do not recall when the causative agents of HIV and / or hepatitis were discovered in relation to the granting of licences. If either or both were unknown at the time of the original licensure it would have been impossible for either the CSM or the Medicines Division to have been aware of the risks or to take them into account when granting licences.

19.2. However, once the risks had been identified then perhaps the CSM and the Medicines Division should have taken action to minimise the potential for harm to patients. If the CSM, and / or the Medicines Division had been aware of the 'named patient' use of these products then it might have been appropriate for clinicians to have been made aware of the associated risks either through a 'Dear Doctor' letter (from the chairman of the CSM) or by an article in Current Problems. That said, it might be the case that this information had already been circulated in a different way which might explain if no such steps were taken by the CSM and / or Medicines Division (but I have no recollection of this and / or whether any such steps were taken).

19.3. I have been asked to give my account of how blood products infected with HIV and hepatitis were given to patients in the UK. It is very difficult to assess this now in any meaningful sense given the time that has elapsed and given the wealth of information and individuals involved at the time (as the Inquiry will well know). It seems to me that this happened because these diseases developed leading to infected blood being donated and used before the pharmaceutical companies, Licensing Authority, CSM, Biologicals Subcommittee, Medicines Division, Medicines Control Agency, prescribing doctors, or any other body or individual involved in the provision of blood products in the UK, knew or understood their devastating implications. As those implications became clear, action was taken but this had to be balanced against the dangers of causing a shortage of Factor VIII concentrates and the harmful knock-on consequences that this too could cause. Whether the correct action was taken – without the

benefit of hindsight – and whether such action was taken swiftly or effectively enough is for others to judge. Similarly, I do not think I can say, beyond what I have written in this statement, that there are further steps which could and / or should have been taken to prevent or reduce or minimise the extent to which patients received infected blood products or that blood products were given to patients which should not have been. All I can say is that I carried out my own responsibilities with great consideration over the years and always took great care when making difficult decisions. I am deeply deeply sorry that, no matter the rights or wrongs of anyone involved, patients in the UK were infected with HIV and hepatitis.

Statement of Truth

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

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

Dated.....24/3/22.....