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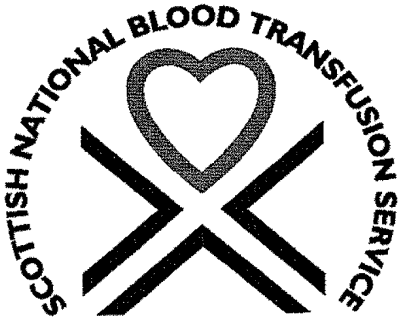

PENROSE INQUIRY

Scottish National Blood Transfusion Service

THE REGULATION OF THE MANUFACTURE OF MEDICINAL PRODUCTS DERIVED FROM BLOOD PLASMA AND THE PREPARATION OF BLOOD AND BLOOD COMPONENTS BY THE SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

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1. EXECUTIVE SUMMARY

1.1 The period in question (early 1970s to the present day) saw extensive changes in the regulation of the manufacture of medicinal products in the United Kingdom (UK), from effectively no legislative control, to the implementation of the Medicines Act in 1971, which sought to control all aspects of medicines manufacture, including those medicinal products derived from human blood plasma.

1.2 Since that time, the Medicines Act has been amended regularly by the adoption and translation into UK law of the relevant European Community (EC) Directives and Regulations.

1.3 Further legislation was also brought into force later (2005) to regulate the preparation of blood and blood components which had been excluded from the Medicines Act and EC Directives.

1.4 Until 1991 the Scottish National Blood Transfusion Service (SNBTS) as part of a crown body was immune from prosecution under the Medicines Act.

1.5 However, at all times during the period in question the SNBTS remained in contact with the relevant Regulatory Agency and its related institutions and continues to do so to the present day. This is shown by the SNBTS obtaining Manufacturing Licences and Product Licences (in some cases prior to the removal of Crown Immunity) and remaining open to the Medicines Inspectorate at all times.

1.6. When, under Crown Immunity, the SNBTS made significant changes to its products or facilities it did so with the full knowledge of the relevant Regulatory Agency.

1.6 Following the removal of Crown Immunity, all areas of the Service made complete and successful transitions to legislative control and all necessary regulatory licences and authorisations have remained in place continuously since that time

1.7 Under both Crown Immunity and full legislative regulation, a total of more than eighty inspections covering all relevant SNBTS facilities have been carried out by the Medicines Inspectorate. In all cases SNBTS responded to the inspection outcomes and where necessary, implemented the agreed remedial actions.

2. INTRODUCTION

2.1 The Penrose Inquiry Preliminary Report contains a summary[1] of the development of the regulatory framework surrounding the production of medicinal products in the UK, starting with the 1968 Medicines Act and commenting on how that related to "blood products".

2.2 The purpose of this paper is to provide some additional information to clarify exactly how the regulation of medicinal products applied to the SNBTS facilities and products and the position of the SNBTS in relation to the regulatory framework in the UK as it developed from the Medicines Act.

2.3 Products derived from human blood plasma (hereafter referred to as human plasma) such as coagulation factor concentrates, human albumin or human immunoglobulin, were considered as medicinal products under the Act whereas preparations of whole blood or blood components (red cells, white cells, plasma, platelets) for transfusion were excluded from the Act [2] and subject to later, separate legislation

2.4 This paper describes, in relation to the regulatory legislation in place at the time, the status of the SNBTS Protein Fractionation Centre (PFC) and the plasma products which were developed, manufactured and distributed from there.

2.5 The regulatory status of the SNBTS Regional Transfusion Centres (RTCs) concerning the preparation of blood and blood components and other relevant activities is also described.

3. SCOPE

3.1 This briefing paper covers the period from the early 1970s to the present day.

3.2 The licensing and inspection of the SNBTS premises for the development, manufacture and distribution of plasma products (i.e. the PFC) together with the product licences themselves are considered here.

3.3 The crystalloid products (parenteral salt solutions) prepared at the PFC did not contain material of human origin and so they are excluded from this paper.

3.4 From their early development it was known that coagulation factor concentrates (used for the treatment of haemophilia) carried a high risk (now much reduced) of transmitting hepatitis and soon after the establishment of HIV in the human population, it was clear that the use of coagulation factor concentrates could also transmit HIV. The background to the licensing of SNBTS Factor VIII and Factor IX concentrates, therefore, has been included in this paper.

3.5 Immunoglobulin for intravenous infusion (IVIgG) has never been associated with HIV transmission. However, some IVIgG products have been previously associated in the wider plasma fractionation industry with HCV transmission including an

isolated incident concerning SNBTS IVIgG[3], and therefore this product has also been included in the discussion on product licences.

3.6 Human albumin products and Human immunoglobulin preparations for intramuscular infusion (IMIgG) are known to be safe from the transmission of HCV and HIV[4]. In fact, there are no recorded cases world wide of HCV/HIV transmission by albumin or IMIgG products when they have been manufactured using the same methods employed at PFC. The licensing of SNBTS Albumin products and IMIgG products, have, therefore, not been included in the discussion on product licences.

3.7 The regulation of the preparation of blood and blood components for transfusion and the licensing of SNBTS premises (RTCs) for these activities together with other functions at RTCs such as the processing of plasma for fractionation and the storage for onward supply and distribution of plasma products will also be considered in this briefing paper.

4. THE MAJOR LEGISLATIVE ELEMENTS INFLUENCING THE REGULATION OF BLOOD AND BLOOD PRODUCTS IN THE UK

Until the UK entered into the European Community (EC), the regulation of medicinal products was controlled by UK law. However, from the time that the UK entered into the Community, primacy transferred to the EC with the overarching requirement that EC legislation and guidelines on the manufacture of medicinal products should be entered into UK law. Some of the key elements of the regulation of medicinal products such as manufacturing licences and product licences have been referred to variously elsewhere in documents supplied previously by the SNBTS to the Inquiry. However, a brief description is given here of the development of the regulatory framework surrounding blood, blood components and plasma products for completeness and to make later discussions clearer.

4.1 **The 1968 Medicines Act**

4.1.1 The 1968 Medicines Act came into force in 1971, as the first legally enforced regulation in the UK of the manufacture and distribution of medicinal products.

4.1.2 When the UK entered the European Communities (EC) in 1973, the 1968 Act, which had been based on the legislation developed in Europe, was the means by which the UK complied with the EC rules on the licensing of medicinal products.

4.1.3 The 1968 Act continues to fulfil the requirements of EC legislation, but has been subject to regular amendments through relevant Statutory Instruments (SI s) in order to ensure that EC legal obligations continue to be met within the UK.

4.1.4 The Medicines Act 1968 provided the legal framework for the control of all medicinal products, released for use in the UK including plasma products. The Act required that an independent assessment of the quality, safety and efficacy of a medicinal product be conducted by the relevant regulatory authority before a licence was granted, which in turn permitted the product to be placed on the market.

4.1.5 The Medicines Act also established the legal status of the British Pharmacopoeia (BP) Commission and of the BP standards for medicinal products in UK. This meant that any product placed on the market had to comply with the specifications in the relevant BP monograph (see Section 9.6).

4.1.6 Supplementary legislation expanded the general provisions set out in the Medicines Act and included:

(a) S.I. 1971/972; Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 – GMP requirements

S.I. 1971/972 specified the standard provisions for licences issued under the Medicines Act 1968, these included the requirement that holders of a manufacturer's licence must carry out their manufacturing operations in accordance with Good Manufacturing Practice (GMP). The Medicines Inspectorate was established within the Medicines Division of the Department of Health and Social Security (DHSS) in 1971 to ensure compliance with Standard Provisions, including GMP and GDP (Good Distribution Practice) by all applicants for, and holders of, manufacturer's and wholesale dealer's licences in the UK.

(b) S.I.1971/973; Medicines (Applications for Product Licences and Clinical Trial and Animal Test Certificates) Regulations 1971Licence application requirements

S.I.1971/973 detailed the information required in licence applications including particulars of all active constituents, methods of manufacture and data on the safety and efficacy of the product.

4.2 The Development of European Legislation of Medicinal Products including Plasma Products

Some of the major steps in the development of EC medicines legislation are given below together with how they related to plasma products.

4.2.1 On the 26th January 1965 Directive 65/65/EEC was released. This was the first EC legislation relating to the regulation of proprietary medicinal products and it required a medicinal product to hold a "Marketing Authorisation" granted by the Competent Authority of a Member State before it could be placed on the market in that state. Whole blood prepared for transfusion and blood components were excluded from this Directive; medicinal products derived from blood or plasma (e.g. plasma products) were not. At this time, of course, the Directive did not apply in the UK.

4.2.2 The UK joined the European Community (EC) in 1973 and as such became bound by European Legislation. However the contents of the Medicines Act (already in force in the UK by this time) were consistent with Directive 65/65/EEC and so Licence applications in the UK continued to be dealt with under the Act.

4.2.3 As part of the progress within the EC to reducing the disparities between the regulation and administration of proprietary medicinal products in member states, Directive 75/318/EEC ("Guidelines on the quality, safety and efficacy of medicinal

products for human use") gave guidance on what should be included in an application for a Marketing Authorisation and Directive 75/319/EEC specified how applications should be presented, in particular with reference to the provision of Expert Reports, and how the application should be assessed. These Directives gave the general requirements for all medicinal products and they have been supplemented by further Directives containing additional specific requirements for particular types of products including those derived from human plasma.

4.2.4 A number of recommendations relating to the safety of plasma derived medicinal products were released by the Council of Europe Committee of Ministers in the early to mid 1980s and these included the following:

(a) Recommendation No R (80)5 of the Committee of Ministers to member states on Blood products for the treatment of haemophiliacs (30th April 1980)

(b) Recommendation No R(81)14 of the Committee of Ministers to member states on the Assessment of the risks of transmitting infectious diseases by international transfer of blood, its components and derivatives (14th May 1981)

(c) Recommendation No R(83)8 of the Committee of Ministers to member states on preventing the possible transmission of acquired immune deficiency syndrome (AIDS) from affected blood to patients receiving blood or blood products (23rd June 1983)

(d) Recommendation No R (85)12 of the Committee of Ministers to member states on the screening of blood donors for the presence of AIDS markers (13th Sept 1985)

4.2.5 Published in June 1989 and effective from 1st January 1992, Council Directive 89/381/EEC extended the scope of Directives 65/65/EEC and 75/319/EEC and laid down special provisions for medicinal products derived from human plasma including measures to ensure the absence of specific viral contamination and independent batch release testing by a designated Official Medicines Control Laboratory (OMCL) (see Section 9.5). Also, Directive 89/381/EEC promoted Community self sufficiency in plasma derived products based on voluntary non remunerated donors.

4.2.6 The first European guideline on the validation of virus removal and inactivation processes in the manufacture of plasma-derived medicinal products was published in 1989 (III/8115/89 EC).Guidance was given on how to evaluate of the effectiveness of manufacturing processes to eliminate or inactivate viruses by the use of small scale laboratory models of the relevant process steps. This guideline came in to operation 15/08/1991 and was later superseded by Note for Guidance CPMP/BWP/268/95.

4.2.7 Directive 91/507/EEC published in July 1991 modified Directive 75/318/EEC in respect of additional specific requirements for the analytical, toxicological and clinical testing of immunological medicinal products, radiopharmaceuticals and medicinal products derived from human blood or human plasma

4.2.8 With the implementation of Directive 89/381/EEC in 1992 (see 4.2.5 above) medicinal products derived from human plasma were brought into line with other

medicinal products on the market within the EC in that they were controlled in all member states to the same standard. Member states had to ensure that products derived from human plasma complied with current EC standards by December 1992.

4.3 **Crown Immunity**

4.3.1 Crown Immunity was the position, previously established in the UK, that since the sovereign could not commit a legal wrong, institutions of the state were exempt from prosecution or civil action. For example, the Common Services Agency (CSA), as the government body with responsibility for the SNBTS, would be exempt from prosecution under the Medicines Act in relation to the manufacture of products at the PFC.

4.3.2 When the Medicines Act came into force, the position of the PFC was initially uncertain as it was considered that the CSA and other Health Boards in Scotland were not entitled to Crown Immunity[6].

4.3.3 However, the CSA was later advised that together with the Health Boards they were Crown bodies and therefore, entitled to Crown Immunity in appropriate cases[7].

4.3.4 The Penrose Inquiry is clear that Crown Immunity applied to the PFC[8] and recent legal advice in the House of Lords[9] emphasises that Crown Immunity did apply to plasma products manufactured elsewhere in the NHS at that time and cannot be removed retrospectively.

4.4 **The Consumer Protection Act 1987**

4.4.1 This Act (implemented in May 1988) transposed into UK law the provisions of EU Directive 85/374/EEC on "laws, regulations and administrative provision of the member states concerning liability for defective products".

4.4.2 Article 6 of this Directive states that a product is defective if it does not provide the safety that persons generally are entitled to expect.

4.4.3 Whole blood, blood components and plasma products are all considered as products under this Directive.

4.5 **The National Health Service Community Care Act 1990**

4.5.1 This Act came into force on 1st April 1991 and removed Crown Immunity from the NHS.

4.5.2 The Act removed Crown Immunity from "health service bodies" and the "Common Services Agency for the Scottish Health Service" was specifically defined as such for this purpose[10], confirming that Crown Immunity had applied to the CSA until that time.

4.6 **Directive 2001/83/EC (Medicinal Products for Human use)**

4.6.1 This Directive consolidated all previous Directives concerning the regulation of medicinal products. Together with its subsequent amendments, it is the current major platform for the regulation of medicinal products in Europe and the UK.

4.6.2 In relation to plasma products, the Directive requires that member states "need to take measures to prevent the transmission of infectious diseases, apply the monographs of the European Pharmacopoeia, recommendations of the Council of Europe and WHO as regards, in particular, the selection and testing of blood and plasma donors. The member states should also promote community self-sufficiency and encourage unpaid voluntary donations".

4.6.3 The Directive specifically excludes whole blood and blood components from the regulations.

4.7 **The Blood Safety and Quality Regulations 2005**

4.7.1 This Statutory Instrument came into effect in the UK in November 2005 and implemented EU Directive 2002/98/EC "setting standards of quality and safety for the collection, testing, processing and storage and distribution of human blood and blood components" into the UK.

4.7.2 The facilities of the UK Transfusion Services used for these activities were required under these regulations to become authorised "Blood Establishments".

4.7.3 Hospital Blood Banks carrying out blood collection or processing activities are also required to seek Blood Establishment Authorisation. Other Blood Banks which are limited to storage and distribution of blood or components do not require Blood Establishment Authorisation, but must maintain quality management and traceability systems to be compliant with the regulations.

4.8 **Specific regulatory requirements relating to the elimination/inactivation of viruses in the manufacture of medicinal products derived from plasma**

4.8.1 Paragraph 12.25 "Licences for blood products" in the Penrose Inquiry Preliminary Report could be interpreted as suggesting that requirements for virus testing and the inclusion of virus elimination/inactivation procedures in the manufacture of plasma derived products was stipulated as early as 1971 in the legislation regulating the production of plasma products. This was not the case.

4.8.2 The first statement of these requirements i.e. "licence holders should take all necessary steps to ensure that the manufacturer notifies the Licensing Authority of methods used to reduce or eliminate pathogenic viruses liable to be transmitted" was not, in fact, enacted into UK law until 1994.The Statutory Instrument which contained this statement [Medicines for Human Use (Marketing Authorisations etc.) Regulations 1994] varied the original 1971 Regulations.

4.8.3 In general, the development of regulatory guidance concerning the virus safety of human plasma products tended to follow actions already taken by manufacturers. Substantive published requirements were not in place until after virus elimination/inactivation procedures had been introduced by the industry world- wide. This is not to say that individual regulatory bodies had not expected manufacturers to take actions to deal with emerging virus safety issues, rather the mechanisms were not the subject of published regulatory advice until sometime later. The first formal EC regulatory guidance of this type was not published until the late 1980s (see document 25 in Appendix I)

4.8.4 Appendix I is a summary obtained from Dr Glenda Sylvester (Regulatory Assessor) of the European Medicines Agency (EMEA). This summary lists the key (non-clinical) documents as of 2009 against which plasma derived medicinal products must be assessed for marketing authorisation and this list contains a number of guidelines for manufacturers on virus elimination/inactivation.

4.8.5 A number of documents were released by the EMEA in the 1990s concerning the measures to be taken and practices to be employed regarding virus testing and inactivation/removal procedures for plasma derived medicinal products. As noted previously, these formal regulatory documents served to codify practices which were already in place, throughout the plasma fractionation industry.

5 COMPETENT AUTHORITIES, INSPECTION AND ASSESSMENT

5.1 Each member state in the European Union (EU) must nominate a Competent Authority, with the responsibility to act on behalf of the Government, to ensure that the requirements of the various EC directives for the manufacture of medicinal products are met. In the UK the present competent authority is the Medicines and Healthcare products Regulatory Agency (MHRA).

5.2 The Inspection, Enforcement and Standards Division of the MHRA inspect and license all UK manufacturers, wholesale dealers and importers of medicinal products. The Licensing Division of the MHRA assesses and approves applications for product licences (marketing authorisations).

5.3 In the UK, all manufacturers of medicinal products are also licensed directly by the MHRA. Most medicines are directly approved by the MHRA, although it is now possible to have Europe wide licences approved by the EMEA.

5.4 Since its inception under the terms of the Medicines Act, the regulatory body in the UK has developed, expanded and evolved. Initially, the licensing and regulatory body was known as the Medicines Division of the Department of Health and Social Security. In April 1989, this became the Medicines Control Agency (MCA), as an independent agency of the Department of Health. In 2003, the MCA merged with the Medical Devices Agency to form the Medicines and Healthcare Products Regulatory Agency (MHRA).

5.5 The Medicines Inspectorate was established in 1971 as part of the Medicines Division of the DHSS. It was set up to inspect for compliance with the standard

provisions of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) in applicants for and licence holders of Manufacturing and Wholesale Dealers licences.

5.6 In addition to licence applicants and holders, the brief history of GMP inspection on the MHRA website also notes that "In 1975 inspections of NHS manufacturing units were begun at the behest of the then Secretary of State"

5. 7 When the MCA was formed in 1989, the Inspectorate was reorganised along more functional lines, including the development of Expert Inspectors in areas such as biological products and plasma fractionation

5.8 The MCA, and previously the DHSS Medicines Division, issued licences on behalf of the UK Licence Authority, which was made up of all the UK Health and Agriculture Ministers including (until 1999 when licensing became a reserved matter) the Secretary of State for Scotland.

5.9 The Scottish Home and Health Department (SHHD), which reported to the Secretary of State for Scotland, defined its own role as "providing information and recommendations regarding present and future activities in Scotland for consideration by the Licensing Authority"[6].

6. THE LICENCE HOLDER FOR SNBTS FACILITIES, ACTIVITIES AND PRODUCTS REQUIRING REGULATORY APPROVAL.

6.1 The named licence holder for all regulated SNBTS facilities and activities concerned with the preparation of whole blood, blood components and plasma products has always been the Common Services Agency (CSA) for the Scottish Health Service, now known as NHS National Services Scotland (NSS).

6.2 So, for example, when reference is made to an SNBTS licence what is meant is a licence held by CSA for the SNBTS facility or product in question.

6.3 In practice, PFC management or staff from the PFC Quality and Regulatory Affairs department communicated directly with the relevant regulatory authority or agency on matters relating to the PFC, and critical communications would be copied to the CSA and the SHHD.

6.4 In the same way, the Director or Quality Manager at each RTC, or later the SNBTS National Quality Manager (when this post was established in 1994), would communicate directly with the relevant regulatory authority over matters at RTCs, copying in the CSA and SHHD as required.

6.5 The Quality and Regulatory staff at the SNBTS (in particular those at the PFC because of the more extensive regulatory portfolio) built up and maintained a continuous working relationship with the regulatory authority and the extensive correspondence over many years has been retained on file.

7. PROTEIN FRACTIONATION CENTRE (PFC): MANUFACTURER'S AND WHOLESALE DEALER'S LICENCES.

The CSA held a number of licences relating to manufacturing activities at the PFC during its operational lifetime and these are summarised in Table 1.

7.1 **Manufacturer's Licence (ML)**

7.1.1 This licence allows the holder to manufacture and/or assemble (package) medicinal products[11]. Under EU legislation which has taken precedence over the primary legislation in each member state, this licence is referred to as a Manufacturer's/Importer's Authorisation and also allows the holder to wholesale deal licensed medicinal products imported from outside the European Economic Area (EEA).

7.1.2 Initially, following the opening of the PFC in 1975, and because of concerns over the status of Health Authorities in Scotland, it was decided that an application should be submitted for a Manufacturer's Licence to cover the manufacturing activities at PFC[6].

7.1.3 An application was made in March 1976 using the procedure set out by the Medicines Division of the DHSS, and a Manufacturer's Licence was granted to the Common Services Agency by the Secretary of State for Social Services in May 1976 "in respect of the premises at Scottish National Blood Transfusion Service, 21 Ellen's Glen Road....." for a period of five years. At that time all licences were issued for a five year period and licence holders were required to apply at the end of that period to renew their licence

7.1.4 The ML for the PFC was not renewed in 1981. Further legal opinion supported the view that Health Authorities in Scotland were in no different a position from those in England and Wales in respect of Crown status and exemption, and the SHHD made it clear that no renewal should be made[12].

7.1.5 Prior to the removal of Crown Immunity in April 1991, an application was submitted to the MCA to renew the Manufacturer's Licence for the PFC and the application was approved in September of that year following a 6 month formal transition period.

7.1.6 Since then a Manufacturer's Licence (or Manufacturer's/ Importers Authorisation – MIA - as it became known) was held continuously by the CSA for the manufacturing activities at PFC until 2008. In 2008 following on from the decision by the Scottish Government to cease manufacturing at PFC, the MIA was withdrawn by SNBTS on behalf of the CSA.

7.2 **Wholesale Dealer Licence (WL)**

7.2.1 This licence allows the holder to wholesale deal all types of medicinal products, including prescription only medicines (the group to which plasma products belong)

within the EC[13]. Wholesale dealing is defined as selling, supplying or procuring to anyone other than the end user.

7.2.2 An application for a WL, including the premises at the PFC and RTCs as distribution sites was made in 1991 as part of the programme for the removal of Crown Immunity. The application was successful and the WL has been renewed at the required intervals since that time.

7.2.3 The WL was retained and amended to reflect changes in distribution following the cessation of manufacturing at the PFC, to allow SNBTS to wholesale deal in the commercial products purchased to replace those produced previously at the PFC and supplied to hospital pharmacies, or in some cases held at the RTCs for issue.

7.3 **Manufacturer Specials Licence (MS)**

7.3.1 This licence allows the holder to manufacture (or import) and supply unlicensed medicinal products for individual patients[14].

7.3.2 Medicines legislation in the UK requires that medicinal products are licensed before they can be marketed. However, some patients may have special clinical needs for which there is no suitable licensed product. So that these special needs may be met, the law allows the manufacture and supply of unlicensed products (commonly known as "specials") under certain conditions.

7.3.3 An application was made for an MS for the PFC in 1995 and, following approval in the same year, it was renewed thereafter on a continuing basis until the requirement to renew was withdrawn in 2008.

7.3.4 The principal reason for adding an MS to the regulatory portfolio of the PFC at this time was the on-going and growing demand from transplant surgeons for anti-Cytomegalovirus IVIgG and anti-Hepatitis B IVIgG to use as prophylaxis against opportunistic infections in immune compromised patients.

7.3.5 The MS was also used to manufacture and supply specialist anti-toxins to the UK Ministry of Defence (MoD) and on delivery of the final batches to MoD in 2008 the MS was withdrawn.

7.4 **Manufacturer/Importers Authorisation for Investigational Medicinal Products [MIA (IMP)]**

7.4.1 Licensed manufacturing activities at the PFC were extended in 2004 to include Investigational Medicinal Products (IMPs) as part of complying with the then new Clinical Trials Directive (2001/20/EC)[15]. This new type of licence allows the holder to manufacture investigational products used in clinical trials. The Centre had a number of new products under development at that time and part of the new Directive on Clinical Trials required that the manufacturing standard for IMPs should be the same as that for licensed products.

7.4.2 Prior to this date, no specific approval was required to prepare products for use in a clinical trial, although the SNBTS had always manufactured such products in the manufacturing facilities at the PFC to the same standards of GMP used for established products released for clinical use.

7.4.3 When it was known that PFC would close, all clinical trials of new plasma products were discontinued and the Manufacturing Authorisation for IMPs was withdrawn in 2007.

8. REGULATORY INSPECTIONS OF THE PFC

8.1 General comments on inspections

8.1.1 The Medicines Inspectorate of the MHRA periodically inspects manufacturing sites to assess compliance with the relevant regulatory requirements. In the same way, the inspectorates of the previous regulatory authorities (DHSS, MCA) also carried out periodic inspections. Satisfactory inspections or agreed responses from companies or organisations to unsatisfactory inspection outcomes are required to prevent action against manufacturing and wholesale dealer's licences or product licences (Marketing Authorisations).

8.1.2 The regulatory requirements for manufacturing sites include operating according to the principles of Good Manufacturing Practice (GMP) and, Good Distribution Practice (GDP).

8.2 GMP/GDP Guidelines

8.2.1 Guidance on the standards of GMP/GDP required is contained in the publication titled "Rules and Guidance for Pharmaceutical Manufacturers and Distributors" prepared by the MHRA and known as the "Orange Guide". The aim of GMP/GDP is to ensure the quality of medicinal products for the safety, well-being and protection of patients[16].

8.2.2 The first edition of the "Orange Guide" was published in 1971 as the Guide to Good Pharmaceutical Manufacturing Practice, with a second edition published in 1977 and a third under this title in 1983. The fourth edition was published as Rules and Guidance for Pharmaceutical Manufacturers in 1993, with the fifth edition taking on the current title of Rules and Guidance for Pharmaceutical Manufacturers and Distributors in 1997. The sixth edition followed in 2002 with the current seventh edition in 2007.

8.2.3 The first European Guidelines on GMP (Volume 4 of the Rules and Regulations Governing Medicinal Products in the European Union) were published in 1989 and Directive 91/356/EEC was the first European legislation which required manufacturers of medicinal products to follow the principles of GMP

8.2.4 GMP includes elements of the International Standard for Quality Management Systems, with additional requirements specific to medicines manufacture. Since the first edition, the "Orange Guide" became one of the most comprehensive and

authoritative publications on UK and EU regulations governing the production and distribution of medicinal products. The current edition has adopted the text of the EU Guidance on GMP with added sections on matters specific to the UK.

8.2.5 However, as the GMP requirements in the EC change and develop more rapidly than before, the on-line collection of the Rules and Regulations governing Medicinal Products in the European Union (EudraLex Volume 4) which has the most up-to-date content has become the main reference text.

8.3 **GMP Inspections of the PFC**

8.3.1 The dates of inspections at the PFC and other SNBTS Centres are shown in Table 2.

8.3.2 A total of twenty three inspections of the PFC were carried out during its working lifetime, often involving more than one inspector, and each inspection normally lasting two to three days. Inspections are by their nature critical as their purpose is to identify areas for improvement and agree a time scale for the improvements to be made. Following each inspection, responses were made to the points raised by the Inspectorate and actions taken to put the required responses in place. Records of these inspection outcomes, responses and actions have been retained on file within SNBTS.

8.3.3 A number of informal visits to the PFC were also made by inspectors. These informal visits were useful opportunities to discuss progress on actions which had been agreed. Records of these informal visits are not complete, however, where they have been recorded, these informal visits are also shown in Table 2.

8.3.4 Inspections would normally be scheduled at two year intervals. Occasionally, additional inspections are carried out to assess progress on remedial actions or on-going projects. These follow up inspections are also shown in Table 2.

8.3.5 The first inspection of the PFC was carried out in January 1980 (the inspection actually began in late December 1979) although earlier requests had been made by the SNBTS for an inspection of the PFC following the completion of its construction in 1974[17].

8.3.6 As a result of this first inspection a number of additions were required to the PFC building. This was not unexpected since the PFC had been designed prior to the first guidelines on GMP being published and these were in their second edition (1977) before the PFC was inspected.

8.3.7 A phased building programme was agreed, including additional quality control laboratories and product storage areas, the final phase of which was completed in 1995.

8.3.8 After the Manufacturer's Licence for the PFC expired in 1981 (see 5.1.4) the Medicines Inspectorate had no formal right to inspection. However, informal visits by the Inspectorate continued and were acknowledged by them[18].

8.3.9 The decision not to renew the Manufacturer's Licence for the PFC was one with which the then Director of the PFC (Mr JG Watt), supported by the SNBTS National Medical Director (Dr JD Cash), did not agree[19]. Mr Watt was a member of the UK Committee on Safety of Medicines and argued that Manufacturing and Product Licences should be obtained for the PFC to demonstrate that appropriate standards were being maintained.

8.3.10 The lack of independent enforceable standards against which the PFC could be measured caused Mr Watt to be concerned that he might be personally liable for the products produced at the PFC. However, Mr Watt was assured that, as an employee of the CSA, he could not be considered liable for the actions of the Agency[20].

8.3.11 The question of personal liability in the absence of a Manufacturing Licence was raised again[21] by Dr RJ Perry (who had succeeded Mr Watt as Director of the PFC) at the time of the implementation of the Consumer Protection Act in 1987.

8.3.12 Dr Perry was assured that the Consumer Protection Act had no effect on the personal liability of staff at the PFC[22]. The SHHD Chief Pharmacist did not accept that the PFC was operating out with the standards required of the pharmaceutical industry, and considered that the products were of the required standard and were clinically safe.

8.3.13 In the same memo, the General Manager of the CSA referred to arrangements having been made for the licensing of the PFC and certain of its products to provide further reassurance. These arrangements had been outlined at an earlier meeting in October 1987[23] and included the inspection of the PFC by the DHSS Medicines Inspectorate.

8.3.14 The licensing procedures outlined by the SHHD were superseded by the removal of Crown Immunity in 1991 and the granting of a Manufacturing Licence for the PFC by the MCA.

8.3.15 Thereafter, inspections of the PFC by the Medicines Inspectorate followed the requirements of the Regulatory Authority with the principal Manufacturer's Licence and other Manufacturing Licences being held continuously until, as a result of the decision to close the PFC, the Licences were withdrawn in 2008.

8.3.16 The PFC was subject to inspection by the relevant regulatory agency throughout its operational lifetime both under crown immunity and following the removal of crown immunity.

8.3.17 During its operational life time, manufacturing activities at the PFC continued on uninterrupted by inspection outcomes with the exception of one occasion following the inspection of January 2006. Following this inspection of the PFC, manufacturing was suspended by local management in order to enable upgrades to be made to the Quality Management System. These actions were successfully implemented and approved by the Inspectorate in a series of follow up inspections.

9. LICENCES FOR PFC PRODUCTS

9.1 General Comments on Product Licences (PL)

9.1.1 For a medicinal product to be sold or supplied to patients in the UK, a number of licences are required. The manufacturers and distributors involved at all stages of production and distribution must have Manufacturer's and Wholesale dealer's licences. In addition, the product itself must have a licence called a Marketing Authorisation (previously called a Product Licence).

9.1.2 Applications for Marketing Authorisations are assessed by the relevant Regulatory Agency who will issue a licence to the applicant if the product is suitable. This is essentially the position established by the Medicines Act. The assessment of applications for Marketing Authorisations or variations to Marketing Authorisations is a lengthy procedure and can take a considerable period of time.

9.1.3 Before a medicine can be approved to go on to the market for sale (or in the case of the SNBTS, issued for use – all SNBTS products used in the Health Service in Scotland were and still are free at the point of use) it must go through a clinical trials process. The purpose of the clinical trials process is to provide information about the product such that a risk benefit analysis can be carried out to ensure that the product is safe and efficacious. There are approval procedures also for using products in clinical trials.

9.1.4 In the Medicines Act, clinical trials required an approved Clinical Trials Certificate (CTC). This was an extensive document and applications for CTCs became long and difficult, with prolonged assessment times. The Clinical Trial Exemption (CTX) scheme was introduced in 1981 to speed up the review and approval of clinical trials to allow important drugs to enter trials without delay. The current scheme for approving clinical trials requires a Clinical Trial Authorisation (CTA); the CTA procedure retains many of the features of the CTX scheme.

9.1.5 When a change is made to the method of manufacture of an existing product or, for example, a new clinical indication has been successful in a trial then an application for a Variation to the Product Licence must be made. The Variation must be approved before products manufactured using the revised method can be issued or the product supplied for a different indication.

9.2 Product Licences (PLs) for Factor VIII Concentrates Manufactured at the PFC

9.2.1 The licensed status of Factor VIII (FVIII) products produced at the PFC is shown in Table 3.

9.2.2 An application was made to the DHSS Medicines Division for a PL for the SNBTS intermediate purity FVIII concentrate (product name NY) in March 1978 and was granted in September that year. The PL was granted for a period of five years

which was normal at that time and was renewed on application to the DHSS in 1983 for a further five years.

9.2.3 The first heat treated NY product (68°C/2hrs) was issued under the same PL, i.e. without applying for and having approved a variation to the method of manufacture given in the PL. This was done to act as quickly as possible with the intention of making the product safe from HIV transmission, and was also done with the knowledge of the DHSS Medicines Division[24].

9.2.4 Successive heat treated intermediate purity products (NY 68 °C /24hrs; Z8 75 °C /72hrs and Z8 80 °C /72hrs) were also issued in this way until Z8 (80 °C /72hrs) became licensed under the transitional arrangements following the removal of Crown Immunity in 1991. An application to vary the method of manufacture of SNBTS FVIII concentrate to that used for Z8 (including heat treatment at 80°C for 72 hours) and to renew the licence had been submitted previously in 1989. This application was under consideration at the time the transitional arrangements came into force. The licence and therefore also the application for a licence variation, were effectively withdrawn in October 1992 when it was confirmed to the MCA that the SNBTS no longer intended to manufacture Z8.

9.2.5 In the aftermath of the issues surrounding HIV infectivity in haemophiliacs there was increasing concern (subsequently shown to be unfounded) that the relatively impure nature of intermediate FVIII products could cause immune disturbances in haemophiliacs and so the trend in the industry developed for evermore pure products. New purification processes for FVIII did have benefits in making more potent products and in using the purification process to recover FVIII from conditions that could be used to inactivate viruses.

9.2.6 To meet this demand for a high purity product, SNBTS entered into a collaborative project with the French Blood Transfusion Service fractionation plant in Lille, and a high purity FVIII product was developed at the PFC, based on technology already established at the Lille plant.

9.2.7 In order to advance this project as quickly as possible, batches for clinical trials were manufactured in Lille from plasma collected in Scotland by the SNBTS or Scottish plasma part processed at the PFC to an intermediate stage that could be shipped to Lille. This product (HP FVIII in Table 3) was used under an approved CTX.

9.2.8 The high purity FVIII product developed from this project and manufactured by the SNBTS (Liberate® in Table 3) was evaluated under a separate CTX and a PL for this product was approved in 1996.

9.2.9 Virus inactivation in the high purity FVIII product developed in this way was by treating the part processed FVIII solution with a mixture of an organic solvent and a detergent and then purifying the FVIII from that mixture. Treatment with solvent and detergent (S/D treatment as it became known) had become even at this time, a widely used method in the plasma fractionation industry for the inactivation of lipid

enveloped viruses, such as HIV and Hepatitis C (HCV). S/D treatment was not effective against non -enveloped viruses such as Hepatitis A (HAV) and Human Parvovirus (HPV) which were, however, sensitive to heat.

9.2.10 With its expertise in heat treatment, the SNBTS was able to develop the high purity product further, such that it could be treated with S/D and also heat treated in the final vial at 80°C for 72 hours. Clinical trials of this double virus inactivated product (Liberate® HT) were carried out under an approved CTX and the product was licensed in 2005 as a variation to the 500IU Liberate® PL.

9.3 **Product Licences for Factor IX Concentrates Manufactured at the PFC**

9.3.1 The licensed status of Factor IX (FIX) products produced at the PFC is shown in Table 4.

9.3.2 An application for a PL for the SNBTS FIX concentrate "DEFIX" was made to the DHSS in October 1978 and approved in July 1979, for what was the usual licensing period at that time of five years.

9.3.3 Taking the same approach as with heat treated FVIII products, heat treated DEFIX (HT DEFIX in Table 4) was issued under the original FIX concentrate PL, i.e. without applying for and having approved a variation to the method of manufacture specified in the PL; at this time also a renewal of the FIX concentrate PL would have been required. Again this was done to make a virus safe heat treated product available as soon as possible.

9.3.4 An application was made in 1989 to the MCA for a delayed renewal and variation (to include heat treatment) of the original FIX concentrate PL. As this was under assessment at the time of the removal of Crown Immunity, HT DEFIX was considered as a licensed product under the transitional arrangements. The PL renewal/variation for HT DEFIX continued to be supported by the SNBTS and remained under assessment by the MCA/MHRA until it was withdrawn by the SNBTS on behalf of the CSA prior to the closure of the PFC in 2008. During this time HT DEFIX remained a licensed product under the terms of the transitional arrangements.

9.3.5 The first Factor IX concentrates were mixtures of the Prothrombin Complex group of proteins, which have similar characteristics and tend to co-purify (FIX concentrates of this period were also known as Prothrombin Complex Concentrates - PCCs). Some of the proteins in this concentrate could have the potential to be thrombogenic (i.e. cause uncontrolled clotting) when infused into patients and so the next major change in the treatment of FIX deficient haemophilia (haemophilia B) after the virus inactivation of FIX concentrates was the use of products containing only FIX (so-called high purity FIX products).

9.3.6 The SNBTS developed a high purity FIX product (HIPFIX in Table 4) which was designed from the outset to be double virus inactivated (S/D and 80°C heat treatment). This product completed clinical trials under the MCA CTX scheme and was licensed in 2001.

9.3.7 In addition to being used as replacement therapy in haemophilia B, PCCs such as DEFIX were also used in other clinical indications such as anticoagulant reversal in patients being treated with warfarin. The manufacture of DEFIX was maintained at the PFC, therefore, to meet this requirement and this product was further developed to include S/D treatment as well as heat treatment (SD DEFIX in Table 4), so as to ensure the same standard of virus inactivation as with other coagulation factor products.

9.3.8 SD DEFIX was approved for clinical trial by the MCA but the development was not completed before the closure of the PFC.

9.3.9. A PCC containing Factor VII that could also be used for the treatment of Factor VII deficiency was approved for clinical trials by the MHRA but this development also was not completed before the closure of the PFC.

9.4 **Product Licences for Intravenous Immunoglobulin (IVIgG) Manufactured at the PFC**

9.4.1 The licences and other approvals for IVIgG products produced at the PFC are shown in Table 5.

9.4.2 Immunoglobulin for intravenous infusion (IVIgG) was introduced by the SNBTS in 1983 and, in that same year, an application was made for a PL for SNBTS IVIgG to be used in the maintenance therapy of hypogammaglobulinaemia (a condition where individuals are unable to synthesise immunoglobulin, the class of protein to which antibodies belong). The application was successful and a PL was granted in 1985.

9.4.3 Immunoglobulin that could be given in large intravenous doses was still a relatively new departure for the plasma fractionation industry at this time and following the granting of a PL, all recipients of all batches of SNBTS IVIgG were monitored for evidence of hepatitis transmission. A total of 165 consecutive batches of SNBTS IVIgG were monitored in this way and, during this exercise, blood samples from four patients from a total of thirteen treated with the same batch were found to have raised levels of the enzyme alanine aminotransferase (ALT), which could be indicative of what was still known at that time as non A non B hepatitis[25]. Although none of the patients in question showed any clinical signs of hepatitis, the presence of hepatitis C was confirmed in stored samples from three of the four patients[26].

9.4.4 The DHSS Medicines Division was kept fully informed of this incident and of the follow up investigation. At no time was the SNBTS requested to stop issuing IVIgG and no action was taken by the regulator against the product licence. There were no further examples of virus transmission by SNBTS IVIgG at that time nor has there been since. The method of manufacture was not changed, although the facilities and equipment used were revised to give a higher degree of containment as a precautionary measure against any future incidents.

9.4.5 The ability to give large doses of immunoglobulin intravenously led to IVIgG being used successfully in other immune related disorders and PL variations were approved by the MCA for the use of SNBTS IVIgG in the prophylaxis of recurrent

bacterial infections in HIV positive children (1989); the treatment of idiopathic thrombocytopenic purpura (1990); maintenance therapy in secondary hypogammaglobulinaemia (1991); the management of Kawasaki disease (1993); prophylaxis in immune compromised bone marrow recipients (1997) and the treatment of Guillain-Barre syndrome (2000).

9.4.6 Later developments included a larger dose size (PL 3473/0032) of the freeze dried product and a ready to use liquid formulation.

9.5 **Testing by the National Institute of Biological Standards and Control (NIBSC)**

9.5.1 Biological medicines are complex materials and because of their complex nature, licensed products of this type are required by law to be subject to independent testing before they can be released on to the market or (in the case of SNBTS) issued for use. This procedure is referred to as independent batch release testing and must be carried out by a designated Official Medicines Control Laboratory (OMCL; see Section 4.2.5).

9.5.2 The NIBSC was established under the Biological Standards Act in 1975 to ensure quality, safety, efficacy and consistency of biological substances. In fulfilling this role it devised standards for the quality, purity and potency of biological substances, tested batches of biological products on behalf of Department of Health (DoH), carried out research and advised a number of bodies, including the Medicines Division of the DoH.

9.5.3 NIBSC continues to work closely with the MHRA (as it did with the previous regulatory bodies) to carry out independent batch release testing of viral vaccines, bacterial vaccines and plasma products as the UK OMCL for these types of medicinal products.

9.5.4 Following the approval of a PL for the SNBTS FVIII concentrate NY in 1978, the PFC commenced sending samples from batches of finished product to the NIBSC on a regular basis and these samples are recorded in the batch issue records which are still on file at the SNBTS.

9.5.5 It was also the practice of the PFC at that time to send samples of all plasma products manufactured at PFC, including those which were at that time without licences[27]. Records are also available for the samples of DEFIX sent to NIBSC during this period

9.5.6 The NIBSC did not supply the SNBTS with batch release certificates at this time and this was regarded as an informal arrangement for information and advice only. The submission of samples to the NIBSC in this way continued on until late 1985, when at the request of the Blood Products Testing Division at the NIBSC, the PFC stopped sending regular samples[28].

9.5.7 Submitting samples of SNBTS plasma products to the NIBSC recommenced in August 1986 and following discussions with Dr Geoffrey Schild, the Director of the NIBSC, it was agreed that samples of all SNBTS plasma products (licensed and

unlicensed) would be sent to NIBSC for testing, from 1st January 1987[29]. This remained at that time an informal procedure in that the NIBSC would not issue batch release certificates but did undertake to notify the PFC promptly should any measurement indicate that a product was out of specification[30].

9.5.8 On the removal of Crown Immunity in 1991, mandatory batch release testing of all licensed PFC products was undertaken by the NIBSC and formal batch release certificates were issued to the PFC on completion of satisfactory testing.

9.5.9 A further role provided by the NIBSC is in the development and production of national and international standards (e.g. samples of coagulation factor preparations with assigned values of clotting factor activity) for use as reference materials in Quality Control Laboratories.

9.5.10 The NIBSC conducts national and international surveys of competent laboratories in order to assign standard values to these reference materials. The PFC was frequently invited by the NIBSC to be involved in these exercises and always participated fully.

9.6 **The European and British Pharmacopoeias**

9.6.1 The European Pharmacopoeia (Ph. Eur.) contains a collection of monographs describing the quality standards for individual generic pharmaceutical products, including blood products, together with specifications for the active substances, excipients, containers, closures and other materials that must be used in their manufacture.

9.6.2 The Ph. Eur. is prepared by the European Directorate for the Quality of Medicines and all licensed medicinal products in the EU must comply with these quality standards; the objective being that consumers will have a guaranteed standard for products obtained from pharmacies or other legal suppliers.

9.6.3 The British Pharmacopoeia (BP) which is prepared by the UK Commission on Human Medicines, is considered as an additional local pharmacopoeia and is consistent with the Ph. Eur. but also contains requirements specific to the UK.

9.6.4 The quality standards for medicinal substances contained in the BP and the Ph. Eur. are referenced by the MHRA in the licensing and inspection processes used to control the manufacture of medicinal products in the UK.

9.6.5 The first monograph for FVIII concentrate was given in the BP in 1973 as being for "Dried Human Anti-haemophilic Factor" and contains no product virus testing or inactivation requirements, but does require that each donation was tested and found negative for Hepatitis B Surface Antigen (HBsAg) a marker for Hepatitis B infection.

9.6.6 In 1980 the BP introduced monographs for "Dried Human Factor VIII" and "Dried Human FIX". The quality characteristics of the products are defined in these monographs, especially relating to potency measurements. However, neither of these monographs made reference to any further testing for virus markers nor any manufacturing requirements for virus inactivation.

9.6.7 The BP monographs for FVIII and FIX concentrate and those for other plasma derived products were revised in 1986 to stipulate that products must be made from plasma derived from "healthy donors (who must, as far as can be ascertained after clinical examination, as well as laboratory tests on their blood and a study of their medical record) be free from diseases transmissible by transfusion of blood or blood products".

9.6.8 The 1988 BP and Ph. Eur. monographs for plasma derived products had extended the requirements of the 1986 versions to include testing for specific viral pathogens i.e. "In particular they [the donors] should be negative for HBsAg and HIV antibodies using suitably sensitive tests". This revision of the monographs also required the manufacture of the plasma products in question to include a "viral inactivation/elimination process".

9.6.9 In the 1994 revision, the Ph. Eur. specified that plasma products must be prepared from "Human plasma for fractionation", the quality standards for which were detailed in a separate monograph, and included testing for anti-HIV-1 antibodies, anti-HIV-2 antibodies, HBsAg and anti-HCV antibodies. In addition the starting plasma pools for manufacture were required to be negative for HBsAg, HIV antibodies and HCV nucleic acid (RNA).

9.6.10 The first monograph defining the quality of IVIgG products (Ph Eur monograph no 918) was published in 1994 and contained the requirements of having to be manufactured from "Human plasma for fractionation" and that the manufacturing method contained a process for virus inactivation.

9.6.11 By their nature, being regulatory documents that must be agreed and published, product monographs will lag behind the latest industry developments. However, it should still be noted that SNBTS FVIII, FIX and IVIgG products complied with each relevant monograph and every one of its revisions in terms of product quality and safety.

9.7 **UK National External Quality Assessment Service (NEQAS)**

9.7.1 The UK NEQAS provides internal quality control and external assessment for a number of different clinical laboratory analyses.

9.7.2 The NEQAS was formed in 1969 and is now made up of a network of twenty four centres based at major hospitals, research institutes and universities in the UK.

9.7.3 Test specimens are distributed for analysis to participating laboratories and reports on their performance are returned to them. Although intended mainly for clinical laboratory medicine, where there was overlap with analytical methods used at the PFC, the PFC participated in the relevant NEQAS programmes including coagulation factor activity assays and testing for virus markers. Similarly, the SNBTS RTCs participated in (and still do participate in) the relevant NEQAS schemes, with virus marker testing being seen as of particular importance.

9.7.4 The NEQAS has no legislative authority, but the MHRA and other bodies recognise it as an important national scheme.

9.8 **Adverse Event Reporting and Pharmacovigilance**

9.8.1 The then Committee on Safety of Drugs (CSD) set up a system in 1964 for the reporting of adverse drug reactions (ADRs). This system became known as the "Yellow Card System" because of cards supplied for reporting ADRs and is still in operation today.

9.8.2. PFC products were issued as prescription only medicines (POMs) for use by prescribing physicians, with the SNBTS identified on the product label and product information leaflet as the manufacturer and giving the contact details for the PFC to whom any reactions or incidents should be reported. Serious ADRs reported in this way would in turn be reported by the PFC to the regulatory authority using the Yellow Card System. Patients and health professionals can also report ADRs directly to the MHRA as part of the same system.

9.8.3 An ADR is defined as "a harmful and unintended reaction that occurs at the dose normally used" for the treatment in question[31]. Biological medicinal products, because of their nature, are considered to be more prone to adverse reactions and, although not frequent, adverse reactions do occur on the infusion of plasma products. These can range, for example, from "allergic" type reactions to nausea, dizziness, reduced renal function or rashes and itching. In addition to these physiological responses, virus transmissions, following administration of blood products, would also be classified as ADRs and when they did occur, they were reported in this way.

9.8.4 Pharmacovigilance is the term used to describe the monitoring of both the risks and benefits of medicines in everyday practice, to optimise their safe and effective use. The assessment of ADRs is only one source of information that the MHRA use as part of their pharmacovigilance function; others include published medical literature, epidemiological and clinical studies and information from other regulatory authorities world -wide.

9.8.5 Information gathered from these sources is assessed by the MHRA, who are advised by the Committee on Safety of Human Medicines (CHM) and its various expert sub-committees, on any action that the MHRA would propose to take as a result of ADRs concerning the products involved and their manufacturers.

9.8.6 No specific actions were ever taken by the MHRA, or its predecessors, against any PFC product as a result of Adverse Drug Reports.

10. REGULATION OF REGIONAL TRANSFUSION CENTRES (RTCs)

10.1 RTC Activities and the Medicines Act

10.1.1 As commented earlier (see Section 4), the preparation of blood and blood components for infusion were exempt from the Medicines Act and the EU Directives which followed it into UK law. This was specifically made clear in Statutory Instrument 1992 No 604.

10.1.2 However, although the processing of blood and components was a large part of the work of an RTC, these were not the only activities carried out in these facilities. Prior to the UK government ban in 1998 on the use of UK plasma for the manufacture of medicinal products as a precautionary measure against the potential transmission of Variant Creutzfeldt- Jacob disease (vCJD), a further role of RTCs was to prepare plasma for shipping to PFC for the manufacture of plasma products. It is the responsibility of the licence holder for the manufacture of plasma products to ensure that the starting plasma for fractionation meets the required specification[5] and the procedures for the collecting, testing, transport and storage of plasma for fractionation must also be included in any application for a Product Licence. The PFC, therefore, was expected to have effective systems in place for ensuring that the starting plasma supplied for manufacture met the appropriate standards, however, this requirement was taken into account when the Medicines Inspectorate visited the RTCs.

10.1.3 The RTCs also acted as the main network for the distribution, storage and onward supply of plasma products manufactured at PFC to hospital pharmacies and treating clinicians. These were also activities that could well be considered as coming under the jurisdiction of the Medicines Act.

10.1.4 In specific cases, such as the West of Scotland RTC at Law Hospital, where parenteral solutions were prepared [32], there is no doubt that these were relevant activities for regulation.

10.1.5 It may well have been that the SNBTS RTCs received manufacturing licences as of right at the implementation of the Medicines Act as, unlike the PFC, these units were established prior to the Act. The SNBTS has no record of such licences but this is implied in correspondence from that time[33] and in the report of an early inspection of the West of Scotland RTC[32].

10.1.6 The DHSS Medicines Division and then the MCA clearly considered the Medicines Act as applying to the activities of RTCs in the UK Blood Transfusion Services. This is shown first by the DHSS carrying out inspections of RTCs (specifically excluding Hospital Blood Banks) on a UK-wide basis in the early 1980s[34], as part of ensuring that NHS production standards were acceptable, and second by the MCA advising that RTCs (again on a UK-wide basis) should operate under Manufacturer's Specials Licences[35] on the removal of Crown Immunity.

10.1.7 In general, therefore, SNBTS RTCs should be considered as facilities to which the Medicines Act did apply but which operated under Crown Immunity until the removal of Crown Immunity under the National Health Service Community Care Act, which came into force in 1991.

10.2 **Guidelines for the Blood Transfusion Services in the UK**

10.2.1 The "Guidelines for Blood Transfusion Services" in the UK, or the "Red Book" as it has come to be known, were first published in 1990 and were compiled by experts from all the UK Blood Transfusion Services and the NIBSC. The objective of the guidelines is to define all of the materials produced by the UK Blood Transfusion Services for both therapeutic and diagnostic use.

10.2.2 This project was started in 1987 and the impetus behind it was the Consumer Protection Act (see Section 4), which came into effect in July 1988, concerning liability for defective products. Blood and blood components are all considered as products under this Act. Guidelines and standards were needed, therefore, to help prevent defective products being produced, to provide standards against which centres could be inspected and, where necessary, against which products could be judged as defective or not.

10.2.3 The "Red Book" is now in its 7th Edition. The group preparing the guidelines has been extended to include experts from outside the Blood Transfusion Services and is known as the Joint UKBTS/NIBSC Professional Advisory Committee (JPAC).

10.2.4 The current edition describes best practice for managing operations in Blood Transfusion Centres, gives standards for the reagents and products produced and the technical details for the processes used to produce them. The "Red Book" also outlines the legal requirements for a Blood Establishment under the Blood Quality and Safety Regulations 2005.

10.2.5 The guidelines themselves have no legal basis but are acknowledged by the MHRA as representing a position of national expert consensus on best practice.

10.2.6 The SNBTS participated fully in the development of the "Red Book" and the guidelines and standards contained it in have been, and still are, an integral part of the SNBTS Quality Management System.

10.3 **Manufacturers Specials Licence (MS) for SNBTS RTCs**

10.3.1 On the removal of Crown Immunity, and following the national guidance from the MCA, the Board of the CSA agreed that "in order to maintain an optimum service to meet the needs of the NHS in Scotland, the best way forward is to apply for a Manufacturer's Specials Licence for each of the five Regional Transfusion Centres"[36]

10.3.2 In the event, a single licence was granted to the CSA with each of the RTCs identified as individual sites on the licence (Table 6).

10.3.3 In this way blood and blood components were to be considered as unlicensed medicinal products or "Specials" (see Section 7.3) supplied in large volumes to other NHS sites

10.3.3 Following the transitional arrangements for the removal of Crown Immunity the activities at RTCs, therefore, were regulated as follows:

- Preparation and supply of blood and blood components – MS
- Production of plasma for fractionation – PFC ML
- Storage and distribution of plasma products - PFC ML/SNBTS WL

10.3.4 The MS for RTC sites was retained and renewed until it was superseded by the Blood Standards and Quality Regulations in 2005 (see Section 4).

10.4 **Blood Establishment Authorisations**

10.4.1 The Blood Safety and Quality Regulations (BSQR) set out for the first time rules governing the preparation of blood and blood components which were previously excluded from earlier legislation on medicinal products.

10.4.2 Specifically, the BSQR set out the requirements for the operation of Blood Establishments (establishments which collect, process and test human blood and components) and Blood Banks (hospital units which store, distribute and perform compatibility tests on blood and blood components for use in hospitals).

10.4.3 SNBTS RTCs met fully all the requirements of the BSQR and, in common with RTCs in the other UK Transfusion Services, became Blood Establishments in 2005. In effect the MS held by CSA became a Blood Establishment Authorisation, with each of the SNBTS RTCs recognised as operating sites on the Authorisation (Table 5).

10.4.5 In the same way as the MHRA operates a pharmacovigilance programme (see Section 9.8), so it also hosts, as part of the BSQR framework, a haemovigilance programme, including the Serious Adverse Blood Reactions and Events (SABRE) reporting system. Blood Establishments and Blood Banks are required by law to notify the MHRA, as the UK Competent Authority, of any serious adverse event and serious reactions.

10.4.6 The SABRE reporting system also links to the Serious Hazards of Transfusion (SHOT) reporting mechanism. The SHOT reporting system is a voluntary haemovigilance scheme set up in 1996 by the UK Transfusion Services. SNBTS were involved (with the other UK blood transfusion organisations in establishing SHOT and the SNBTS continues to be heavily involved in its operation and management.

10.4.7 In addition to reporting all adverse reactions and events Blood Establishments must allow the MHRA access to inspect establishments for compliance with the regulations.

10.4.8 The Regulatory Authority has not been required to take action concerning blood or blood components prepared by the SNBTS as a result of adverse reactions.

11. INSPECTIONS OF RTCs BY REGULATORY AGENCIES

11.1 The SNBTS records indicate that some sixty six regulatory inspections have been carried out of SNBTS RTCs up to 2010 and the dates of these are shown in Table 2.

11.2 Some of the earlier inspections shown in Table 2 (e.g. Aberdeen in 1977) are known only because they are referred to in a report by the Medicines Inspectorate (MI) of a later visit. However from the 1980 and 1981 inspections of the West of Scotland RTC and the 1982 round of inspections onwards, the SNBTS has a near complete set of records.

11.3 The 1980 inspection of the West of Scotland RTC (located at that time in Law Hospital, Carluke) was concerned initially with the pyrogen testing carried out at Law for the release of PFC products. However, the inspection went on to include other aspects of operations at Law, notably the preparation of parenteral solutions and the processing of freeze dried plasma as a medicinal product.

11.4 The 1982 round of inspections (and it could be assumed the 1981 series of informal visits that preceded it) were part of a UK-wide initiative[34] by the DHSS Medicines Division to ensure that pharmaceutical processing activities in the NHS were of an acceptable standard. The inspections were therefore general in their approach (although reference was made to the "Orange Guide"), and the Inspectorate were also conscious of the role of the RTCs in supplying plasma for fractionation[37].

11.5 The 1988 series of inspections, and those inspections which followed on in 1989 and 1990, were again general in nature.

11.6 From 1992 through to 2005, the inspections followed a regular biennial pattern and, as the RTCs were operating under an MS Licence, the standards against which they would have been inspected would be those defined in the "Orange Guide" of that time.

11.7 From 2005 onwards the inspections have followed the same two year timetable and the purpose of MHRA inspections has been to ensure that the RTCs complied with the requirements of the BSQR.

11.8 Responses were made by the SNBTS to all points raised by the MI following each and all of the inspections of the RTCs and remedial actions were taken. In some cases, as with the building programme at the PFC, the remedial actions involved major changes in the Service. For example, the cessation of parenteral solution preparation and freeze dried plasma processing at the West of Scotland RTC (1982); the relocation of components processing in the South East BTS from Livingston House to new purpose built accommodation in the BTS Centre at Lauriston Place in the early 1990sandthen later to the new Edinburgh Royal

Infirmary site and the relocation of the West of Scotland RTC from Law Hospital to Gartnavel Hospital in Glasgow in 2001.

11.9 The Licences for activities at the SNBTS RTCs have been held continuously without interruption since their initial approval.

12. CONCLUSIONS

12.1 The period in question saw the introduction and development of the legislative control of the manufacture and supply of medicinal products in the UK including blood and products derived from blood.

12.2 As part of a Crown body, the SNBTS was, until 1991, exempt from prosecution under the Medicines Act. It is clear from the actions of the DHSS and the MCA that they saw the PFC and the SNBTS in general as operating under Crown Immunity.

12.3 Nevertheless, the SNBTS did not seek to disregard the legislation but worked continuously towards the contemporary standards required of blood collection, testing and processing and plasma products manufacture. Manufacturing licences and product licences were obtained while still under Crown Immunity; the SNBTS participated fully in the development of professional standards, maintained a dialogue with the Regulatory Authority and as far as possible remained open to inspection.

12.4 The efforts made by the SNBTS in working towards contemporary best practice during Crown Immunity were critical to all areas of the Service making a full transition to operating under legislative control when Crown Immunity was withdrawn.

13. REFERENCES

(1) The Penrose Inquiry Preliminary Report Chapter 12

(2) SNBTS Corrections and omissions to the Preliminary Report Chapter 12

(3) Foster et al Transfusion Medicine (1997) 7, 67-69

(4) Tabor, Transfusion (1999) 39, 1160-1168

(5) Annex 14, MHRA Rules and Guidance for Pharmaceutical Manufacturers and Distributers, Pharmaceutical Press, 2007

(6) Letter from J Walker (SHHD) to CSA 3rd July 1975

(7) Memo of 11 May 1987 to J R Y Mutch, Secretary CSA, from J I McCubbin, Legal Adviser

(8) The Penrose Inquiry Preliminary Report Chapter 12 Para. 12.23

(9) House of Lords Friday 22 October 2010; Contaminated Blood (Support for Infected and Bereaved Persons Bill) Second Reading

(10) Letter from G M D Thomson SHHD to NHSiS General Managers (10 January 1991) concerning NHS Circular No1991 (GEN) 1

(11) MHRA Guidance Note 5: Notes for applicants and holders of manufacturer's licences

(12) Memo of 31 December 1981 from A F Neilson, Legal Advisor CLO to R Y Anderson, Assistant General Administrator CSA

(13) MHRA Guidance note 6: Notes for applicants and holders of a wholesale dealers Licence

(14) MHRA Guidance Note 14: The supply of unlicensed relevant medicinal products for individual patients

(15) The Medicines for Human use (Clinical Trials) Regulations 2004: SI 2004/1031

(16) Introduction to the 2007 edition of the MHRA Rules and Guidance for Manufacturers and Distributers, Pharmaceutical Press

(17) Events concerning the safety of blood and blood products with special reference to the treatment of haemophilia. Briefing paper to the Penrose Inquiry from the SNBTS

(18) Medicines Inspectors Report PFC 6th April 1988

(19) Letter from Dr JD Cash to JRY Mutch CSA 15th December 1981

(20) Letter from JRY Mutch CSA to Dr JD Cash 7th January 1982

(21) Letter from Dr RJ Perry to JT Donald 16th October 1987

(22) Memo from JT Donald to Dr RJ Perry 13 June 1988

(23) Blood Transfusion Service: Miscellaneous Issues. Note of Meeting on 26th October 1987.

(24) Letter from ME Duncan Medicines Division DHSS to Dr JD Cash 26th November 1984

(25) Williams et al (1989) Vox Sanguinis, 57, 15-18

(26) Yap et al (1994) J of Hepatology, 21, 455-460

(27) Letter from J Watt, Director PFC to J A Sutherland SHHD; June 1980

(28) B Cuthbertson personal communication

(29) Letter from B Cuthbertson to Geoffrey Schild, December 1986

(30) Letter to Duncan Thomas from RJ Perry 14th January 1987

(31) Glossary of MHRA Terms (www.mhra.gov.uk)

(32) Report of Inspection of West of Scotland RTC Law in January 1980

(33) Letter from J A Sutherland to SNBTS NMD 26 November 1976

(34) Notes of Medicines Inspectorate/RTDs Meeting: 18th September 1981, DHSS

(35) Letter from G Calder (SHHD) to J Donald (CSA) 18th February 1991

(36) Letter from J Donald to G Calder 27th February 1991

(37) Letter from DHSS (10 July 1981) inviting participants to a meeting on the proposed inspection of Regional Transfusion Centres.

14. GLOSSARY

Medicinal product	Any substance or combination of substances presented for treating or preventing disease in human beings. A substance is defined as any matter, irrespective of origin which may be human, animal, vegetable or chemical. (Directive 2001/83/ EEC)
Blood	Whole blood collected from a single donor and processed either for transfusion or further manufacturing. (EU Guidance on Good Manufacturing Practice 2007)
Blood components	Therapeutic components of blood (red cells, white cells, plasma, platelets) that can be prepared by centrifugation, filtration and freezing using conventional blood bank technology. (EU Guidance on Good Manufacturing Practice 2007)
Medicinal products derived from blood or plasma	Medicinal products based on blood constituents which are prepared industrially by public or private establishments; these medicinal products include, in particular, albumin, coagulation factors, and immunoglobulin of human origin. (Directive 89/381/EEC)

TABLE 1:
MANUFACTURER'S AND WHOLESALE DEALERS LICENCES FOR the PFC

Type of Licence	Licence Number	Status
Manufacturer's Licence (ML/MIA)	ML3473/01	Application: 1976 Approval: 1976 Expiry: 1981 Renewal: 1991 Renewal: 1996 Renewal: 2001(1) Withdrawn: March 2008
Wholesale Dealers Licence (WL)	WL3473/01	Application: 1991 Approval: 1991 Renewal: 1996 Renewal: 2001(1)
Manufacturer Specials Licence (MS)	MS3473/01	Application: 1995 Approval: 1995 Renewal: 2001 Renewal: 2000 Renewal: 2005 (2) Withdrawn: April 2008
Manufacturer/Importer Authorisation for Investigational Medicinal Products (MIAIMP)	MIAIMP3473/01	Application: 2004 Approval: 2004 Withdrawn: August 2007

Notes:
(1) As of the 30th October 2005, the MHRA no longer required licence holders to renew the licences every five years.
(2) The renewal date for the PFC Manufacturers Specials Licence fell in 2005 before the 30th of October.

TABLE 2: REGULATORY INSPETIONS OF SNBTS FACILITIES

Year	PFC	Aberdeen RTC	Dundee RTC	Edinburgh RTC	Glasgow RTC	Inverness RTC
1977		March (1)				
1978						
1979	December					
1980	January				January	
1981	June October	June (1)	June (1)	June (1) July (1)	June (1)	June (1)
1982		March	March	May	March	May
1983						
1984	March(1)				February(2)	
1985						
1986						
1987						
1988	April(1) June		October	November	October	November
1989	November(1)			March(2)		
1990	October(1)	January				
1991	January May(2)					
1992	May (1)	October	October	September	February	March
1993	January					
1994	April	December			April	
1995			January	March		March
1996	March				June	
1997		January	February	June		February
1998	June July					
1999		June	June	November	March	June
2000	August					
2001		June	June	December	March	June
2002	July December					
2003		June	May	November	October	September
2004	March					
2005	April	June	June	December	November	December
2006	January April(2) September(2)					
2007	February(2) August	June	June		November	November
2008	January			January		
2009		June	June		November	November
2010				January		

Notes: (1) Informal Visit (2) Follow up visit

TABLE 3: PFC FACTOR VIII PRODUCT LICENCES

Product	Period	Type	Clinical Trial	PL (MA)	PL/MA Status
NY	1975 to 1984	Intermediate Purity	Previous established use	PL 3473/0007	PL Application: 1978 PL Approval: 1978 Renewed: 1983
NY(68/2)	1984 to1985	Intermediate Purity Heat Treated (68°C/2hrs)	Evaluation by treating clinicians	PL 3473/0007	Issued under original FVIII PL
NY(68/24)	1985 to 1987	Intermediate Purity Heat Treated (68°C/24hrs)	Evaluation by treating clinicians	PL 3473/0007	Issued under original FVIII PL
Z8 (75/72)	1987	Intermediate Purity Heat Treated (75°C/72hrs)	Evaluation by treating clinicians	PL 3473/0007	Issued under original FVIII PL
Z8 (80/72)	1987 to 1992	Intermediate Purity Heat Treated (80°C/72hrs)	Evaluation by treating clinicians	PL 3473/0007 Variation	Issued under original FVIII PL : 1987-1991 Application for PL Variation:1989 Issued under transitional arrangements post Crown Immunity: 1991-1992
HP FVIII	1991 to 1992	High Purity Solvent/Detergent Treated	CTX 02629/0004/A Approved 1992	N/A	Manufactured in Lille France from SNBTS plasma and used in clinical trials only
Liberate®	1992 to 2005	High Purity Solvent/Detergent Treated	CTX 02629/0005/A Approved 1992	PL 3473/0036	PL Application: 1994 PL Approval: 1996
Liberate® HT	1997 to 2006	High Purity Solvent /Detergent Treated and Heat Treated (80°C/72hrs)	CTX 02629/0016/A Approved 1997	PL 3473/0036 Variation	Application for PL Variation: 2003 Approval of PL Variation : 2005 PL withdrawn : 2008

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TABLE 4: PFC FACTOR IX PRODUCT LICENCES

Product	Period	Type	Clinical Trial	PL/MA	PL/MA Status
DEFIX	1976 to 1985	Partial Prothrombin Complex Concentrate (PCC) containing Factors II,IX and X	Evaluation by treating clinicians	PL 3473/0008	Application: 1979 Approved: 1979
HT DEFIX	1985 to 2006	Partial PCC containing Factors II,IX and X Heat Treated (80°C/72hrs)	Evaluation by treating clinicians	PL 3473/0008	Issued under original DEFIX PL: 1985-1991 Issued under transitional arrangements post Crown Immunity: 1991-2008 Application for variation: 1989 Remained under determination by MHRA Withdrawn: 2008
HIPFIX	1993 to 2006	High Purity Factor IX Solvent/Detergent Treated and Heat Treated (80°C/72hrs)	CTX 02629/0012/A	PL 3473/0035	PL Application: 1998 PL Approval : 2001
SD DEFIX	2000 to 2006	Partial PCC containing Factors II, IX and X Solvent/Detergent Treated and Heat Treated (80°C/72hrs)	CTX 02629/0020/A	N/A	N/A
Four Factor PCC	2004 to 2006	PCC containing Factors II,VII, IX and X	CTA 02629/0023/1	N/A	N/A

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TABLE 5: PFC IVIgG PRODUCT LICENCES

Product	Period	Type	Clinical Trial	PL/MA	PL/MA Status
IVIgG 3 gram 5 gram	1983 to 2006	Human Normal Immunoglobulin for Intravenous Infusion Freeze Dried	Evaluation by treating clinicians	PL 3473/0011	Application: 1983 Approval: 1985 Renewal: 1990 and thereafter PL Variations for the treatment of different clinical indications: 1989, 1990, 1991, 1993, 1997 and 2000 Withdrawn: 2008
IVIgG 10 gram	1997 to 2006	Human Normal Immunoglobulin for Intravenous Infusion Freeze Dried	Laboratory studies only required by MCA	PL 3473/0032	Application: 1996 Approval: 1997 (all indications included) Renewal: 2002 and thereafter Withdrawn: 2008
LIG 5 gram	1998 to 2006	Human Normal Immunoglobulin for Intravenous Infusion Liquid Formulation	CTX 02629/0019/A	N/A	Application: 2003 Approval not completed prior to closure of the PFC

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TABLE 6: RTC LICENCES

Licence/Authorisation	Aberdeen RTC	Dundee RTC	Edinburgh RTC[1]	Glasgow RTC[1]	Inverness RTC
Manufacturers Specials Licence (MS) MS 11504/01 Application: 1991 Approval: 1991 Renewal: 1996 Renewal: 2001 Withdrawn: 2005	Site number: 21113	Site number: 92150	Site number: 89701	Site number: 89382	Site number: 315830
Blood Establishment Authorisation (BEA) BEA 3473 Application: 2005 Approval: 2005 [2]	Site number: 21113	Site number: 92150	Site number: 89701	Site number: 89382	Site number: 315830

Notes

(1) The Processing and Testing of blood donations in SNBTS is now centralised in Edinburgh and Glasgow.

(2) From 2005 the MHRA no longer required licence holders to renew their licences periodically.

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APPENDIX I

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 28 September 2009
Doc. Ref: EMEA/619114/2009

Key Documents for Plasma Derived Medicinal Products

Key document

1. Council Directive – 89/381/EEC – 14 June 1989
2. Council Directive – 75/318/EEC – 20 May 1975
3. Guideline on Plasma-derived Medicinal Products – CPMP/BWP/269/95 rev. 4 – 19 February 2009
4. Concept Paper on the Revision of the Note for Guidance on Plasma-derived Medicinal products – EMEA/CHMP/BPWP/495530/2006 – 6 December 2006
5. Guideline on Assessing the Risk for Virus Transmission – New Chapter 6 of the Note for Guidance on Plasma-derived Medicinal Products (CPMP/BWP/269/95 – CPMP/BWP/5180/03 – 21 October 2004
6. Note for Guidance on Plasma-derived Medicinal Products – CPMP/BWP/269/95 rev. 3 – 25 January 2001
7. Note for Guidance on Plasma-derived Medicinal Products, Revision of Section 3.2.5 of CPMP/BWP/269/95 rev. 2, Albumin and Other Plasma-derived Products Used in the Manufacture and Formulation of Medicinal Products – CPMP/BWP/1595/00 – 27 July 2000
8. Explanatory Note: The Expiry Date of Products Incorporating Plasma-derived Products as Stabilisers or Excipients (CPMP/BWP/305/99), Addendum to Note for Guidance on Plasma-derived Medicinal Products (CPMP/BWP/269/95 rev. 2) – CPMP/BWP/305/99 – 24 March 1999
9. Plasma –derived Medicinal Products: Position Paper on ALT Testing – CPMP/BWP/385/99 – 29 July 1999
10. Position Statement on Polysorbate 80 – CPMP/BWP/1952/98 – 22 October 1998
11. Note for Guidance on Plasma-derived Medicinal Products – CPMP/BWP/269/95 rev. 2 – 23 July 1998
12. The Introduction of Nucleic Acid Amplification Technology (NAT) for the Detection of Hepatitis C Virus RNA in Plasma Pools (CPMP/BWP/269/97), Addendum to Note for Guidance on Plasma-derived Medicinal Products (CPMP/BWP/269/95) – CPMP/BWP/390/97 – 24 March 1998
13. Note for Guidance on Plasma-derived Medicinal Products – CPMP/BWP/269/95 rev. 2[1] - 27 June 1997

[1] Revision 2 concerns, points 2.3.1, 2.3.2, 2.3.3 and 2.3.4 of chapter 2 on Collection and Control of Source Materials. Change introduced also in chapter 3, expanding on manufacture and use of intermediate plasma fractions, genomic amplification testing and in-process controls.
[2] This revision concerns the parts on viral validation (section 3, point 3.3, section 5, and annexes I and II). This revision has been done in parallel with the revision of the CPMP guideline, "Virus Validation Studies (CPMP/BWP/268/95)"

APPENDIX I (CONTINUED)

14. Note for Guidance on Plasma-derived Medicinal Products - revised[2] - CPMP/BWP/269/95 – 13 March 1996
15. Implementation of CPMP/117/95 Recommendation "Intramuscular Immunoglobulins Nucleic Acid Amplification Tests for HCV RNA Detection" – CPMP/BWP/391/95 – 4 July 1995
16. (EC) Intramuscular immunoglobulins: nucleic acid amplification tests for HCV RNA detection – CPMP/117/95 – 6-7 April 1995
17. Validation of virus removal/inactivation procedures: choice of viruses – III/5543/94 – June 1994
18. Validation of virus removal/inactivation procedures: priority setting – III/5544/94 – June 1994
19. (EC) Background Document on Medicinal Products Derived from Human Blood or Plasma – 16 March 1994
20. Note for Guidance: Plasma pool testing – III/5193/94 – 1 November 1994
21. Blood Products and Non-enveloped Viruses – III/5830/93 – 1 December 1993
22. (EC) Press Release – Committee for Proprietary Medicinal Products, meeting 3-4 December 1992 – 4 December 1992
23. Position Statement with regard to HepCV screening of plasma used in the manufacture of medicinal products – 16-17 March 1992
24. Biotech Mode 24-25 February 1992
25. Guidelines for Medicinal Products Derived from Human Blood and Plasma – 89/381/EEC
26. CPMP Position Statement on West Nile Virus and Plasma-derived Medicinal Products – EMEA/CHMP/BWP/3752/03 – 25 July 2003
27. CPMP Position Statement on Non-remunerated and Remunerated Donors: Safety and Supply of Plasma-derived Medicinal Products – EMEA/CPMP/BWP/1818/02 – 30 May 2002
28. EMEA Workshop on Viral Safety of Plasma-derived Medicinal Products with Particular Focus on Non-enveloped Viruses – CPMP/BWP/BPWG/4080/00 – 28 March 2001
29. Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses – revised – CPMP/BWP/268/95 – 14 February 1996
30. Validation of Virus Removal and Inactivation Procedures
31. Guideline on the Investigation of Manufacturing Processes for Plasma-derived Medicinal Products with Regard to vCJD Risk – CPMP/BWP/CPMP/5136/03 – 21 October 2004
32. Discussion Paper on the Investigation of Manufacturing Processes for Plasma-derived Medicinal Products with Regard to vCJD Risk – CPMP/BWP/CPMP/5136/03 – 20 November 2003
33. Concept paper on the Need to Update the CHMP Position Statement on CJD and Plasma-derived and Urine-derived Medicinal Products (EMEA/CPMP/BWP/2879/02 rev. 1) – EMEA/CHMP/BWP/253246/2009 – 23 July 2009
34. Report on Expert Workshop on CJD Risk and Urine-derived Medicinal Products – EMEA/CHMP/BWP/472717/2009 – 23 July 2009
35. CHMP Position Statement on Creutzfeldt-Jakob Disease and Plasma-derived and Urine-derived Medicinal Products – EMEA/CPMP/BWP/2879/02 rev. 1 – 23 June 2004
36. CPMP Position Statement on Creutzfeldt-Jakob Disease and Plasma-derived and Urine-derived Medicinal Products – EMEA/CPMP/BWP/2579/02

APPENDIX I (CONTINUED)

37. EMEA Expert Meeting on Human TSEs and Medicinal Products derived from Human Blood and Plasma – EMEA/CPMP/BWP/450/01 – 28 March 2001

38. EMEA Workshop on Application to Pharmaceuticals of Assays for Markers of TSE Held on 19-20 January 1999 – EMEA/CPMP/BWP/257/99 – 24 February 1999

39. CPMP Position Statement on New Variant CJD and Plasma-derived Medicinal Products – CPMP/201/98 – 25 February 1998

40. Directive 91/356/EEC (GMP) – 13 June 1991

41. Annex to the EC guide to GMP: Manufacture of products derived from human blood or human plasma – III/3232/92-EN – 22 December 1992

42. Contribution to Part II of the structure of the dossier for applications for marketing authorisation – Control of starting materials for the production of blood derivatives – III/5272/94 – December 1994

43. Contribution to Part II of the structure of the dossier for applications for marketing authorisation – Viral safety studies – III/5512/93 – December 1994