INFECTED BLOOD INQUIRY

PRESENTATION BY COUNSEL TO THE INQUIRY

OVERVIEW CHRONOLOGY OF THE LICENSING OF COMMERCIAL BLOOD PRODUCTS IN THE UNITED KINGDOM DURING THE 1970s AND 1980s

APPENDIX 1: OVERVIEW OF COMMERCIAL BLOOD PRODUCTS

Table 1: Factor VIII Products

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Kryobulin	Immuno	Kryobulin was licensed between 22 Mar. 1973 and 14 Apr. 1992 The licensed product became available on the UK market from 2 Jul. 1973. It was included in the first central contract for Factor VIII concentrates, which commenced on 1 Nov. 1973. Amendments include: • 14 Oct. 1975: to allow RIA testing. • 28 Mar. 1978: to allow use of plasma from the USA in the manufacture of the concentrate. A red pack was used for European plasma, and a blue pack for American plasma. • 7 Feb. 1985: to allow dry heat treatment, 60°C for 10 hours (Kryobulin TIM 2). In Dec. 1984, the non-heat treated Kryobulin ceased to be available on the UK market.	Kryobulin was supplied to the UK in small quantities in 1970-1972 prior to a licence being issued, including for treatment on a named-patient basis. Several applications to vary the heat treatment method for Kryobulin were rejected from July 1986 onwards. From Dec. 1984 to Feb. 1985 dry-heat treated Kryobulin TIM 2 ("Kryobulin Heat-treated") was available in the UK on an unlicensed (named-patient) basis. This product was later licensed. From Oct. 1986 to at least Nov. 1989, and possibly later, "steam" (or vapour) heat treated Kryobulin was available in the UK on an unlicensed (named patient) basis. Several applications to vary the licence to allow for steam/vapour heat-treatment were refused. No such product was ever licensed for use in the UK.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Hemofil	Hyland	Hemofil received a product licence on 19 Feb. 1973 Hemofil was included in the first central contract for Factor VIII concentrates, which commenced on 1 Nov. 1973. Hemofil was a high purity concentrate. The licensing position between 19 Mar. 1983 and 30 Nov. 1984 is unclear. The product licence expired on the former date and was not renewed until the latter, but it is not clear what led to this situation and whether it affected the status of the product at that time. <u>Amendments include</u> • 13 Jun. 1975: to allow RIA testing. • 3 Nov. 1981: to allow manufacturing of Hemofil in the Hyland plant in Lessines, Belgium. • 27 Feb. 1985: to allow for dry heat treatment (60°C for 10 hours). The heat treated product was called Hemofil T. Hemofil M, which used a solvent-detergent method to reduce viral risk, received a clinical trial exemption in Jan. 1988. An application for a product licence was made initially in Jun. 1989 but was later resubmitted under a different regulatory regime. It was granted a licence in Jun. 1994.	Hemofil was being imported into the UK on a named patient basis in Jul. 1972, when the company was warned about the relevant statutory provisions. Between 1979 and Nov. 1982 an intermediate purity product Hemofil II (sometimes known as Interhem) was available on the UK market. The Inquiry has not identified documents relating to a product licence application for this product. 502,000 i.u. of Hemofil II/Interhem were used in the UK in 1980. The product was removed from the UK market for commercial reasons. Representatives of Travenol Laboratories Ltd met with DHSS officials in April 1983 to discuss, among other matters, a prospective product licence for the heat-treated product, Hemofil T. The application was made in May 1983 and was refused in Oct. 1983. Letters sent to doctors in May 1983 indicate that the product was made available in the UK on a named-patient basis. Hemofil T was later granted a licence on 27 Feb. 1985. Efforts appear to have been made to introduce Hemofil M onto the UK marked in or around Oct. 1987 on a named-patient basis. Small stocks of Hemofil M were available on a named-patient basis in May 1990. A product licence was granted in Jun. 1994.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Factorate	Armour	Factorate was licensed in the UK from 25 Mar. 1976 to 7 Oct. 1986. The original application for a product licence was considered in a submission to and meeting with the Minister of State for Health, Dr David Owen, in Jan. 1976. According to a later letter from Armour Pharmaceutical Company Ltd, Factorate was introduced into the UK market in Jun. 1976. High Potency Factorate was licensed for use in the UK between 13 Jun. 1979 and 7 Oct. 1986. It appears to have become *"commercially available"* at some point between Feb. 1980 and Nov. 1982. The product licences for both Factorate and High Potency Factorate were varied to allow for dry heat treatment (60°C for 30 hours) in Feb. 1985. Both heat treated products were withdrawn from the market on 7 Oct. 1986 following reports of HIV seroconversions associated with their use.	It is not clear whether non-heat treated Factorate was supplied on a named-patient basis before the product licences was issued. There is some evidence in later correspondence to suggest that it was not. High Potency Factorate was described as being *"recently introduced"* to the UK market in Jul, 1978, before an application had been made for a product licence. However, other evidence may suggest that it was not made *"commercially available"* until at least Feb. 1980. An application was made for a clinical trial exemption certificate for Heat Treated Factorate in Aug. 1983. The trial, which concerned NANB hepatitis infection, was unsuccessful and the certificate was surrendered in Nov. 1984. An application for a product licence for Heat Treated High Potency Factorate was not supported by the CSM(B) and CSM in Jul. 1984. The same product was licensed in Feb. 1985.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Profilate	Abbott / Alpha	Profilate was licenced in the UK from 22 May 1975. The licence was originally held by Abbott Laboratories Ltd. It was transferred to Alpha Therapeutic GmbH in Sep. 1979 and was renewed in May 1980. In Jan. 1985, Alpha Therapeutics UK Ltd applied for a product licence for Profilate HT (heated in a heptane solution at 60°C for 20 hours). This was granted on 19 Feb. 1985. Following an inspection of the facilities in Los Angeles where Profilate HT was manufactured in Oct. 1989, consideration was given to whether regulatory action should be taken on the UK product licence. The Minister of State agreed that the company should be informed of an intention to suspend the licence. The company then decided not to import further Profilate HT. By that time, an application had been made to vary the product licence for Profilate HT to allow for a solvent/detergent method of viral separation. This was granted in Mar. 1990 and the product was marketed as Profilate SD.	It is not clear whether non-heat treated Profilate was supplied on a named-patient basis before the product licences was issued. There was an unsuccessful application for a variation to the product licence to allow for the introduction of a polyethylene glycol step in production in Aug. 1982. Profilate HT appears to have been used by UK clinicians after it received an FDA licence in Feb. 1984 but before its UK licence was granted in Feb. 1985.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Koate	Cutter	Non-heat treated Koate was licensed in the UK from 27 Aug. 1976 to 15 Aug. 1988. The original application was made by Bayer UK Ltd, but this was withdrawn and the first licence was issued to Speywood Laboratories Ltd. Subsequently the product licence for non-heat treated Koate was held by Cutter Laboratories Ltd. Cutter appears to have ceased production of non-heat treated Koate in Oct. 1984. Dry heat treated Koate HT (68°C for 72 hours) received a product licence on 18 Feb. 1985. It appears that Koate HT ceased to be supplied to the UK market at some point between Nov. 1989 and May 1991.	The Inquiry has not identified evidence of non-heat treated Koate being supplied on a named-patient basis in the UK. A clinical trial exemption was granted for Koate HT in Sep. 1984. Koate HT was supplied to UK clinicians on a named-patient basis from the end of Nov. 1984 until the granting of a product licence in Feb. 1985.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Haemate P	Behringwerke	Haemate P was a heat treated product (heated in solution at 60°C for 10 hours). A product licence application was made on 26 Jul. 1983, the first such application for a heat treated product. The product licence was considered and supported by the CSM(B) and CSM in Mar. 1984, subject to certain conditions. Following correspondence on those matters the licence was granted on 6 Feb. 1985. The product was not formally introduced to the UK market until after 1990 for what were described as commercial reasons. Hoechst UK, who held the licence, negotiated with Armour about a distribution agreement in 1987, but the following year those negotiations broke down. The product licence was renewed in Apr. 1991 and it appears that the product was marketed in the UK in the 1990s.	The product was not formally marketed in the UK until the 1990s. However, there is evidence to suggest that it was being used in the UK by 1988 and that it was considered by Haemophilia Centre Directors as the second choice Factor VIII concentrate, after BPL's 8Y, for the treatment of patients who did not have significant prior exposure to blood products.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Humanate	Speywood	Humanate was a brand name used by Speywood Laboratories Ltd to sell relabelled Koate obtained from Cutter through an intermediary company. Speywood received a variation to their Koate product licence in Feb. 1980 to allow them to import and re-label Koate for sale in the UK. Concerns was soon raised by NIBSC about the lack of a direct chain of evidence and information from the manufacturer (Cutter) to the company holding the product licence (Speywood). In Jul. 1980, a letter was sent to Speywood informing them that action may be taken on the product licence. Speywood exercised their right to a hearing before the CSM on this matter, which took place on 22 Jan. 1981. The CSM advised that the product licence be varied to meet the concerns that had been expressed by NIBSC. Speywood do not appear to have imported any more Humanate after this hearing. The product was last sold in the UK in Jun. 1981.	The Inquiry is not aware of any evidence of the use of Humanate on an unlicensed or named-patient basis.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Mono VIII / Mono VIII:C	Speywood	Mono VIII was a Factor VIII product manufactured from human plasma using polyelectrolyte fractionation. A small batch was produced using BPL cryoprecipitate and was used clinically in 1980 to 1981. In 1982 an application was made for a clinical trial certificate to allow for a trial of Mono VIII that would be produced by Speywood Laboratories Ltd using imported cryoprecipitate supplied by Alpha Therapeutics Corp. The certificate was refused in Mar. 1983. It appears that the trial did not proceed.	Small amounts of Mono VIII obtained from the BPL cryoprecipitate were used in clinical practice, seemingly on a named-patient basis. The Inquiry is not aware of any other unlicensed use of Mono VIII.

Table 2: Factor IX and other products for inhibitor patients

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Prothromplex (Factor IX)[1]	Immuno	17 Aug. 1973 to 14 April 1992 Only non-heat treated Prothromplex was licensed in the UK. This product was available on the UK market until Dec. 1984.	Several applications to vary the licence to allow for heat-treatment were rejected from Mar. 1985 onwards. Unlicensed heat-treated Prothromplex was available from Dec. 1984 to at least Nov. 1989. The first heat-treated product was dry heat treated at 80°C for 10 hours. Other variants were heated in vapour and under pressure at 60°C, and later 80°C and 60°C.

[1] Prothromplex also contained other coagulation factors.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
FEIBA (Factor Eight Inhibitor Bypassing Agent)	Immuno	A licence was granted on 17 Oct. 1985 for dry heat-treated FEIBA (TIM4, 80°C for 10 hours). Dry heat treated FEIBA was supplied to the UK market under licence until 21 Jul. 1986. This ten month period is the only time before 1993 that FEIBA was supplied to the UK market under a contemporary licence. This licence was varied on 10 Jun. 1993 to allow for vapour heat-treatment (60°C for 10 hours under pressure + 80°C for 1 hour under pressure).	Doctors were informed of a new product called Fraction R (an early name for FEIBA) in August 1975 and there is evidence that it was being administered at the Manchester Royal Infirmary in 1976. By 1982, 14.5m i.u. of FEIBA had been used by the NHS. Usage at that time, and in 1985, was estimated at around 1m i.u. per annum. Non heat-treated FEIBA was never licensed for use in the UK. Dry heat-treated FEIBA was supplied on a named-patient basis before it was licensed in Oct. 1985, and was reported in Apr. 1985 to be selling in *"substantial quantities"*. Various applications to vary the licence to allow for vapour heat treatment were unsuccessful. Unlicensed vapour heat-treated FEIBA was available on a named-patient basis from Jul. 1986 (60°C for 10 hours under pressure + 80°C for 1 hour under pressure). This product received a licence in Jun. 1993.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Proplex	Hyland	Licensed between 15 Oct. 1976 and 15 Oct. 1992. The original application for the licence was made in May 1975. It was considered by the CSM(B) in November 1975 and further information was sought on pool sizes and the reasons for and rates of donor rejections. Further information was provided, but it is not clear whether this included the rates of donor rejections. The application was granted in Oct. 1976. UK Haemophilia Centre returns for 1978 recorded that only 12,000 i.u. of Proplex had been used that year. It is not possible to explore fully the variations and renewals of the product licence from the documents identified by the Inquiry. The product licence expired on 15 Oct. 1992. According to internal Baxter documents, by that time the Proplex had not been sold in the UK for many years, seemingly because the product was not heat-treated.	In Aug. 1974, prior to any application for a product licence, Travenol Laboratories Ltd. undertook to make efforts to obtain an emergency supply of Proplex for Dr Biggs (Oxford Haemophilia Centre). The company stated that the product did not have a licence and was in *"extremely short supply."* A six month import licence was obtained for Proplex in Mar. 1975. It appears from the documents identified by the Inquiry that the heat-treated variant of Proplex was never licensed in the UK.

Product	Manufacturer	Information about the licensed product	Information about unlicensed use
Konyne	Cutter	It appears that neither the unheated nor the heat treated variants of Konyne received product licences in the UK.	Konyne HT was supplied on a named patient basis from the end of Nov. 1984.
Profilnine	Alpha	It appears that neither the unheated nor the heat treated variants of Profilnine received product licences in the UK during the 1970s and 1980s.	There is evidence that heat treated Profilnine was used on a named patient basis during 1984 and 1985, at a time when no NHS heat treated Factor IX product was available.
Hyate C	Speywood	Hyate C was a porcine Factor VIII product used for the treatment of inhibitor patients. It was produced using plasma taken from pigs. A product licence for Hyate C was granted on 3 Dec. 1984. The product appears to have been used thereafter for treatment of a relatively small number of inhibitor patients in the UK. It was not licensed for use on non-inhibitor patients.	Hyate C was described by Speywood Laboratories Ltd as being ready for clinical use from 7 Dec. 1979. The first time it was used for a human patient appears to have been in Jul. 1980. A small number of inhibitor patients were treated with the product on a named-patient basis between Jul. 1980 and the granting of the licence on 3 Dec. 1984. There was discussion in the medial literature of the product's benefits and risks during this period.