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

This chronology seeks to capture the principal events concerned with the licensing of commercial factor blood products in the UK in the 1970s and 1980s. The intention is to provide a document that is readily understandable. It is not intended to be comprehensive. Further information is provided in the transcripts of the Presentations of Counsel to the Inquiry on pharmaceutical products between 23 September 2021 and 6 October 2021 and in the witness evidence.

The document is accompanied by an Appendix containing a brief description of the main commercial blood products that were used in the United Kingdom in the 1970s and 1980s.

The third column of the table below is intended to help the reader identify which product is being discussed in each entry. Reference is made to the company most associated with the manufacture of the product. It is recognised that the corporate identities of the companies producing blood products changed over time and that there is an important distinction to be drawn between the company that produced the product (usually based in the USA or in Europe) and the company that imported, marketed and licensed the product in the United Kingdom (usually based in the United Kingdom). Further details are contained in the Presentations of Counsel to the Inquiry and in the witness evidence.

Glossary

DHSS	Department of Health and Social Security
MCA	Medicines Control Agency
CSM	Committee on the Safety of Medicines
CSM(B)	Committee on the Safety of Medicines Sub-Committee on Biologics
NIBSC	National Institute for Biological Standards and Control
FDA	US Food and Drug Administration
i.u.	International Units

Date	Event	Firm / Product
1970 -1972	Immuno A.G. documents for annual sales record that small amounts of **Kryobulin** were sold to *"Crown Agents, London"*, named individuals in London, and to St Thomas' Hospital. The product was not licensed at that time. **SHPL0000071_185, p.1, p.4, p.6**[1]	Immuno (Kryobulin)
29 Jul. 1972	DHSS inspectors attended the premises of Travenol Laboratories Ltd after coming into possession of promotional literature relating to **Hemofil**. The inspectors ascertained that Hemofil had been imported and supplied to *"a number of doctors."* A subsequent letter, dated 12 Oct. 1972, warned the company of the relevant statutory provisions concerning the importation of unlicensed medical products. The letter noted that the company was preparing an application for a product licence for Hemofil. **SHPL0000276_181**	Hyland[2] (Hemofil)
24 Oct. 1972	An inspection was conducted of Hyland Laboratories in California by Dr Duncan Thomas of the CSM(B) Secretariat. He also inspected a blood bank in Los Angeles owned by Hyland. A summary report noted the hepatitis hazard associated with the products that were being manufactured as a result of the donors (who *"do not inspire confidence"*) and the *"very large plasma pools"*. It was noted that *"the firm make no attempt to disguise this potential hazard"*. The fractionation process was said to be carried out *"under excellent conditions in a modern, well-equipped plant."* **DHSC0105593_006, p.15; DHSC0003742_080**	Hyland (Hemofil)
3 Nov. 1972	Travenol Laboratories Ltd. applied for a product licence for **Hemofil**. The application stated that the product was manufactured in Hyland Laboratories' plant in California. **DHSC0003741_104; SHPL0000275_029; SHPL0000275_004**	Hyland (Hemofil)
8 Dec. 1972	Serological Products Ltd. submitted a product licence application for **Kryobulin**. **MHRA0033325_002; MHRA0033323_009**	Immuno (Kryobulin)
20 Dec. 1972	Serological Products Ltd. submitted a product licence application for **Prothromplex**. **SHPL0000197_078; SHPL0000197_092**	Immuno (Prothromplex)

[1] All references to page numbers are to the electronic page numbers of the documents, unless otherwise stated.

[2] Hyland Laboratories was a division of Travenol Laboratories, which was owned in the 1970s and 1980s by Baxter International Inc. For the purpose of this table, reference is made to Hyland.

Date	Event	Firm / Product
22 Dec. 1972	Serological Products Ltd. submitted an application for a clinical trial certificate for **Prothromplex**. **SHPL0000665_019**	Immuno (Prothromplex)
22 Dec. 1972	Dr Duncan Thomas, of the CSM(B) Secretariat, stated in a letter to Serological Products Ltd. that there was no objection to the company supplying Dr (Rosemary) Biggs with **Kryobulin** for the treatment of a named haemophilia patient. **MHRA0033323_003**	Immuno (Kryobulin)
1972	At some stage during 1972 the manufacturing premises and one or more of the plasma collection centres operated by and on Bayer/Cutter were visited by or on behalf of the DHSS. **DHSC0003742_080**	Cutter (Koate)
10 Jan. 1973	CSM(B) considered the product licence applications for **Kryobulin** and **Hemofil**. A licence was recommended in both cases, subject to certain conditions. Among the documents considered were reports prepared by Dr Duncan Thomas, which referred to the hepatitis risk of the products. In respect of Hemofil, Dr Thomas concluded: *"The major disadvantage of currently available commercial preparations, such as Hemofil, is that they are prepared from very large plasma pools, and carry the risk of transmitting hepatitis virus. Hyland screen all their donors for hepatitis-associated antigen, which reduces but does not eliminate this risk. However, no attempt is made to disguise the risk of hepatitis and it may be considered that the decision to use this material could be left to the individual clinician who can balance the potential hazard against the anticipated therapeutic benefit to patients."* **DHSC0105593_002; DHSC0105593_003; MHRA0033322_060 (Kryobulin); DHSC0105593_006 (Hemofil)**	Immuno (Kryobulin) Hyland (Hemofil)
Feb. 1973	The CSM recommended the **Kryobulin** application be granted, subject to certain conditions. **DHSC0003952_048, p.13**	Immuno (Kryobulin)
19 Feb. 1973	The product licence for **Hemofil** was granted. **DHSC0003741_104**; **SHPL0000276_159**	Hyland (Hemofil)
22 Mar. 1973	The product licence for **Kryobulin** was granted. **SHPL0000071_170**; **SHPL0000071_172**; **MHRA0033322_061**	Immuno (Kryobulin)

Date	Event	Firm / Product
May 1973	Austrian Inspectors conducted an inspection of Immuno facilities on behalf of the DHSS. **DHSC0003742_080**	Immuno (Kryobulin)
Jun. 1973	The DHSS undertook what was described as an *"informal visit to manufacturing premises and blood centres"* owned or managed by Immuno. **DHSC0003742_080**	Immuno (Kryobulin)
2 Jul. 1973	Serological Products Ltd wrote to the DHSS to inform them that **Kryobulin** was on the UK market as from that day. **MHRA0033322_014**	Immuno (Kryobulin)
14 Aug. 1973	The DHSS wrote to Serological Products Ltd. to inform them that the product licence application and the application for a clinical trial certificate for **Prothromplex** had been approved, subject to certain conditions. **SHPL0000197_078; SHPL0000665_019**	Immuno (Prothromplex)
17 Aug. 1973	Formal date on which the product licence for **Prothromplex** was granted. **SHPL0000197_004**	Immuno (Prothromplex)
1 Nov. 1973	Commencement date for a one-year central contract between the DHSS / Welsh Office and Serological Products Ltd / Travenol Laboratories Ltd for the supply of **Kryobulin** and **Hemofil** to haemophilia centres. It was proposed that 5m. i.u. of each product could be supplied under the contract. **DHSC0003741_025; DHSC0003741_024; DHSC0100005_044**	Immuno (Kryobulin) Hyland (Hemofil)
Aug. 1974	Dr Rosemary Biggs (Oxford Haemophilia Centre) made enquiries of Travenol Laboratories Ltd. to obtain **Proplex**, Hyland's unlicensed Factor IX concentrate, for emergency use. She was told that the product was in *"extremely short supply"* but that efforts would be made to provide some on a named-patient basis. **OXUH0000630**	Hyland (Proplex)
22 Aug. 1974	Abbott Laboratories Ltd made an application for a product licence for **Profilate**. The application referred to the hepatitis risk of the product. It provided a list of locations at which plasma was obtained, which were owned by a company that was in turn owned by Abbott. The application included copies of forms used in plasma collection centres, including *"the donor rejection list."* **DHSC0003742_080; MHRA0000091_005**	Abbott/Alpha (Profilate)

Date	Event	Firm / Product
Nov. 1974	Dr Duncan Thomas prepared a medical report on the application for a product licence for **Profilate** ahead of the CSM(B) meeting in Nov. 1974. This identified the hepatitis risk and noted that the manufacturer in California had not been inspected by the Licensing Authority. He recommended the granting of a licence. **MHRA0000091_005**	Abbott/Alpha (Profilate)
10 Dec. 1974	Dr Mary Duncan of the DHSS wrote to Abbott Laboratories Ltd to inform them that the CSM had advised that a product licence be granted for **Profilate**, subject to conditions concerning batch release and the use of international units. The company accepted those conditions by letter of 13 Dec. 1974. **MHRA0000091_012, pp.15-16**	Abbott/Alpha (Profilate)
9 Jan. 1975	Abbott Laboratories Ltd applied for a variation in its product licence application for **Profilate**. This included a change to the method of production and the addition of a number of further centres for plasma collection. These were all in the Unites States. One was owned by a company that was in turn owned by Abbott. The other eight were owned by American Blood Components; no further details were provided about that company. **MHRA0000091_012, pp.1-2**	Abbott/Alpha (Profilate)
11 Mar. 1975	A temporary (six month) licence was granted allowing the importation of **Proplex**. The application for the licence had been made by Travenol Laboratories Ltd. on 4 Mar. 1975. **MHRA0033317_093**	Hyland (Proplex)
25 Mar. 1975	Armour Pharmaceutical Company Ltd. applied for a product licence for **Factorate**. The application included details of plasma collection in the "Raw Material Specifications", which were dated Oct. 1973. **ARMO0000001; ARMO0000002**	Armour (Factorate)
May 1975	An inspection was conducted, seemingly by or on behalf of the DHSS, of Abbott's manufacturing premises and collection centres in the USA. **DHSC0003742_080**	Abbott/Alpha (Profilate)
15 May 1975	Following a telephone call from an official from the DHSS, Abbott Laboratories Ltd wrote to repeat their acceptance of the conditions on the **Profilate** product licence suggested by the CSM in Dec. 1974. The letter added that the company would *"appreciate your progressing this with all speed as we do feel that this matter has dragged on for too long."* **MHRA0000091_008**	Abbott/Alpha (Profilate)

Date	Event	Firm / Product
21 May 1975	Travenol Laboratories Ltd. applied for a product licence for **Proplex**. **MHRA0033317_095**	Hyland (Proplex)
22 May 1975	The product licence for **Profilate** was granted to Abbott Laboratories Ltd. **CBLA0000006_009; DHSC0003742_080**	Abbott/Alpha (Profilate)
13 Jun. 1975	An application to vary the product licence for **Hemofil** was approved, allowing for the use of radioimmunoassay (RIA) testing for hepatitis B antigen. **SHPL0000276_185; SHPL0000276_076, p.2**	Hyland (Hemofil)
12 Aug. 1975	Doctors were informed by letter of a new product for patients with Factor VIII inhibitors called Fraction R, an early name for **FEIBA** (Factor Eight Inhibitor Bypassing Activity). **CBLA0008057**	Immuno (FEIBA)
14 Oct. 1975	The product licence for **Kryobulin** was amended to allow for testing for hepatitis B antigen by RIA rather than electrophoresis. **MHRA0033321_097; MHRA0033321_099**	Immuno (Kryobulin)
16 Oct. 1975	Dr R.D. Andrews prepared a report on **Factorate** for the CSM(B). This noted the hepatitis risk associated with the product and certain pieces of further information that had been requested of the company. It commented that it was not clear who supplied the donated plasma. It recommended the application be granted subject to the approval of the quality control process. **DHSC0105603**	Armour (Factorate)
16 Oct. 1975	Bayer UK Ltd applied for a product licence for **Koate**. **DHSC0003742_080; BAYP0000001_098**	Cutter (Koate)
12 Nov. 1975	The CSM(B) considered the application for a product licence for **Factorate**. It recommended that the application be granted, subject to certain conditions. They included the provision of further information about the plasma pool size and the reasons for and rate of donor rejections. **DHSC0105604_002; DHSC0105604_005**	Armour (Factorate)
12 Nov. 1975	The CSM(B) considered the application for a product licence for **Proplex**. It recommended that a licence be granted, subject to certain conditions. These included the provision of further information about the plasma pool size and the reasons for and rate of rejections of donors and donations. **MHRA0033317_079; DHSC0105604_006; DHSC0105604_002**	Hyland (Proplex)

Date	Event	Firm / Product
25 Nov. 1975	US Assistant Secretary for Health, Theodore Cooper, wrote to the Chief Medical Officer, Sir Henry Yellowlees, setting out some of the licensing requirements imposed by the FDA on manufacturers of factor concentrates in the USA. The letter was prompted by the inquiries of Granada Television in relation to the World in Action documentaries broadcast in Dec. 1975. **DHSC0100001_036**	Hyland (Hemofil)
Nov. 1975	The CSM advised that a product licence be granted for **Factorate**, subject to certain conditions. These included the provision of further information about donors, in line with the CSM(B) recommendation. No action had been taken to grant the licence by the time of a Ministerial submission and meeting concerning the application in Jan. 1976. **DHSC0003742_076**	Armour (Factorate)
1 Dec. 1975	The World in Action documentary, *"Blood Money: Part 1"*, was broadcast, featuring an investigation into Hyland facilities. **MDIA0000113**	Hyland (Hemofil)
8 Dec. 1975	The World in Action documentary, *"Blood Money: Part 2"*, was broadcast. **MDIA0000114**	-
9 Dec. 1975	The World in Action documentaries were discussed at the DHSS Divisional Management Group. The criticisms of the **Travenol/Hyland** facilities were said to be *"in conformity with an inspection report carried out on behalf of the Division"* (possibly a reference to Dr Thomas' report of Oct. 1972). The Minister of State (Dr David Owen) had been briefed and had expressed concern. The ongoing **Factorate** application was noted. The Supply Division were stated to be *"anxious"* that Factorate be licensed as it was cheaper than **Hemofil**. It was suggested that information about collection centres and the rate of donor rejections would be more useful than inspections of facilities overseas. The same meeting approved a correction to the minutes of the previous meeting to include a reference to a shortage of funds inhibiting visits to manufacturers' premises abroad. **MHRA0004180**	Hyland (Hemofil) Armour (Factorate)
17 Dec. 1975	Dr R.D. Andrews of the DHSS prepared a report for the CSM on the application for a product licence for **Koate**. This was supportive of the granting of a licence, but	Cutter (Koate)

<table>
<tr><th>Date</th><th>Event</th><th>Firm / Product</th></tr>
<tr><td></td><td>noted that the CSM had sought information about donor rejections from other companies.
Dr Andrews commented that the product "suffers from being prepared from multi-centre donations which cannot be properly controlled by inspection." He wrote that plasma was supplied from 54 different firms under various ownership, including US State prisons.
Dr Andrews recorded that each donation was RIA tested for HBV antigen and there had been no reports attributing hepatitis to Koate since its introduction in the USA in Feb. 1974.
MHRA0009305, pp.3-9</td><td></td></tr>
<tr><td>24 Dec. 1975</td><td>A note made by Bayer UK Ltd representatives of a telephone conversation with Dr Andrews of the DHSS recorded the latter stating that "the Minister is personally vetting all submissions on Factor VIII because there is a lot of publicity and emotional feeling about it at the moment." The application for Koate was at that time being considered by the DHSS. It was also stated that the price of Koate would be "important and will probably affect the success of our application." The note also referred to the process of submitting a tender.
BAYP0000022_097</td><td>Cutter (Koate)</td></tr>
<tr><td>Jan. 1976</td><td>A submission was made to the Minister of State (Dr David Owen) concerning the Factorate product application.
Among other matters, the submission noted that a representative of NIBSC had recently visited the fractionation plant but it was argued that visiting the plasmapheresis centres would not be money well spent. Further discussion was contained about steps that could be taken in the UK licencing regime to influence the way in which Armour obtained plasma from donors in the USA and in centres outside of the USA.
The Minister was asked to decide if he agreed: that a product licence should be issued without further inspection; that Armour should be asked to agree to certain conditions; and that those conditions should also be applied to other companies.
DHSC0003742_078; DHSC0003742_079; DHSC0100001_036; DHSC0003742_080</td><td>Armour (Factorate)</td></tr>
<tr><td>Jan. 1976</td><td>An appendix to the submission to the Minister of State provided information about, among other matters, the DHSS' understanding of the sources of blood/plasma for the different commercial Factor VIII products.<table><tr><td>Abbott (Profilate)</td><td>"All in USA"</td></tr><tr><td>Cutter (Koate)</td><td>"Various agencies in USA and Mexico"</td></tr></table></td><td>Abbott/Alpha (Profilate)

Cutter (Koate)

Immuno</td></tr>
</table>

Date	Event	Firm / Product
	<table><tr><td>Immuno (Kryobulin)</td><td>*"Manufacturers own centres [in Austria and W. Germany]. Under contract from centres in USA."*</td></tr><tr><td>Hyland (Hemofil)</td><td>*"centres in USA and Travenol International Centres in South America"*</td></tr></table> **DHSC0003742_080**	(Kryobulin) Hyland (Hemofil)
21 Jan. 1976	A meeting was held to consider the submission put to the Minister of State (Dr David Owen) on the **Factorate** product licence application. The record of the meeting stated that Dr Owen agreed that negotiations with Armour could begin over the supply of Factorate to the NHS, but that the overall policy of the Government was to aim for self-sufficiency. **DHSC0003742_076**	Armour (Factorate)
22 Jan. 1976	The CSM considered the application for a product licence for **Koate**. The CSM(B) had previously considered the application, seemingly on 9 Jan. 1976. Both bodies recommended the licence be granted, subject to certain conditions. These included information about the pool size and *"ongoing information"* about the reasons for and rate of donor rejections on a centre by centre basis. **MHRA0009305; MHRA0009276; BAYP0000022_097**	Cutter (Koate)
27 Jan. 1976	The DHSS wrote to Armour requesting more information before the licence application for **Factorate** was determined. This included information about the pool size and the reasons for and rate of donor rejections on a centre by centre basis. The DHSS also sought confirmation that plasma would only be used from donor centres in the USA or in other specified countries. **ARMO0000004**	Armour (Factorate)
29 Jan. 1976	Travenol Laboratories Ltd provided further information in support of its application for a product licence for **Proplex**. This included information about the pool size (approximately 6,000 litres) and about the reasons for donor rejections, but not about rates of donor rejections. **MHRA0033317_077**	Hyland (Proplex)
2 Feb. 1976	Armour replied to the DHSS regarding the information requested in respect of the **Factorate** product licence application. The pool size was provided (approximately 1,540 donors for a 1,000 litre pool), and some information was provided about the reasons for donor rejections and donor rejection rates (*"The rejection rate at blood collection centres is below 1% for accepted*	Armour (Factorate)

Date	Event	Firm / Product
	donors"). The company stated that the plasma used would be from *"donor centres in the USA and from USA sources."* **ARMO0000005**	
2 Feb. 1976	Dr Andrews of the DHSS wrote to Bayer UK Ltd stating that the product licence for **Koate** would be granted, subject to certain conditions. These included information about the pool size and *"ongoing information"* about the reasons for and rate of donor rejections on a centre by centre basis. **BAYP0000001_110**	Cutter (Koate)
27 Feb. 1976	A representative of Bayer UK Ltd. wrote to Dr Andrews of the DHSS about the further information requested as part of the licensing process. She stated that each pool comprised 2,500 litres of plasma and was contributed to by *"at least 1,000 individual donors".* Three to five pools would be combined to form the final product. **MHRA0009298; BAYP0000001_112; BAYP0000020_008; BAYP0000020_014**	Cutter (Koate)
4 Mar. 1976	A further letter was sent from the representative of Bayer UK Ltd to Dr Andrews of the DHSS in respect of the **Koate** product licence application. This stated that Cutter did not *"collect information about the rejection of donors, but the collection of plasma is carried out according to the US Code of Federal Regulations."* **BAYP0000001_113; BAYP0000020_048**	Cutter (Koate)
25 Mar. 1976	A product licence was issued for **Factorate**. The licence contained provisions in line with the DHSS letter of 27 Jan. 1976. **ARMO0000320**	Armour (Factorate)
Jun. 1976	According to a later letter from Armour Pharmaceutical Company Ltd, **Factorate** was introduced into the UK market in Jun. 1976. **BPLL0002161**	Armour (Factorate)
1 Jul. 1976	Cutter Laboratories and Speywood Laboratories Ltd entered into an agreement for Speywood to import and sell Koate on the UK market. **IPSN0000139_003**	Cutter (Koate) Speywood
29 Jul. 1976	The Secretary to the CSM sent a minute to the Licensing Authority. This advised that a product licence for **Koate** could now be granted, as amended by material received from or relating to the FDA and NIBSC in May and Jun. 1976. **MHRA0009276**	Cutter (Koate) Speywood

<table>
<tr><th>Date</th><th>Event</th><th>Firm / Product</th></tr>
<tr><td>16 Aug. 1976</td><td>A letter was sent from Mr T. Power of the DHSS to Bayer UK Ltd concerning the inclusion of extra provisions in the Koate product licence application. Those provisions concerned the batch release process.
MHRA0009279</td><td>Cutter (Koate)</td></tr>
<tr><td>18 Aug. 1976</td><td>Bayer UK Ltd. withdrew its application for a product licence for Koate as the importation and marketing of the product in the UK would be solely in the hands of Speywood Laboratories Ltd. Bayer UK Ltd stated that there was no objection to the Licensing Authority considering the data it had submitted when considering Speywood's application for a licence.
MHRA0009278; BAYP0000020_048; BAYP0000020_046</td><td>Cutter (Koate)</td></tr>
<tr><td>27 Aug. 1976</td><td>The product licence for Koate was granted to Speywood Laboratories Ltd. The document recording the grant of the licence is dated 1 Mar. 1977. The licence contained no condition requiring the provision of ongoing data about donor rejections.
IPSN0000312_036; BAYP0000020_048</td><td>Cutter (Koate)

Speywood</td></tr>
<tr><td>15 Oct. 1976</td><td>Proplex was granted a product licence. It is not clear what further information, if any, was provided in relation to the product between Jan. 1976 and the decision to grant the licence.
SHPL0000232_001, p.1</td><td>Hyland (Proplex)</td></tr>
<tr><td>1 Nov. 1976</td><td>Speywood Laboratories Ltd wrote to the DHSS to inform it that Koate had gone on sale in the UK as of 1 Nov. 1976.
IPSN0000312_038</td><td>Cutter (Koate)

Speywood</td></tr>
<tr><td>11 Nov. 1976</td><td>An application for the variation of the Kryobulin product licence was signed. This sought permission to use plasma from licensed plasmapheresis stations in the United States in the manufacture of Kryobulin. The existing licence specified that the plasma used came from plasmapheresis stations in Austria and Germany.
MHRA0033321_085; SHPL0001094[3]</td><td>Immuno (Kryobulin)</td></tr>
<tr><td>21 Dec. 1976</td><td>Internal DHSS correspondence recorded the following annual figures and value for factor concentrates
<table>
<tr><td>Armour (Factorate)</td><td>897,308 i.u. (8%)[4]</td><td>£71,785 (6%)</td></tr>
<tr><td>Travenol (Hemofil)</td><td>5,231,146 i.u. (49%)</td><td>£627,738 (51%)</td></tr>
<tr><td>Immuno</td><td>4,098,815 i.u.</td><td>£491,041</td></tr>
</table></td><td>Immuno (Kryobulin)

Hyland (Hemofil)</td></tr>
</table>

[3] Translation obtained by the Inquiry of the original document, SHPL0000071_083.
[4] Percentage figures are calculated by Counsel to the Inquiry and do not appear in the original table.

Date	Event	Firm / Product
	(Kryobulin) (39%) (40%) Abbott (Profilate) 383,624 i.u. (4%) £38,308 (3%) **Total 10,610,893 i.u. £1,228,872** **DHSC0003719_118**	Armour (Factorate) Abbott/Alpha (Profilate)
Jan. – Feb. 1977	The DHSS and Immuno Ltd corresponded about the application to vary the product licence for **Kryobulin** to allow for the use of plasma from the United States. It appears that the DHSS did not receive, or did not process, the Immuno Ltd response and as a result no action was taken on the application for around a year. **SHPL0000271_077; SHPL0000271_073; SHPL0000271_059; SHPL0000271_058**	Immuno (Kryobulin)
30 Mar. 1977	Date of an application for a product licence for **FEIBA** made by Immuno Ltd. By that time, the product had been administered to patients in the Manchester Royal Infirmary. **SHPL0000086_011; SHPL0000086_031**	Immuno (FEIBA)
9 Aug. 1977	The CSM indicated to Immuno Ltd its provisional conclusion that it was unable to recommend a product licence for **FEIBA** as the application was *"inadequate to judge the product on safety, quality and efficacy."* **SHPL0000085_114**	Immuno (FEIBA)
26 Aug. 1977	Travenol Laboratories Ltd. submitted an application to vary the product licence for **Hemofil** to add the facility at Lessines, Belgium as a manufacturer, and to correct information about the screening process for hepatitis B antigen. The application was subsequently withdrawn on 30 Jan. 1978. **SHPL0000276_106; SHPL0000276_081**	Hyland (Hemofil)
Sep. 1977	Immuno Ltd met representatives of the DHSS to discuss the **FEIBA** licence application. According to internal Immuno correspondence, *"A large hint was dropped"* that the company would be successful in an application for a Clinical Trial Certificate. Immuno Ltd suggested that if Immuno A.G. provided further information about the product it might be possible to have the product licence decision reconsidered. **SHPL0000085_111**	Immuno (FEIBA)
Oct. 1977	The sales figure for **Koate** for the first 12 months of its sale in the UK (Nov. 1976 to Oct. 1977) showed that 2.74m i.u. had been sold. **IPSN0000146**	Cutter (Koate) Speywood
19 Feb. 1978	The product licence for **Hemofil** was renewed. **SHPL0000283_005, p.17**	Hyland (Hemofil)

Date	Event	Firm / Product
22 Mar. 1978	The product licence for **Kryobulin** was renewed. The application for renewal was dated 23 Dec. 1977. The licence was issued on 27 Oct. 1978, with retrospective effect from 22 Mar. 1978 (the date at which the previous licence expired). **MHRA0033321_076; MHRA0033321_077; SHPL0000376_005, p.5**	Immuno (Kryobulin)
28 Mar. 1978	The product licence for **Kryobulin** was varied to allow for the use of plasma from the United States, in addition to plasma from Europe. Kryobulin produced from United States plasma was sold in a blue pack; a red pack was used for Kryobulin produced from European plasma. **SHPL0000376_005, p.3**; **SHPL0000271_057**; **DHSC0046258_098**	Immuno (Kryobulin)
1 Jul. 1978	Armour Pharmaceutical Company Ltd wrote to consultant haematologists to advertise **Factorate**, including referring to it as being the lowest priced product on *"the existing contract for Factor VIII concentrate by 23-42%."* The same letter stated that the same price structure applied for *"the recently introduced"* High Potency Factorate, which at that time was unlicensed. **BPLL0002161**	Armour (Factorate)
17 Aug. 1978	The product licence for **Prothromplex** was formally renewed. **SHPL0000377, p.19**	Immuno (Prothromplex)
20 Nov. 1978	Armour Pharmaceutical Company Ltd applied for a product licence for **High Potency Factorate**, which had been developed *"to meet the demands of increased unitage of the anti-haemophilic factor and to eliminate the need for manipulating multiple vials with attendant sterility problems."* **ARMO0000021**	Armour (Factorate)
Nov. 1978	**The Medicines (Exemption for Licences) (Importation) Order 1978** came into operation. Among other matters, this required those importing medical products for use on a named patient basis to inform the Licensing Authority within 21 days of the first receipt of the product, and to keep records about the imported products. The Order also prohibited advertising of products that were provided on a named-patient basis. They were only to be provided *"in response to a bona fide unsolicited [offer]"*. **Transcript, 23 Sep. 2021, p.17-18**[5]	-

[5] References to transcript page numbers are to the internal page numbers on the transcript.

Date	Event	Firm / Product
1978	The UK Haemophilia Centre returns for 1978 recorded that a total of 1.9m i.u. of **FEIBA**, 149,000 i.u. of **Proplex** and 12,000 i.u. of **Prothromplex** had been used to treat patients with Factor VIII inhibitors. **OXUH0000212_002**	Immuno (Prothromplex, FEIBA) Hyland (Proplex)
13 Jun. 1979	The product licence for **High Potency Factorate** was granted. **ARMO0000023**	Armour (Factorate)
10 Sep. 1979	The DHSS cancelled the product licence for **Profilate** held by Abbott Laboratories Ltd and granted and transferred it to Alpha Therapeutic GmbH. **MHRA0000091_006; MHRA0000091_007**	Abbott/Alpha (Profilate)
4 Dec. 1979	Correspondence between Speywood Laboratories Ltd and Cutter Laboratories referred to concerns that the potency of certain batches of Koate was lower than stated on the label. A stop order had been implemented by NIBSC over one batch, and a haemophilia centre was seeking replacement material in respect of another. **IPSN0000575**; **IPSN0000291**	Cutter (Koate) Speywood
7 Dec. 1979	Speywood Laboratories Ltd wrote to Prof. Arthur Bloom to inform him that the porcine Factor VIII product **Hyate C** was ready for clinical use following animal trials. It was first used in a human patient in or around Jul. 1980 and was used on a named patient basis in relatively small quantities before being granted a product licence in 1984. **IPSN0000334_004; IPSN0000324_011; IPSN0000331_001; IPSN0000005_023; IPSN0000156_101; IPSN0000005_024; BPLL0016008_034**	Speywood (Hyate C)
1979	An intermediate purity product, **Hemofil II**, was introduced into the UK market. The Inquiry has not identified documents relating to a product licence application for Hemofil II. **Hemofil** was a high purity product. **DHSC0002223_055**	Hyland (Hemofil)
24 Jan. 1980	Cutter Laboratories Ltd. applied for a product licence for **Koate**, replacing Speywood Laboratories Ltd as the company responsible for importing and marketing the product in the UK. The agreement between Cutter and Speywood had expired in 1979. **BAYP0000001_140; BAYP0000021_063; IPSN0000331_001; MHRA0036365_018**	Cutter (Koate) Speywood

Date	Event	Firm / Product
Feb. 1980	Speywood Laboratories Ltd obtained a variation to its product licence to allow it to: (i) sell its remaining stock of Koate for one year, and (ii) import unlabelled vials of Factor VIII concentrate manufactured by Cutter for relabelling and sale under the name **Humanate**. Later documents show that Humanate was re-labelled Koate. The last batch of Koate imported by Speywood was released by NIBSC in Feb. 1980. **MHRA0036365_018; IPSN0000139_022**	Cutter (Koate) Speywood (Humanate)
22 May 1980	The product licence for **Profilate**, held by Alpha Pharmaceutical GmbH, was renewed. **MHRA0000091_006**	Abbott/Alpha (Profilate)
10 Jun. 1980	A product licence was granted to Cutter Laboratories Ltd for **Koate**. **BAYP0000001_140; BAYP0000001_142**	Cutter (Koate)
3 Jul. 1980	Cutter Laboratories Ltd prepared an application for **Konyne**, a Factor IX concentrate. It is not clear if this application was submitted, but it appears in any event that no product licence was granted as a result either of this application or another in 1982. **BAYP0000004_285; BAYP0000008_071**	Cutter (Konyne)
29 Jul. 1980	Following concerns raised by NIBSC, the Licensing Authority wrote to Speywood Laboratories Ltd to inform them that the CSM might have reason to advise the Licensing Authority to vary the product licence for **Humanate**. This was due to the lack of a direct chain of evidence and information from the manufacturer of the product (Cutter) to the company who held the product licence (Speywood). The letter was sent in compliance with the Medicines Act 1968. **MHRA0036365_018**	Speywood (Humanate)
30 Jul. 1980	Speywood Laboratories Ltd wrote to the CSM giving notice that they intended to avail themselves of the opportunity to appear before the committee regarding the **Humanate** product licence. The company had a right to do so under the Medicines Act 1968.	Speywood (Humanate)
30 Jul. 1980	Speywood Laboratories Ltd. wrote to Dr Tony Aronstam of Treloars advertising its sale of **Humanate**. The product was described as being *"not an intermediate product [with] a specific activity of approximately one AHF unit per milligram of protein."* Dr Aronstam was not informed in this letter that Humanate was Koate under a different label. **IPSN0000331_001**	Speywood (Humanate)

Date	Event	Firm / Product
31 Oct. 1980	Speywood Laboratories Ltd wrote to Dr Evans at the Royal Manchester Children's Hospital in reply to a letter he had sent in Aug. 1980. Speywood stated, seemingly in response to a question posed by Dr Evans, that **Humanate** *"is manufactured for us by Cutter Laboratories"* and was identical to Koate. Dr Evans was asked to keep that information confidential. The letter did not explain that Speywood purchased the product through an intermediary company, Parlier Medical Support. **IPSN0000338_001; BAYP0000021_063**	Speywood (Humanate)
27 Nov. 1980	The Licensing Authority wrote to Speywood Laboratories Ltd stating it proposed to vary the product licence for **Humanate** to require (among other matters) the production of evidence about the source and date of collection of the donor blood, the date of manufacture and the results of tests done on completion of the product. This letter was sent in compliance with the Medicines Act 1968. The Licensing Authority noted that the information requested had been provided by Speywood prior to 8 Feb. 1980 (i.e. when importing Koate for sale as Koate) and was *"routinely supplied by other manufacturers."* It was stated that without such evidence *"there was no means of ensuring that the product had been manufactured under conditions which could be shown to minimise the risk to patients of contracting, for example, non-A non-B hepatitis."* **MHRA0036365_018**	Speywood (Humanate)
16 Dec. 1980	The board of Cutter Laboratories Ltd discussed the sale by Speywood Laboratories Ltd of **Humanate** (Koate marketed under a different name). It was noted that Dr Duncan Thomas of NIBSC *"was very concerned regarding Humanate and the impossibility of tracing its manufacture back to its source."* **BAYP0000021_063**	Speywood (Humanate)
22 Jan. 1981	A hearing took place before the CSM concerning the Licensing Authority's proposal to vary the product licence for **Humanate**. Following the hearing the CSM advised the Licensing Authority that it should vary the product licence in the way that had been proposed. The reason given for the advice was that *"because of the risk to patients from lack of evidence as to the origins and provenance of the donor blood, the Committee were not satisfied as to the safety of this product."* **MHRA0036365_001, p.3; MHRA0036365_018**	Speywood (Humanate)
20 Mar. 1981	NIBSC recommended that a batch of unlabelled Koate intended to be sold as **Humanate** should not be	Speywood (Humanate)

<table>
<tr><th>Date</th><th>Event</th><th>Firm / Product</th></tr>
<tr><td></td><td>released as part of the batch release process. This appears to be linked to the proposed variation of the Humanate product licence. The batch samples and accompanying protocol had been received in Jan. 1981.
MHRA0000049</td><td></td></tr>
<tr><td>25 Mar. 1981</td><td>The product licence for Factorate was renewed as of 25 Mar. 1981. The document granting this renewal is, however, dated 31 Jul. 1984. The Inquiry has not identified the reason for the distinction between the two dates. There had been a number of variations to the licence between 1976 and 1984.
ARMO0000320, p.2</td><td>Armour (Factorate)</td></tr>
<tr><td>1 May 1981</td><td>Travenol Laboratories Ltd. applied to vary the product licence for Hemofil to allow the addition of the Hyland manufacturing plant in Lessines, Belgium as a manufacturing location.
SHPL0000276_028</td><td>Hyland (Hemofil)</td></tr>
<tr><td>Jun. 1981</td><td>Speywood Laboratories Ltd. ceased to sell Humanate in the UK. It seems likely that the product being sold as of Jun. 1981 came from the last batch of unlabelled Koate imported into the UK by Speywood sometime in or around Oct. 1980. This had been released for sale by NIBSC on 23 Dec. 1980, before the final CSM advice to vary the product licence.
MHRA0000049</td><td>Speywood (Humanate)</td></tr>
<tr><td>4 Sep. 1981</td><td>Internal Immuno correspondence recorded that at that time the company “only had permission to use European plasma for Prothromplex.”
SHPL0000271_040</td><td>Immuno (Prothromplex)</td></tr>
<tr><td>25 Sep. 1981</td><td>Immuno Ltd. made an application for a product licence for FEIBA.
SHPL0000091_005, SHPL0000209</td><td>Immuno (FEIBA)</td></tr>
<tr><td>3 Nov. 1981</td><td>The application to vary the Hemofil product licence to add the Hyland plant at Lessines, Belgium as a manufacturing site was approved. This followed an inspection of the site by David Haythornthwaite of the Medicines Inspectorate in Sep. 1981.
SHPL0000276_025; SHPL0000276_026; SHPL0000276_027; SHPL0000276_028; SHPL0000276_037</td><td>Hyland (Hemofil)</td></tr>
<tr><td>1980 and 1981</td><td>A table containing the quantities of Factor VIII concentrates used in the UK by haemophilia patients in 1980 and 1981 recorded the following:
<table>
<tr><td>Product</td><td>1980 (i.u.)</td><td>1981 (i.u.)</td></tr>
</table></td><td>Immuno (Kryobulin)

Hyland</td></tr>
</table>

<table>
<tr><th>Date</th><th>Event</th><th>Firm / Product</th></tr>
<tr><td></td><td>
<table>
<tr><td>Abbott: Profilate</td><td>1,649,000 (5%)[6]</td><td>1,909,000 (5%)</td></tr>
<tr><td>Armour: Factorate</td><td>16,576,000 (48%)</td><td>14,646,000 (42%)</td></tr>
<tr><td>Cutter: Koate</td><td>4,935,000 (14%)</td><td>3,823,000 (11%)</td></tr>
<tr><td>Hyland: Hemofil</td><td>5,095,000 (15%)</td><td>5,554,000[7] (16%)</td></tr>
<tr><td>Immuno: Kryobulin[8]</td><td>5,377,000 (15%)</td><td>7,377,000 (21%)</td></tr>
<tr><td>Speywood: Humanate</td><td>615,000 (2%)</td><td>1,561,000 (4%)</td></tr>
<tr><td>Hyland: Interhem[9]</td><td>502,000 (1%)</td><td>-</td></tr>
<tr><td>Total</td><td>34,749,000</td><td>34,870,000</td></tr>
</table>
PRSE0003437
</td><td>(Hemofil)

Armour (Factorate)

Abbott/Alpha (Profilate)

Speywood (Humanate)</td></tr>
<tr><td>25 Feb. 1982</td><td>The CSM provisionally concluded that it was unable to advise the granting of a product licence for FEIBA on the grounds of quality and efficacy. The accompanying documentation indicated that nearly 1m. i.u. of FEIBA were used in the NHS in the last complete year for which records were available, and total usage over the previous six years was 14.5m i.u.
DHSC0105547_002, p.1 and p.10</td><td>Immuno (FEIBA)</td></tr>
<tr><td>19 Mar. 1982</td><td>Immuno Ltd. were informed of the CSM's provisional conclusion that it would not recommend a product licence for FEIBA.
SHPL0000093_018</td><td>Immuno (FEIBA)</td></tr>
<tr><td>30 Aug. 1982</td><td>Alpha Therapeutic GmbH applied for a variation to the product licence to allow for the introduction of a polyethylene glycol step in the production of Profilate.
MHRA0000091_004, p.2</td><td>Abbott/Alpha (Profilate)</td></tr>
<tr><td>By 20 Oct. 1982</td><td>Applications were made by Speywood Laboratories Ltd and Alpha Therapeutic (UK) Ltd for a clinical trial exemption for Mono VIII (or Mono C). This product was to be manufactured in the UK by Speywood using bulk cryoprecipitate imported from Alpha in the US.
DHSC0003949_102; DHSC0003949_106; IPSN0000398; IPSN0000232_001</td><td>Alpha

Speywood (Mono VIII)</td></tr>
</table>

[6] Percentage figures are calculated by Counsel to the Inquiry and do not appear in the original table.
[7] The 1981 figure includes the figure for Interhem. Counsel to the Inquiry understand this to be a reference to the intermediate purity Hemofil that Hyland had introduced into the UK market in 1979, also known as Hemofil II.
[8] No distinction is made in the table between Kryobulin red (European plasma) and Kryobulin blue (American plasma).
[9] Counsel to the Inquiry understand this to be a reference to the intermediate purity Hemofil that Hyland had introduced into the UK market in 1979, also known as Hemofil II.

Date	Event	Firm / Product
26 Oct. 1982	Immuno Ltd. provided further information in support of its application for a product licence for **FEIBA**. It stated that the product had recently been licensed for use in the USA (in addition to the other countries listed in the application). **SHPL0000104_037**	Immuno (FEIBA)
15 Nov. 1982	Armour Pharmaceuticals Company Ltd wrote to the DHSS requesting a licence variation to extend the shelf-life of **High Potency Factorate**. It appears from this and other correspondence that the product was made *"commercially available"* between Feb. 1980 and Nov. 1982. **ARMO0000116; ARMO0000047**	Armour (Factorate)
Nov. 1982	An intermediate purity product, **Hemofil II**, which had been introduced in 1979 was taken off the UK market for commercial reasons. The Inquiry has not identified any applications or approvals for a product licence for Hemofil II. **Hemofil** was a high purity product. **DHSC0002223_055; DHSC0002223_056; DHSC0002223_058**	Hyland (Hemofil)
16 Dec. 1982	Travenol Laboratories Ltd. sought to submit an application to renew the product licence for **Hemofil**. The DHSS subsequently requested that the renewal application be resubmitted under a different form. The company complied, but were later told that blood products were not covered by the relevant scheme. As a result, the original product licence expired on 19 Mar. 1983, and was not renewed until 30 Nov. 1984. **MHRA0009345; SHPL0000283_005, p.17**	Hyland (Hemofil)
9 Mar. 1983	The CSM(B) considered the application to vary the **Profilate** product licence to introduce a polyethylene glycol step in the manufacturing process. It was unable to recommend the licence be varied and considered that inadequate information had been presented in support. The pharmaceutical assessment considered by the CSM(B) was prepared by Mr Betts. Among his observations was that further information should be provided about the control exercised by Alpha in the US over the plasmapheresis centres listed in its application. The application was not considered further by the CSM. **MHRA0000091_004, p.1, p.23**	Abbott/Alpha (Profilate)
22 Mar. 1983	The product licence for **Kryobulin** was renewed. The application for renewal was dated 2 Mar. 1983. The licence was issued on 8 Sep. 1983, with retrospective effect from 22 Mar. 1983 (the date at which the previous licence expired).	Immuno (Kryobulin)

Date	Event	Firm / Product
	MHRA0033321_110; MHRA0033321_026; SHPL0000376_005, p.1-2, p.17	
24 Mar. 1983	The CSM refused the application of Alpha Therapeutic (UK) Ltd and Speywood Laboratories Ltd to import cryoprecipitate from the US to allow for the manufacture and clinical trial of **Mono VIII**. One of the CSM's provisional conclusions was that Alpha should only use cryoprecipitate from their own licensed plasmapheresis centres. It also recommended that donor lists should be made available and that further information should be provided about the control of material during transportation. Among the remarks on the final product was a comment that evidence should be provided concerning its long-term toxicity. **DHSC0003946_060; DHSC0003950_016**	Alpha Speywood (Mono VIII)
25 Apr. 1983	Representatives of Travenol Laboratories Ltd and the DHSS met and discussed, among other matters, studies relating to the dry heat treated product **Hemofil T** (60°C for 72 hours), and information that may be required for an application for a product licence. The DHSS representatives also noted that the named-patient exemption was likely to be *"'tightened up' to prevent continued abuse by large companies."* **SHPL0000233_058**	Hyland (Hemofil)
May 1983	Travenol Laboratories Ltd. submitted an application to vary the **Hemofil** product licence to incorporate a heat treatment step (60°C for 72 hours). The resulting product was **Hemofil-T**. **DHSC0105556_028**	Hyland (Hemofil)
9 May 1983	Travenol Laboratories Ltd. wrote to doctors concerning AIDS and the steps taken by Hyland in response to the suggestion that the disease was cause by a blood-transmitted virus. The company noted that it had introduced **Hemofil-T**. While Hyland did not claim that heat treatment *"eliminates"* the risk of AIDS, it believed that *"the administration of the heat treated product, designed to reduce active viral content, may increase patient and centre personnel safety."* **PRSE0004496**	Hyland (Hemofil)
1 Jun. 1983	Immuno Ltd. made further written representations in support of its product licence application for **FEIBA**. **SHPL0000093_009**	Immuno (FEIBA)
2 Jun. 1983	Representatives of Speywood Laboratories Ltd met representatives of the DHSS to discuss the refusal of the clinical trial licence for **Mono VIII** and possible	Speywood (Mono VIII)

<table>
<tr><th>Date</th><th>Event</th><th>Firm / Product</th></tr>
<tr><td></td><td>future steps that could be taken. It appears that no clinical trial eventuated.
IPSN0000165_009; IPSN0000021, p.12; Transcript, 1 Oct. 2021, p.176[10]</td><td></td></tr>
<tr><td>28 Jun. 1983</td><td>An internal DHSS table, based on questionnaires sent to pharmaceutical companies, recorded the following levels of annual UK sales.
<table>
<tr><td>Armour: Factorate</td><td>15m. to 20m. i.u. (36% to 41%)[11]</td></tr>
<tr><td>Armour: High Potency Factorate</td><td>1m. to 1.5m. i.u. (2% to 3%)</td></tr>
<tr><td>Alpha: Profilate</td><td>5m. i.u. (12% to 10%)</td></tr>
<tr><td>Hyland: Hemofil</td><td>8m. to 9m. i.u. (19%)</td></tr>
<tr><td>Immuno: Kryobulin Red[12]</td><td>0.9m. i.u. (2%)</td></tr>
<tr><td>Immuno: Kryobulin Blue[13]</td><td>4.1m. i.u. (10% to 8%)</td></tr>
<tr><td>Immuno: Prothromplex</td><td>0.8m. i.u.</td></tr>
<tr><td>Immuno: FEIBA</td><td>1.5m. i.u.</td></tr>
<tr><td>Cutter: Koate</td><td>8m. i.u. (19% to 16%)</td></tr>
</table>
The total of figure for sales of the Factor VIII concentrates taken from the information in this table was 42m. to 48.5m. i.u.[14] This compares to a figure of 10.6m. i.u. taken from the DHSS table contained in the document dated 21 Dec. 1976.
DHSC0002229_055</td><td>Immuno (Kryobulin, Prothromplex, FEIBA)

Hyland (Hemofil)

Armour (Factorate)

Abbott/Alpha (Profilate)

Cutter (Koate)</td></tr>
<tr><td>13 Jul. 1983</td><td>The CSM(B) discussed “the question of AIDS and licensed blood products”, assisted by Prof. Bloom, Dr Craske, Dr Galbraith, Dr Gunson and Dr Mortimer. Among the conclusions reached was that “withdrawing US preparations from the UK … is not at present feasible on grounds of supply. Moreover, the perceived level of risk does not at present justify serious consideration of such a solution.”
The CSM(B) expressed its support for securing self-sufficiency in UK blood products, which “should reduce</td><td>-</td></tr>
</table>

[10] References to transcript page numbers are to the internal page numbers on the transcript.
[11] The percentage figure is calculated by Counsel to the Inquiry and does not appear in the original table. The figure represents the percentage of the total amount of Factor VIII used in the UK (hence Prothromplex and FEIBA are excluded). The first figure is the percentage at the lower end of the estimated figures (i.e. the percentage of 42m. i.u. represented by the stated figure), and the second figure is the percentage at the higher end of the estimated (i.e. the percentage of 48.5m. i.u. represented by the stated figure). All percentage figures are rounded to the nearest 1%.
[12] Manufactured from European plasma.
[13] Manufactured from US plasma.
[14] Prothromplex and FEIBA are not included in this categorisation as they were not Factor VIII products. For the same reason they are not included in the calculations used to give percentage figures.

Date	Event	Firm / Product
	markedly, although not eliminate, the risks to recipients of these products." The meeting also commented on other matters, including the approach to be taken to considering licence applications for heat treated products when they were made. It concluded that it would be important to examine the clinical effectiveness of such products as well as the improved safety margin. The CSM(B) criticised *"unjustified claims"* that were being made about the safety of heat-treated Factor VIII and expressed concern about the use of unlicensed products on a named-patient basis. **ARCH0001710; DHSC0003824_085; DHSC0001209; DHSC0003824_086; DHSC0002229_059**	
21 to 22 Jul. 1983	The CSM discussed the conclusions of the CSM(B) at its meeting on 13 Jul. 1983 and endorsed its recommendations. **WITN5281030; DHSC0001208**; **DHSC0002353_051**	-
26 Jul. 1983	Hoechst UK Ltd applied for a product licence for what would later be called **Haemate P**. This was a Factor VIII concentrate manufactured by Behringwerke A.G. that was heat treated in solution at 60°C for 10 hours. The report prepared for the CSM(B) described this as the first application in the UK for a heat treated Factor VIII concentrate. It stated that *"The manufacturers claim this produces a product free from active hepatitis contamination."* **MHRA0000090, p.47, p.63; MHRA0033410_032**	Behringwerke (Haemate P)
12 Aug. 1983	Armour Pharmaceutical Company Ltd applied for a clinical trials exemption certificate for a study to assess the value of **Heat Treated Factorate** in reducing NANB hepatitis transmission. The application also referred to the *"upsurge in incidence"* of AIDS, and the possibility of viral infection through blood products, but noted the lack of knowledge of the aetiology of AIDS at that time. The trial did not achieve the desired objective in respect of NANB hepatitis and the certificate was surrendered in Nov. 1984 **ARMO0000121; ARMO0000164, p.5; CBLA0001861; HCDO0000561; ARMO0000125; ARMO0000137; ARMO0000314; ARMO0000143; ARMO0000144; ARMO0000148**	Armour (Factorate)
16 Aug. 1983	A product licence for **Koate** was granted to Miles Laboratories Ltd, trading as Cutter Laboratories (Division of Miles Laboratories Ltd). The application had been made on 14 Oct. 1982. **BAYP0000002_196**	Cutter (Koate)

Date	Event	Firm / Product
14 Sep. 1983	The CSM(B) advised against varying the **Hemofil** licence to allow for a dry heat-treatment stage (**Hemofil-T**), primarily on the basis of a lack of evidence justifying the use of heat-treatment. It *"strongly deprecated"* what it considered to be *"unjustified claims"* in *"promotional letters"* about improved safety margins for infection and AIDS. The CSM(B) commented that evidence of the long-term safety of patients using heat treated products was *"regarded as an important prerequisite of licensing."* **DHSC0003951_006; DHSC0105556_028; PRSE0004496**	Hyland (Hemofil)
5 Sep. 1983	Immuno Ltd. were informed that the CSM were still unable to recommend a product licence for **FEIBA** on the grounds of efficacy and quality. The matter had been considered by the CSM at its meeting on 21 Jul. 1983. **SHPL0000104_026**	Immuno (FEIBA)
27 Sep. 1983	Immuno Ltd informed Immuno A.G. that the CSM were unable to recommend a product licence be granted for **FEIBA**. It was stated that as the grounds for concern did not include safety *"we will not be prevented from continuing to sell on a doctor/named patient basis."* **SHPL0000085_037**	Immuno (FEIBA)
14 Oct. 1983	Travenol Laboratories Ltd were informed that the application to vary the **Hemofil** licence to allow for heat treatment (**Hemofil T**) had been refused. Among the reasons given were *"inadequate evidence of safety and efficacy"* and a lack of justification for heat treatment. **SHPL0000283_005, p.17**	Hyland (Hemofil)
28 Nov. 1983	Speywood Laboratories Ltd applied for a product licence for **Hyate C**, the porcine Factor VIII product. The application stated that the product was intended to be licensed for the use of inhibitor patients. There is some evidence to suggest that officials within the DHSS were aware of and supported the decision to apply for a full product licence rather than a clinical trial certificate. **MHRA0033477_011; IPSN0000007_001; MHRA0033477_003 IPSN0000477; IPSN0000277; IPSN0000230**	Speywood (Hyate C)
22 Feb. 1984	Armour Pharmaceutical Company Ltd submitted a product licence application for **Heat Treated High Potency Factorate** (dry heat, 60°C for 10 hours). It was proposed that the data sheet include a statement that *"experimental studies have shown that heat-*	Armour (Factorate)

Date	Event	Firm / Product
	treatment …. may remove or reduce the risk of transmission of non-A non-B hepatitis." **MHRA0000088, p.66**	
7 Mar. 1984	The CSM(B) considered the product licence application for the product that would later be named **Haemate P**. The sub-committee advised the grant of a licence subject to a number of conditions. These included the provision of further technical information and data, and amendments to the data sheet. It was specified that no claims should be made that the transmission of HBV and NANB hepatitis had been excluded, and that there be *"no reference to AIDS being included [on the data sheet] except as a warning that blood products may transmit the syndrome."* The sub-committee also made the remark that further studies on the effectiveness of the inactivation process should be undertaken. **MHRA0000090, pp.58-59**	Behringwerke (Haemate P)
7 Mar. 1984	Among the documents considered by the CSM(B) regarding **Haemate P** was a report that had been prepared by pharmaceutical and medical assessors. Dr Keith Fowler, in his medical comment, supported the grant of a product licence subject to the conditions that the CSM(B) later approved. In his view, the product was of satisfactory solubility, efficacy and safety. He thought it probable that HBV would be less likely due to heat treatment, but it could not be excluded. There was no evidence to suggest that heat treatment would affect the transmission of NANB hepatitis. He criticised the application for including *"irresponsible innuendo"* on AIDS, a reference to a section of the application on *"the possible risk of AIDS"* that concluded that the product *"would provide additional safety."* Dr Fowler noted that *"as the cause of AIDS is not known, any claims [that heat treatment protected against AIDS] appear irresponsible at present."* **MHRA0000090, p.85, p.88, p.89, pp.60-99**	Behringwerke (Haemate P)
22/23 Mar. 1984	The CSM considered the product licence application for the product that would later be named **Haemate P**. The committee advised the grant of a licence subject to the same conditions and remark as had been recommended by the CSM(B) on 7 Mar. 1984. **MHRA0000090, pp.56-57**	Behringwerke (Haemate P)
22/23 Mar. 1984	The CSM considered the product licence application for **Hyate C**, the porcine Factor VIII product. The Committee advised in favour of granting the licence, subject to certain conditions. These included the suggestion that the company should be encouraged to	Speywood (Hyate C)

Date	Event	Firm / Product
	put in place post-marketing surveillance studies to monitor the long-term effects of the product. **MHRA0033475_018**	
May to Jun. 1984	Dr Mark Winter of the Kent Haemophilia Centre told the Inquiry that after Alpha obtained an FDA licence for **Profilate HT** (in Feb. 1984) he and others approached the company to obtain the product on a named patient basis. All of his patients were transferred to heat treated product in May and Jun. 1984. He thought other centres took similar steps. Profilate HT was heated in a heptane solution at 60°C for 20 hours. **INQY1000059, pp.136-140**	Abbott/Alpha (Profilate)
6 Jun. 1984	**The Medicines (Exemption from Licences) (Importation) Order 1984** came into operation. This required information to be provided to the Licensing Authority before a product was imported for use on a named-patient basis and provided a mechanism whereby the Licensing Authority could, under certain conditions, prevent a company from making use of the named-patient exemption. The Order also limited the amount of product that could be imported for each named patient. Other provisions, such as the requirement to keep records and the prohibition on advertising, were retained. The Order replaced and revoked the previous statutory instrument governing the importation of products to be used on a named-patient basis, the Medicines (Exemption for Licences) (Importation) Order 1978, which had taken effect in Nov. 1978. **PRSE0000177; Transcript, 23 Sep. 2021, pp.17-26**[15]	-
13 Jun. 1984	The product licence for (non-heat treated) High Potency Factorate was renewed. **ARMO0000153**	Armour (Factorate)
4 Jul. 1984	The CSM(B) considered the application for a product licence for **Heat Treated High Potency Factorate**. It was unable to recommend the grant of a licence on grounds of safety, quality and efficacy. It considered that there was inadequate evidence in support of the application, including in respect of the effect of heat-treatment on infectivity, and no clinical evidence relating to any changes brought about by heat treatment in relation to the transmission of hepatitis. **MHRA0000088, p.65-112**	Armour (Factorate)

[15] References to transcript page numbers are to the internal page numbers on the transcript.

Date	Event	Firm / Product
27 Jul. 1984	The CSM considered the application for a product licence for **Heat Treated High Potency Factorate**. It was unable to recommend the grant of a licence on grounds of safety, quality and efficacy in essence for the reasons given by the CSM(B). **MHRA0000088, p.64**	Armour (Factorate)
15 Sep. 1984	A meeting of the UK Haemophilia Centre Directors Hepatitis Working Party discussed trials of heat treated Factor VIII. The **Hemofil HT** trial showed a 63% incidence of *"elevated transicence"* in previously untreated patients (possibly a dictation error for *"elevated transaminase"*). The Armour **Heat Treated Factorate** trial had been suspended by the company after the occurrence of two cases of symptomatic NANB hepatitis. The meeting concluded that the results so far suggested that dry heat treatment had *"little effect (if any) on the incidence of Non-A non-B hepatitis in first time treated patients."* **HCDO0000561**	Hyland (Hemofil) Armour (Factorate)
Sep. 1984	Travenol Laboratories Ltd. made a second application to vary the licence for **Hemofil** to allow for dry heat-treatment (**Hemofil-T**). In Nov. 1984, the DHSS requested that an abridged application in place of a licence variation. **SHPL0000283_005, p.1, p.18**	Hyland (Hemofil)
3 Sep. 1984	Cutter received approval from the DHSS for a clinical trial of **Koate HT** (dry heat, 68°C for 72 hours), which was permitted to commence on 12 Sep. 1984. **BAYP0000025_019**	Cutter (Koate)
26 Oct. 1984	In a letter sent to US haemophilia clinicians, Cutter Biological (US) stated that it was immediately converting all manufacture of **Koate** to **Koate HT**. **CGRA0000447**	Cutter (Koate)
29 Oct. 1984	Immuno Ltd. informed the Medicines Commission that it wished to make representations at a hearing about the FEIBA product licence application. The company also provided written data in support of its position. **SHPL0000104_017**	Immuno (FEIBA)
26 Nov. 1984	Dr Mary Duncan of the DHSS wrote to Robert Nicholson of Immuno Ltd. confirming that the UK Licensing Authority wished to encourage all companies involved in the production of Factor VIII concentrates to use a dry heat treatment process in the course of manufacture. The companies were encouraged to make early, abridged applications for new product licences.	Immuno (Kryobulin) Hyland (Hemofil) Armour (Factorate) Abbott/Alpha (Profilate)

Date	Event	Firm / Product
	A letter in similar terms was written to Armour Pharmaceuticals Company Ltd, and presumably to other companies as well. **SHPL0000067_028; ARMO0000156**	Miles (Koate)
28 Nov. 1984	An internal DHSS minute written by Dr Mary Duncan recorded that an abridged application had been received from Miles Laboratories for a product licence for **Koate HT**. Dr Duncan wrote that *"this will be handled as a matter of some urgency."* **DHSC0002251_015**	Cutter (Koate)
29 Nov. 1984	Internal Cutter documents show that **Koate HT** and **Konyne HT** were being sold on a named-patient basis in the UK from 29 Nov. 1984. One document reported on press coverage of the deaths of two haemophilia patients with AIDS and stated that: *"For one year the [DHSS] has blocked every application for registration of heat-treated factor VIII and now in the space of one week they are in a panic responding to the newspaper demands for action…"*[16] **BAYP0000025_087; BAYP0000025_081; BAYP0000025_093; BAYP0000024_047; CGRA0000554; CGRA0000559**	Cutter (Koate; Konyne)
30 Nov. 1984	Travenol Laboratories Ltd. prepared an abridged application to vary the **Hemofil** product licence to allow for dry heat treatment (**Hemofil-T**). This replaced an application made in Sep. 1984 to vary the licence. The change of application was made at the request of the DHSS. **SHPL0000283_005, p.1-2**	Hyland (Hemofil)
Nov. 1984	Immuno Ltd. and Immuno A.G. prepared an unsuccessful application to vary the product licence for **Prothromplex** to allow for a dry heating process (80°C for 10 hours, TIM 4). It is not clear when this application was made, but it had been rejected by 5 Mar. 1985. **SHPL0000168_020; SHPL0000168_022; SHPL0000068_070**	Immuno (Prothromplex)
3 Dec. 1984	The product licence for **Hyate C**, the porcine Factor VIII product, was granted. **IPSN0000477; MHRA0033477_011**	Speywood (Hyate C)
17 Dec. 1984	The DHSS received an application (dated 12 Dec. 1984) to alter the Kryobulin product licence to allow for a heat treating step. The proposed method was	Immuno (Kryobulin)

[16] If the statement was intended to refer to all applications by all companies then it is incorrect. The CSM(B) and CSM had recommended the granting of a product licence for heat treated Behringwerke's Haemate P in Mar. 1984, subject to certain conditions, although the licence itself had not been granted as of Nov. 1984.

Date	Event	Firm / Product
	Kryobulin TIM 2, a dry heat treatment at 60°C for 10 hours. **MHRA0033320_066; SHPL0000271_022**	
19 Dec. 1984	Representatives of Armour Pharmaceuticals Company Ltd met with Dr Mary Duncan of the DHSS to discuss product licence applications for heat treated **Factorate** and **High Potency Factorate**. **ARMO0000156**	Armour (Factorate)
Dec. 1984	Internal Immuno correspondence recorded that the non-heat treated **Kryobulin** and **Prothromplex** ceased to be available on the UK market from Dec. 1984, and that dry heat treated **Kryobulin TIM 2** and **Prothromplex TIM 4** were supplied on a named patient (unlicensed) basis. **SHPL0000066_001, p.80**	Immuno (Kryobulin; Prothromplex)
3 Jan. 1985	Alpha Therapeutic UK Ltd applied for a product licence for **Profilate HT** (heated in heptane solution at 60°C for 20 hours). **MHRA0033388_033; MHRA0033388_029**	Abbott/Alpha (Profilate)
4 Jan. 1985	Armour Pharmaceutical Company Ltd applied to vary the product licences for **Factorate** and **High Potency Factorate** to allow for a heat treatment step (60°C for 30 hours). **ARMO0000156; ARMO0000157; ARMO0000164**	Armour (Factorate)
8 Jan. 1985	Dr Duncan Thomas (NIBSC) wrote to Dr Mary Duncan (DHSS) regarding the product licence applications made in respect of heat treated variants of **Hemofil, Koate** and **Kryobulin**. Dr Thomas noted the discrepancies between the approaches taken to heat treatment and to testing the efficacy of viral reduction. He also noted that the Licensing Authority (i.e. the Medicines Division of the DHSS, acting on behalf of the Secretary of State) had decided to deal with the matter *"in house"* rather than referring it to the CSM for advice. Dr Thomas stated that *"On the basis of the data provided, I am more impressed with that supplied by Miles Laboratories (Koate, Cutter)."* **MHRA0019502**	Immuno (Kryobulin) Hyland (Hemofil) Cutter (Koate)
17 Jan. 1985	Dr Duncan Thomas wrote to Dr Mary Duncan having been invited to comment on the product licence application for **Profilate HT**. He thought the company had made *"a serious attempt to reduce the infectivity of their product"* and a *"reasonable case for their modified product"*. In his view, *"the main worry about these heat treated products is whether evidence will emerge from long-term studies of the formation of neo-antigens and,*	Abbott/Alpha (Profilate)

Date	Event	Firm / Product
	particularly, antibodies to Factor VIII." He noted that the problem did not seem to have developed over 18 months of use in other countries, and concluded: *"I suppose it is reasonable to swap an uncertain hazard of antibody development some time in the future for a very definite hazard from unheated Factor VIII in the present."* **MHRA0033388_026**	
18 Jan. 1985	Dr Mary Duncan of the DHSS wrote to Alpha Therapeutic UK Ltd to inform them that the Licensing Authority would require the data sheet for **Profilate HT** to state that the product was heated at 60°C for 20 hours *"in order to reduce the risk of transmission of infectious agents."* **MHRA0033388_018; MHRA0033389_049, p.3**	Abbott/Alpha (Profilate)
6 Feb. 1985	A product licence was granted for **Haemate P**. The warnings section of the licence included the statement that *"no procedure has been shown to be totally effective in removing hepatitis infectivity from Antihemophilic Factor (Human)."* No reference was made to AIDS or HTLVIII. The application had been amended by letters dated 6 Jul. 1984, 28 Nov. 1984, 4 Jan. 1985 and 15 Jan. 1985, indicating that the company had responded to issues raised by the CSM prior to the award of the licence. This was the first product licence granted for a heat treated Factor VIII product. **MHRA0000090, pp.47-55; MHRA0033415_035; MHRA0033312_039; MHRA0033415_039**	Behringwerke (Haemate P)
7 Feb. 1985	The product licence for **Kryobulin TIM 2** (dry heat, 60°C for 10 hours) was approved. **SHPL0000271_011**	Immuno (Kryobulin)
18 Feb. 1985	A product licence was granted to Miles Laboratories Ltd for **Koate HT**. Prior to the granting of the licence the company had agreed to include in the data sheet a statement that the product had been heated at 68°C for 72 hours *"to reduce the risk of infectivity"*. **BAYP0000003_309**; **BAYP0000024_034**; **BAYP0000003_301**	Cutter (Koate)
19 Feb. 1985	A product licence was granted for **Profilate HT**. **MHRA0033388_014; MHRA0033388_015**	Abbott/Alpha (Profilate)
21 Feb. 1985	An internal record from the MHRA archive recorded a conversation between Dr Thomas and the author of the note about the batch release process for **Haemate P**. Included in the note was the comment, *"Hoechst will*	Behringwerke (Haemate P)

Date	Event	Firm / Product
	probably never market in the UK." No information is given for the source of this information. **MHRA0000090, p.46**	
27 Feb. 1985	A product licence was granted to **Hemofil T** (dry heat, 60°C for 72 hours). The application had specified that the product could be manufactured at the Hyland Division plant in Los Angeles or the Travenol Laboratories S.A. plant in Lessines, Belgium. **CBLA0000006_023; SHPL0000283_005, p.6**	Hyland (Hemofil)
27 Feb. 1985	The DHSS wrote to Armour Pharmaceutical Company Ltd indicating that a product licence would be issued for **Heat Treated Factorate** and **Heat Treated High Potency Factorate** subject to the name being changed to indicate that the products were heat treated. **ARMO0000167**	Armour (Factorate)
5 Mar. 1985	Correspondence between Immuno Ltd and Immuno A.G. indicated that the former had been informed that the information provided with its application for a variation of the **Kryobulin TIM 2** product licence was *"most inadequate"* and that it would have been refused *"but for the panic situation which existed to get everyone on heat-treated material as quickly as possible."* The same correspondence recorded that the application to vary the **Prothromplex** licence to allow for dry heat treatment (80°C for 10 hours, TIM 4) had been unsuccessful. Reference was made to the same reason being given as in respect of Kryobulin, namely inadequate supporting information, with *"added clinical proof being required that heat treating this product does not cause thrombogenicity."* **SHPL0000048_026**	Immuno (Kryobulin; Prothromplex)
11 Mar. 1985	Immuno Ltd. wrote to doctors to inform them that it could supply **Kryobulin Heat Treated** (a reference to the TIM 2 method of heat treatment). It appears that this product was available until Dec. 1986. The same letter recorded that the licensed form of **Prothromplex**, which was not heat treated, was no longer available in the UK. However, the heat treated **Prothromplex TIM 4**, for which a product licence had been refused, could be supplied on a named-patient basis. **PRSE0002530; SHPL0000066_001, p.80**	Immuno (Kryobulin; Prothromplex)
11 Apr. 1985	Internal Immuno correspondence recorded that Immuno Ltd. was selling *"substantial quantities"* of heat treated **Prothromplex** and dry heat treated **FEIBA** (TIM4, 80°C	Immuno (Prothromplex, FEIBA)

Date	Event	Firm / Product
	for 10 hours), notwithstanding the absence of product licences. **SHPL0000048_024; SHPL0000048_025; SHPL0000068_074**	
8 May 1985	A product licence application was made for **Konyne HT**. **BAYP0000008_071**	Cutter (Konyne)
21 Jun. 1985	A Medicines Commission hearing on the **FEIBA** product licence application took place. It was noted that the product had been available on a named-patient basis for nine years and that current usage was around 1m i.u. per annum. The hearing considered data concerning the dry heat treated version of FEIBA (TIM 4). **SHPL0000078_010; SHPL0000078_011; SHPL0000104_010**	Immuno (FEIBA)
13 Sep. 1985	The product licence for non-heat treated **Prothromplex** was renewed. The renewal was given retrospective effect, to 17 Aug. 1983, the date at which the previous licence expired. **SHPL0000377, p.14**	Immuno (Prothromplex)
22 Aug. 1985	Immuno Ltd. were informed by the DHSS that the Medicines Commission would advise that a product licence be granted for heat treated **FEIBA** (TIM 4) subject to certain conditions (including that it be licensed for use only for haemophilia A patients with Factor VIII inhibitors).	Immuno (FEIBA)
17 Oct. 1985	A licence was granted for the dry heat treated **FEIBA (TIM 4)**. Internal Immuno documents show that on the same day the company was considering how and when to seek to amend licence to allow for “steam” heat treatment. **SHPL0000109_049; SHPL0000050_011; SHPL0000067_030**	Immuno (FEIBA)
26 Oct. 1985	The CSM provisionally advised against granting a product licence for **Konyne HT** on grounds of safety, quality and efficacy, citing a lack of adequate evidence and information. **BAYP0000004_326; BAYP0000008_071**	Cutter (Konyne HT)
Nov. 1985	Internal Immuno correspondence recorded that (unlicensed) **Prothromplex TIM 4** ceased to be available on the UK market. **SHPL0000066_001, p.80**	Immuno (Prothromplex)

Date	Event	Firm / Product
28 Nov. 1985	Representatives of Cutter and NIBSC met to discuss, among other matters, the unsuccessful product licence for **Konyne HT**. According to the Cutter note of the meeting, the company was told that *"they [seemingly the Licensing Authority] were tightening up on blood products and required more detailed information concerning screening of donors for HTLV-III … [they] wished to see results of viral inactivation studies which used a range of relevant marker viruses."* The point was also made that the heat-treatment step for **Koate HT** had never been approved by the CSM as the product was given *"fast-track approval"*. **BAYP0000007_161**	Cutter (Koate; Konyne)
Jan. 1986	Internal Immuno correspondence recorded that unlicensed **Prothromplex Steam 2** (which appears to have been heated at 60°C for 1 hour under pressure) became available on the UK market. **SHPL0000066_001, p.80; SHPL0000068_070**	Immuno (Prothromplex)
5 Mar. 1986	An application was made by Immuno Ltd. to vary the product licence for Kryobulin Heat Treated to alter the heat treatment process to "steam" treatment (60°C for 5-10 hours under pressure). This method was known as **Kryobulin TIM 3 (steam)**, or Neo TIM 3. **MHRA0033320_040**	Immuno (Kryobulin)
11 Jul. 1986	The CSM, on the advice of CSM(B), rejected the application to vary the product licence for **Kryobulin Heat Treated** to allow for a new heat treatment method – **Kryobulin TIM 3 (steam)** – on the grounds of quality and safety. The Committee also found that, *"The term 'steam treatment' is a misnomer and is unacceptable."* **MHRA0033320_044; SHPL0000271_008**	Immuno (Kryobulin)
17 Jul. 1986	A letter from the DHSS to Immuno Ltd. indicated that an application had by that time been made to vary the **FEIBA** product licence to allow for "steam" heat-treatment. The DHSS set out the concerns that would have to be satisfied before the variation could be approved. **SHPL0000102_142**	Immuno (FEIBA)
21 Jul. 1986	Immuno Ltd. wrote to doctors in the UK to inform them that, as of that date, they would only supply (unlicensed) "steam" heat treated **FEIBA** (60°C for 10 hours under pressure + 80°C for 1 hour under pressure). The letter explained that Immuno A.G. were no longer able to produce the (licensed) dry heat treated product for the UK market as all other countries had switched to the "steam" heat treated product. It was	Immuno (FEIBA)

Date	Event	Firm / Product
	noted that an application had been made to vary the product licence. **SBTS0000330_115**	
Sep. 1986	Internal Immuno correspondence recorded that (unlicensed) **Prothromplex Steam 2** ceased to be available on the UK market. **SHPL0000066_001, p.80**	Immuno (Prothromplex)
7 Oct. 1986	**Heat Treated Factorate** and **Heat Treated High Potency Factorate** were withdrawn from the UK market and the product licences were relinquished. This followed the notification by a UK physician of two cases of HIV antibody sero-conversion associated with the use of the product.[17] **ARMO0000602**	Armour (Factorate)
Oct. 1986	Internal Immuno correspondence suggested that the "steam" heat–treated **Kryobulin TIM 3 (steam)** was made available on the UK market on a named-patient (unlicensed) basis. The product was apparently still available on the same basis in Nov. 1989, the date of the correspondence. **SHPL0000066_001, p.80**	Immuno (Kryobulin))
Dec. 1986	Internal Immuno correspondence suggested that the dry heat–treated **Kryobulin TIM 2** ceased to be available on the UK market from Dec. 1986. **SHPL0000066_001, p.80**	Immuno (Kryobulin)
23 Dec. 1986	Immuno Ltd. submitted an application to vary the product licence for **Kryobulin Heat Treated** to allow for a *"vapour heated"* process (60°C for 10 hours). The proposed name of the product was **Kryobulin Vapour Heated (Method 3)**. The product was stated to be different in its heat treatment and viral inactivation profiles from that which was the subject of the unsuccessful application in Mar. 1986. On the same day, the company also submitted applications to vary the product licences for Prothromplex and FEIBA. **MHRA0033319_017; MHRA0033320_006; MHRA0033320_033**	Immuno (Kryobulin; Prothromplex; FEIBA)
Jan. 1987	Internal Immuno correspondence recorded that unlicensed **Prothromplex TIM 4 steam** (which appears to have been heated at 80°C for 1 hour under pressure, and at 60°C for 10 hours under pressure) became available on the UK market.	Immuno (Prothromplex)

[17] See separate chronological presentation on the withdrawal of Heat Treated Factorate from the UK market.

Date	Event	Firm / Product
	SHPL0000066_001, p.80; SHPL0000068_070	
23 Feb. 1987	Hoechst UK Ltd wrote to Dr Duncan Thomas of NIBSC about **Haemate P**. It was noted that despite the grant of a product licence *"for commercial reasons the product has not yet been introduced on to the UK market."* The company was re-evaluating the situation and asked to provide samples of the product for batch testing. **MHRA0000090, p.43**	Behringwerke (Haemate P)
Jul. 1987	The CSM(B) considered the application relating to **Kryobulin Vapour Heated (Method 3)** and determined that it could not recommend variation of the licences on grounds relating to quality and safety. **MHRA0033319_044**	Immuno (Kryobulin)
12 Aug. 1987	A meeting took place between representatives of Immuno A.G., Immuno Ltd. and the Licensing Authority regarding applications to vary the product licences for **Kryobulin Heat Treated**, **Prothromplex** and **FEIBA** to allow for "steam" heat-treatment. **MHRA0033319_040; SHPL0000141_136**	Immuno (Kryobulin; Prothromplex, FEIBA)
8 Sep. 1987	Immuno Ltd. withdrew its applications to vary the product licences for **Prothromplex** and **FEIBA**. **SHPL0000106_220**	Immuno (Prothromplex; FEIBA)
16 Sep. 1987	The Licensing Authority formally rejected the application relating to **Kryobulin Vapour Heated (Method 3)**. **MHRA0033321_021**	Immuno (Kryobulin)
8 Oct. 1987	Hoechst UK Ltd wrote to the DHSS seeking a variation to the data sheet for **Haemate P**. The company stated that, *"It is planned to introduce this product to the UK market in the near future"*, with Armour to be nominated as the distributor. It was planned to change the name of the product to **Humate P** (the name used by Armour for the product in the US. **MHRA0033414_011**	Behringwerke (Haemate P)
20 Oct. 1987	An internal Travenol Laboratories Ltd memorandum suggested that efforts would be made to introduce **Hemofil M** (which used solvent-detergent viral separation) into the UK market following the anticipated granting of an FDA licence in Nov. 1987. It was noted that **Hemofil T** had not been accepted by the market place due to *"poor solubility and record on viral safety."* The author urged the submissions of a product licence application for Hemofil M *"without delay"* once data was compiled. **SHPL0000409_072**	Hyland (Hemofil)

Date	Event	Firm / Product
7 Dec. 1987	Travenol Laboratories Ltd. applied for a clinical trial exemption for **Hemofil M** (solvent-detergent treatment). **SHPL0000496_191**	Hyland (Hemofil)
29 Jan. 1988	The clinical trial exemption for **Hemofil M** was granted for a period of three years. The trial was to take place in conjunction with Dr Savidge at St Thomas' Hospital. **SHPL0000496_191**	Hyland (Hemofil)
3 Mar. 1988	Immuno Ltd. applied to renew the licence for **Kryobulin Heat Treated**, the dry heat treated product, even though this was no longer being sold in the UK. The purpose was to maintain the licence so that an application could be made to vary it to reflect the latest heat treatment method (vapour heated). **MHRA0033319_001; MHRA0033319_002; SHPL0000067_001**	Immuno (Kryobulin)
22 May 1988	The UK Haemophilia Reference Centre Directors issued guidance on Factor VIII and Factor IX products. **Haemate P**, **Koate HS** (heated in solution at 60°C for 10 hours), **Kyrobulin TIM3**, **Monoclate-P**, **Octa VI (Octapharma)** and **Hemofil M** were included in the list of *"products available or soon to be available"*. Other than Haemate P, those products were stated to be unlicensed and available on a named-patient basis. The Directors stated a preference for licensed products, or those with clinical trial certificates or exemptions, other those used on a named patient basis. For patients who had received little or no previous exposure, NHS 8Y was the preferred choice of treatment, followed by Haemate P and then **Profilate HT**. **NHBT0000037_014**	Abbott/Alpha (Profilate) Behringwerke (Haemate P) Armour (Monoclate P) Immuno (Kryobulin) Cutter (Koate) Hyland (Hemofil)
7 Jul. 1988	Internal Immuno correspondence suggested that at least one UK doctor was continuing to use "steam" or vapour treated **Kryobulin TIM 3** on an unlicensed, named-patient basis in or around July 1987. **SHPL0000141_097; NHBT0000037_014**	Immuno (Kryobulin)
8 Jul. 1988	The DHSS wrote to Armour Pharmaceutical Company Ltd. to communicate concerns about the product licence application for **Monoclate-P**, a product derived from monoclonal antibodies that was dry heated at 60°C for 36 hours. **ARMO0000212; Transcript, 29 Sep. 1991, pp.26-27**[18]	Armour (Monoclate-P)
15 Aug. 1988	The product licence for the non-heat treated **Koate** expired. It appears from internal Bayer/Cutter	Cutter (Koate)

[18] References to transcript page numbers are to the internal page numbers on the transcript.

Date	Event	Firm / Product
	documents that the licence was allowed to lapse as the product was no longer produced. **BAYP0000011_090; BAYP0000015_101, p.2**	
19 Aug. 1988	Hoechst UK Ltd wrote to the DHSS concerning **Haemate P**. The company stated that commercial negotiations with Armour had broken down, and hence it wished to withdraw related applications to vary the product licence and maintain Hoechst UK as the distributor of the product. **MHRA0033308_022**	Behringwerke (Haemate P)
21 Feb. 1989	The produce licence for the non-heat treated **Prothromplex** was renewed. **SHPL0000377, p.3; SHPL0000175_009**	Immuno (Prothromplex)
12 Jun. 1989	Baxter Healthcare Ltd. submitted a product licence application for **Hemofil M**. Discussions followed as to which regulatory regime applied given that Hemofil M was deemed a high technology product. The licence application was resubmitted in 1992 and was granted in Jun. 1994. **SHPL0000375_063; SHPL0000496_149; SHPL0000293_182; SHPL0000402_033; SHPL0000468_064**	Hyland (Hemofil)
2 Oct. 1989	Hoechst UK Ltd applied for the renewal of the product licence for **Haemate P**. The application stated that the product was not currently on the UK market and that a launch was planned for 1 Jan. 1990. **MHRA0000090, p.28**	Behringwerke (Haemate P)
6 – 10 Oct. 1989	The DHSS conducted an inspection of the Alpha Therapeutics Corp. facilities in Los Angeles, where **Profilate HT** was manufactured. The inspection revealed that the company had failed to correct a major deficiency found at a previous inspection in Feb. 1988. **DHSC0001349; DHSC0002412_093**	Abbott/Alpha (Profilate)
25 Oct. 1989	Alpha Therapeutics UK Ltd applied to vary the product licence for **Profilate HT** to change to a solvent/detergent method of viral inactivation. The varied product would be known as **Profilate SD**. **MHRA0033386_023; MHRA0033386_021**	Abbott/Alpha (Profilate)
2 Nov. 1989	Bayer UK Ltd applied to renew the product licence for **Koate HT**. It appears from later documentation that this application was successful. **BAYP0000005_143; BAYP0000033_012**	Cutter (Koate)
13 Nov. 1989	The Inspection Action Group of the DHSS met to discuss the inspection report of Alpha's facilities in Los	Abbott/Alpha (Profilate)

<table>
<tr><th>Date</th><th>Event</th><th>Firm / Product</th></tr>
<tr><td></td><td>Angeles and the consequences. The meeting agreed to recommend the recall of all Factor VIII material manufactured by Alpha, and the immediate suspension of the product licence for Profilate HT.
DHSC0001349</td><td></td></tr>
<tr><td>14 Nov. 1989</td><td>A minute from Mr Wilson of the MCA expressed concerns about the approach suggested by the Inspection Action Group in respect of Profilate HT. He requested further consideration of the matter and stated that it would be necessary to consult ministers. Further minutes were provided in response.
DHSC0001351; DHSC0001357; DHSC0001350; DHSC0002412_074; DHSC0001363</td><td>Abbott/Alpha (Profilate)</td></tr>
<tr><td>14 Nov. 1989</td><td>An internal DHSS document provided estimates about the annual supply of Factor VIII concentrates in the UK. This was intended to assist in the discussion of what action should be taken in respect of Alpha's Profilate HT.
It was noted that there was a shortfall of around 30m. i.u. between UK demand and NHS supply. This was filled by commercial products. The amount supplied by the NHS and commercial companies other than Alpha was estimated to be as follows:[19]
<table>
<tr><td>NHS Factor 8 (8Y and Z8)</td><td>80m. i.u.</td></tr>
<tr><td>Miles Cutter (Koate)</td><td>5m. i.u.</td></tr>
<tr><td>Baxter (Hemofil M)</td><td>2m. i.u.</td></tr>
<tr><td>Armour (? Monoclate-P)</td><td>4m. i.u.</td></tr>
<tr><td>Immuno (Kryobulin, TIM 3)</td><td>Unknown</td></tr>
<tr><td>Bayer (recombinant product)</td><td>Undergoing trials</td></tr>
<tr><td>Speywood (Hyate C)</td><td>~500,000 i.u.</td></tr>
</table>
Of the products listed in the table, only one true Factor VIII concentrate, Koate, was licensed.[20]
It was stated in the minute that "Hoescht have withdrawn from the UK market."
It is emphasised that the figures were presented as rough estimates and that the source or sources for them were not stated.
DHSC0002412_077</td><td>Alphas (Profilate)

Cutter (Koate)

Hyland (Hemofil)

Armour (? Monoclate-P)

Immuno (Kryobulin)

Bayer (recombinant)

Speywood (Hyate C)

Behringwerke (Haemate P)</td></tr>
<tr><td>24 Nov. 1989</td><td>A submission was made to the Minister of State for Health, Virginia Bottomley, on the inspection of the Alpha facilities and the question of whether action should be taken on the Profilate HT product licence. The submission proposed that the better course of action would be to open discussions with Alpha with a</td><td>Abbott/Alpha (Profilate)</td></tr>
</table>

[19] The original document lists only the company names. The product names are suggested by Counsel to the Inquiry. Those marked with a question mark are uncertain.
[20] It is relevant to note that both Profilate HT and Hyate C were also licensed. The licence of the former was at that point under scrutiny. The latter was a product for patients with Factor VIII inhibitors.

Date	Event	Firm / Product
	view to securing the early withdrawal of Profilate HT from the UK market, with action also taken to speed up consideration of the company's application for the licence to be varied to allow for **Profilate SD** to be marketed instead. **DHSC0001368**	
30 Nov. 1989	Immuno correspondence indicated that the unlicensed products **Kryobulin TIM 3 (steam)** and **Prothromplex TIM 4 steam** were still available on the UK market, although it is unclear the extent to which, if at all, they were being purchased at that time. **SHPL0000066_001, p.80**	Immuno (Kryobulin; Prothromplex)
6 Dec. 1989	Virginia Bottomley responded to the ministerial submission of 24 Nov. 1989, stating that she was not happy with the line proposed and would prefer regulatory action to be taken in respect of **Profilate HT** and Alpha. She welcomed advice on this. **DHSC0001366**	Abbott/Alpha (Profilate)
13 Dec. 1989	**Monoclate P** received a product licence. **MHRA0034658_013**	Armour (Monoclate P)
15 Dec. 1989	A further ministerial submission was made in respect of proposed regulatory action on the **Profilate HT** licence. This discussed the comparative advantages of either immediate suspension or informing Alpha that the Licensing Authority proposed to suspend the licence unless the company agreed voluntarily to cease marketing Profilate HT (in the knowledge that the application for **Profilate SD** was under consideration). The submission advised the latter course. **DHSC0001375**	Abbott/Alpha (Profilate)
11 Jan. 1990	It was reported to the CSM(B) that the new facility for the manufacture of **Profilate SD** had been inspected and found to be acceptable. The Inspectorate were to keep the site under review. **MHRA0033382_007**	Abbott/Alpha (Profilate)
19 Jan. 1990	Virginia Bottomley replied to the submission of 15 Dec. 1989 on **Profilate HT** by saying that she accepted the advice that the company be advised of a proposal to suspend the product licence, rather than immediate suspension. **DHSC0001374**	Abbott/Alpha (Profilate)
26 Jan. 1990	Alpha Therapeutics UK Ltd wrote to the CSM to confirm that the last batch of **Profilate HT** was imported into the UK in the middle of Dec. 1989 and it was not intended to import any further batches. The letter stated: *"I would*	Abbott/Alpha (Profilate)

Date	Event	Firm / Product
	like to emphasise that the decision not to import further batches of Profilate Heat-Treated has been made on the basis of the heavy demands on our manufacturing facility in the USA and also the current market situation in the UK." **MHRA0033386_009**	
Mar. 1990	The **Profilate HT** licence was varied to allow for a solvent detergent product, **Profilate SD**, following consideration by the CSM and the CSM(B). **MHRA0033386_023; MHRA0033386_021; MHRA0034913_003**	Abbott/Alpha (Profilate)
25 - 26 Sep. 1990	A further application was made to vary the **Prothromplex** licence to allow for vapour heat treatment. **SHPL0000311_039**	Immuno (Prothromplex)
21 May 1990	Internal Baxter Healthcare Ltd. correspondence recorded that *"small stocks"* of **Hemofil M** were held in the UK and could be provided on a named-patient basis. **SHPL0000293_142; SHPL0000293_141**	Hyland (Hemofil)
3 Jul. 1990	An application was made to vary the FEIBA licence to allow for vapour treatment. **SHPL0000106_098; SHPL0000311_055; SHPL0000266_045**	Immuno (FEIBA)
20 Jul. 1990	Immuno Ltd. applied to renew the existing licence for dry heat treated **FEIBA**. That product was no longer being supplied to the UK market. **SHPL0000102_119**	Immuno (FEIBA)
30 Apr. 1991	The MCA wrote to Immuno Ltd approving the renewal application for **Kryobulin Heat Treated** dated 3 Mar. 1988. An accompanying letter stated that *"since April 1988 product licence renewals have been subject to increasing delays as priority was being given to other work and a substantial backlog has since built up."* **SHPL0000067_0010**	Immuno (Kryobulin)
30 Apr. 1991	The product licence for **Haemate P** was renewed. The original product licence had been granted on 6 Feb. 1985 for 5 years, but an application had been made to renew before it expired. **MHRA0000090, p.27**	Behringwerke (Haemate P)
10 May 1991	Bayer UK Ltd informed the DHSS, further to a telephone call, that **Koate HT** was no longer imported into or sold or supplied in the UK. **BAYP0000005_189**	Cutter (Koate)

Date	Event	Firm / Product
Jun. 1991	The CSM concluded that it was unable to recommend variation of the **FEIBA** product licence to allow for TIM 4 vapour heat treatment. **MHRA0034575_059**	Immuno (FEIBA)
Jun. 1991	The CSM concluded that it was unable to recommend variation of the **Prothromplex** product licence to allow for TIM 4 vapour heat treatment on the grounds of safety, quality and quality. Among the reasons given was the view that the risk/benefit ratio for hepatitis transmission was *"inappropriate"*. **MHRA0034575_060**	Immuno (Prothromplex)
19 Jul. 1991	Immuno Ltd were informed that the CSM would not support its application to vary the **FEIBA** product licence to allow for TIM 4 vapour heat treatment. **SHPL0000266_045**	Immuno (FEIBA)
27 Jun. 1991	The CSM rejected a further application to vary the **Kryobulin Heat Treated** licence on grounds relating to safety and quality. Among the reasons given were concerns about the transmission of HBV and NANB hepatitis. It was stated that *"the risk/benefit ratio was unacceptable."* **MHRA0034575_058**	Immuno (Kryobulin)
8 Oct. 1991	Representatives of Immuno A.G. and Immuno Ltd met with the MCA to discuss the application to vary the **FEIBA** product licence to allow for vapour heat treatment. There was also discussion of the licensing position of **Kryobulin Heat Treated** and **Prothromplex**. **SHPL0000106_080**	Immuno (Kryobulin; Prothromplex; FEIBA)
25 Feb. 1992	An internal Cutter document recorded that **Koate HT** had been withdrawn from the market *"a couple of years ago"* as safer products were available and as it was no longer manufactured by Cutter. It was suggested that the licence be allowed to lapse. **BAYP0000033_012**	Cutter (Koate)
14 Apr. 1992	The MCA cancelled the product licences for **Kryobulin Heat Treated** and **Prothromplex**, having been informed by Immuno Ltd. that they wished to surrender the licences. **SHPL0000067_005; SHPL0000067_006**	Immuno (Kryobulin; Prothromplex)
26 Mar. 1992	An application was made to vary the **FEIBA** product licence to allow for vapour heat treatment. **SHPL0000266_041**	Immuno (FEIBA)

Date	Event	Firm / Product
15 Oct. 1992	The product licence for **Proplex** expired. This is a reference to the non-heat treated product which, according to internal Baxter documents, had not been sold in the UK for many years. **SHPL0000231_003; SHPL0000229_003**	Hyland (Proplex)
4 May 1993	The MCA informed Immuno Ltd. that the CSM had "*approved*" the application to vary the **FEIBA** product licence to allow for vapour heat treatment. **SHPL0000266_039**	Immuno (FEIBA)
10 Jun. 1993	The formal variation to the **FEIBA** licence was granted, such that vapour heat treated FEIBA became licensed in the UK. **SHPL0000109_001**	Immuno (FEIBA)
6 Jun. 1994	The product licence for **Hemofil M** (solvent detergent treatment) was granted. **SHPL0000468_064**	Hyland (Hemofil M)

Matthew Hill

Elena Stagni

6 December 2022