Chronology of events with relevance to "self-sufficiency", hepatitis C transmission and the establishment of terminal dry heat-treatment for UK coagulation factor concentrates

Source: litigation files maintained at BPL.
Definitions: HT1 = 60°C for 72 hours; HT2 = 70°C for 24 hours; HT3 = 80°C for 72 hours
Key date: ***

Date	Event
1967	HCDs determine to carry out a study of hepatitis in treated patients
1972	Donor screening for hepatitis Bs antigen established
3 Dec 1972	Baxter apply for UK licence for Hemofil
8 Dec 1972	Immuno apply for UK licence for Kryobulin
1973	Biggs (BJH, 1974): seminal paper on hepatitis in haemophiliacs, showing inter alia: 1.83% incidence in treated patients; freeze-dried concentrates no worse than frozen cryo; about 80% of hepatitis due to hepatitis virus(es) other than hepatitis B
19 Feb 1973	Baxter Hemofil licensed in the UK
20 Mar 1973	1st meeting of the DHSS Expert Group on the Treatment of Haemophilia
22 Mar 1973	Immuno Kryobulin licensed in the UK
20 Jun 1973	1st meeting of the Joint Steering Committee on Blood Products to co-ordinate activities at BPL and PFC
20 Jul 1973	1st meeting of RTDs to discuss provision of plasma for factor VIII for England & Wales
Nov 1973	1st meeting of SNBTS and HCDs to discuss factor VIII supply in Scotland
22 Jan 1974	David Owen – written answer announcing commitment to UK self-sufficiency in factor VIII and authorising special finance for that purpose
22 Aug 1974	Abbott apply for UK licence for Profilate
1975 et seq	Elimination of hepatitis B infective donors reveals patients still contracting non-A, non-B hepatitis
25 Feb 1975	David Owen – allocation of £500,000 to increase production of factor VIII within the NHS
25 Mar 1975	Armour apply for UK licence for Factorate
6 May 1975	David Owen announces distribution of £500,000 to Regions for plasma increase by RTCs
8 May 1975	2nd meeting of SNBTS and HCDs to discuss factor VIII supply in Scotland
22 May 1975	Abbott Profilate licensed in the UK
21 Jul 1975	Speywood apply for UK licence for Humanate
02 Aug 1975	Craske (Lancet): significance of donor pool size for hepatitis infection risk by factor VIII
13 Aug 1975	Lister Institute advised by DHSS that BPL should seek licences for its products
31 Dec 1975	Wd'AM notifies BPL staff of requirement to seek licences for BPL products
Jan 1976	BPL RIA test for hepatitis Bs antigen introduced
25 Mar 1976	Armour Factorate licensed in the UK
5 Apr 1976	BPL apply for UK licences for factor VIII manufactured at BPL (Elstree) and PFL (Oxford)
8 Jul 1976	BPL apply for UK licence for factor IX manufactured at PFL (Oxford)
9 Nov 1976	Supplementary data to DHSS in support of BPL/PFL licence applications
3 Feb 1977	D'Cruz to Wd'AM: authority given for grant of product licences to BPL and PFL
28 Feb 1977	Wd'AM to Rizza: low priority given to "Working Party to study the incidence of hepatitis in Haemophiliacs because: RIA test sensitivity (for hepatitis B) good; NANB hepatitis not yet proven: "hepatitis may have attracted undeserved attention".
17 Mar 1977	JKS to Wd'AM: UK demand for factor VIII estimated at 50Miu p.a.
May 1977	HCDs establish a Hepatitis Working Party (with BPL representation)
Sep 1977	Craske survey "Haemophilia-associated hepatitis – 1974-75 in the UK": mostly on Hemofil, showed 17.7% incidence of hepatitis (two types, B and non-B)
22 Nov 1977	Firstbrook to Roderick: interim exemption granted to BPL & PFL, pending facilities inspection
20 Dec 1977	Wd'AM to Parrott: "Stop-Gap" proposal to double BPL's factor VIII output over 4 years
17 Apr 1978	Lister Institute announce closure of its Vaccines and Sera Laboratories at Elstree
28 Jul 1978	Final version of "Stop-Gap" proposal agreed
30 Sep 1978	Responsibility for managing BPL & PFL transferred from Lister Institute to NW Thames RHA
23 Apr 1979	Medicines Inspectorate Inspection at BPL (23rd to 27th April)
13 Jul 1979	Harley to RSL: advises suspension of "Stop-Gap" expenditure pending Inspection report
13 Aug 1979	BPL receive draft copy of Inspection report
14 Sep 1979	RSL responds to Inspection report
22 Oct 1979	Richard Lane to DoH on the future needs of BPL and the NBTS
Nov 1979	First report by Dr John Craske on hepatitis after treatment with coagulation factors
Apr 1980	RSL (paper): "Short-Term upgrading of the BPL"

Chronology of events with relevance to "self-sufficiency", hepatitis C transmission and the establishment of terminal dry heat-treatment for UK coagulation factor concentrates

24 Apr 1980	Walford (paper): "Measures considered by the Department to be critical for the short-term operation of BPL
2 Jul 1980	Craske protocol: "Prospective study of the incidence of acute and chronic Hepatitis in Haemophiliacs as a result of first exposure to factor VIII concentrate or cryoprecipitate"
12 Sep 1980	Zuckerman paper: "Transmission of Heptatitis viruses by plasma and blood clotting factors. The risk of Commercial donors"
Sep/Oct 1980	BPL/PFL donor pool size increase from 2,500 to 5,000 to increase factor VIII output.
Oct 1980	First meeting of Department's "Hepatitis Advisory Group"
11 Oct 1980	Letters to BMJ (281, p.1006) on factor VIII supply and demand
26 Nov 1980	Medicines Inspectorate at BPL
9 Dec 1980	Medicines Inspectorate at BPL
12 Dec 1980	Craske to JKS: proposes a study of the impact of factor VIII donor pool size on hepatitis risk
15 Dec 1980	8th Meeting of HCD's Hepatitis Working Party: some Hepatitis B infection still occurring; commercial concentrates associated with 4-10 times the risk of transmitting overt NANB
17 Dec 1980	Milne (Haemophilia Soc) to RSL: concern about quantity of imported commercial factor VIII
22 Dec 1980	Harley to RSL: reports of Medicines Inspectorate visits to BPL (26 Nov 1980, 9 Dec 1980)
27 Feb 1981	BPL research project proposal: "The development of methods for the production of coagulation factor concentrates with reduced risk of hepatitis transmission
5 Mar 1981	Medicines Inspectorate (Ayling & Flint) inspect BPL (5-6 Mar 1981)
26 Mar 1981	Draft report on Medicines Inspectorate visit of 5-6 Mar 1981
23 Apr 1981	Joint meeting of HCDs and RTDs to consider coagulation factor requirements for UK
29 Apr 1981	JKS on small-pool freeze-dried cryoprecipitates to reduce hepatitis risk
13 May 1981	Medicines Inspectorate (Haythornthwaite) at BPL
18 Jun 1981	Draft report of Haythornthwaite inspection of 13 May 1981
Oct 1981	Craske paper "HCD Hepatitis Working Party report for 1980/1981": donor screening for HBsAg had eliminated the difference in HB infection risk between US commercial and NHS concentrates; 4-20 times the risk of transmitting overt NANB hepatitis associated with US commercial concentrates compared with NHS concentrates.
Jan 1982	BPL/PFL donor pool size increased to 7,500 donations
Jun 1982	BPL QA visits to RTCs begun to evaluate the systems in place for HBsAg testing of donations
13 Sep 1982	Craske (comment recorded at HCD's Hepatitis Working Party): first treatment with NHS or commercial factor VIII concentrate had a 90% chance of NANB hepatitis transmission
13 Sep 1982	UK HCD's Hepatitis Working Party minutes recorded "Hepatitis reduced" Hemofil available from Hyland and Biotest patent of pasteurised (with sugars) factor VIII and IX.
15 Dec 1982	BPL meeting noted "hepatitis safe" products available from Armour, Immuno and Hyland, typically heat-treatment in the presence of sugars; substantial yield penalties incurred.
21 Apr 1983	BPL meeting noted that heat-treatment was now being associated with AIDS-risk reduction. Concluded BPL should proceed with both heat-treated and small-pool product development.
11 Jul 1983	Craske paper for UK HCD's Hepatitis Working Party: three types of "hepatitis reduced" products: dry heated products such as Hemofil T and Factorate HT; chemical treated such as the Biotest product and Immuno Kryobulin; pasteurised product from Behringwerke. Recorded the dilemma -- use of hepatitis-reduced commercial product with residual AIDS risk cf. low AIDS risk product from UK plasma with 100% risk of transmitting NANB hepatitis.
14 Sep 1983	Craske (comment recorded at HCD's Hepatitis Working Party): 100% chance of NANB hepatitis transmission following treatment of virgin patients with NHS or commercial product
17 Oct 1983	UK HCD's meeting: TJS reported probable loss of 10-15% factor VIII by dry heating; BPL encouraged to prepare limited amounts for trial on a named patient basis. NHS or commercial concentrate were still the treatment of choice compared to frozen cryoprecipitate.
7 Nov 1983	BPL dry heated concentrate offered to HCDs in the Northern Region for clinical evaluation
29 Mar 1984	Update on "hepatitis reduced" factor VIII products under trial was circulated to UK HCDs: Dry heated ... Armour, Cutter, Hyland Wet heated ... Alpha, Behringwerke Donor panel selected products from UK fractionators BPL and PFC had products under development for release later in the year
May 1984	*** Trial issues of HT1 factor VIII
15 May 1984	Paper entitled "Patients who have received special batches of factor VIII, updated 10.5.84": reduced (<100%) but still significant transmission of NANB hepatitis by small pool products.
5 Jul 1984	Craske to JKS (letter): 2 patients treated with Armour dry heated product >> NANB hepatitis
11 Jul 1984	JKS to RSL (memo): 1 patient free from hepatitis at 12 weeks post-treatment with heated BPL

Chronology of events with relevance to "self-sufficiency", hepatitis C transmission and the establishment of terminal dry heat-treatment for UK coagulation factor concentrates

	factor VIII
12 Oct 1984	RSL to DHSS: BPL actively planning for introduction of dry heating for all factor VIII
20 Oct 1984	MMWR update on AIDS in Haemophiliacs: treaters should strongly consider switching to heat-treated products
8 Nov 1984	DHSS (Harris) to RSL: is evidence for inactivation of HTLV-III by heat sufficient to warrant heating all factor VIII, especially if a (donor) screening test could be made available? Notes the implications for plasma supply if all product heated and heating affect factor VIII yield.
9 Nov 1984	BPL report on 8Y to Central Committee: timescale for availability of product approximately one year; no great loss of yield forecast. Committee recommended commencement of dry heat treatment of existing product whilst working on methods to safeguard yield.
12 Nov 1984	JKS (memo): three patients treated with heated NHS concentrate remained infection-free; first studies on heated commercial concentrates indicated only a 30% reduction in NANBH risk; development of 8Y assigned as single highest priority at PFL (Oxford).
13 Nov 1984	BPL internal meeting: full implementation of dry heating (existing product) by April 1985.
28 Nov 1984	CBLA approved expenditure on heat-treatment ovens to serve proposed BPL programme.
10 Dec 1984	HCD's meeting at BPL: heated product preferred for all patients, subject to availability; otherwise preferentially for treatment of HIV-antibody negative patients. BPL confirmed all factor VIII would be heated by April 1985. Heating would carry a 15-20% yield penalty.
12 Dec 1984	JKS (memo): HT1 (PFL Oxford only) to be replaced by HT2 (BPL and PFL); PFL (Oxford) would devote all resources to development of HT3 for 8Y, then transfer technology to BPL.
13 Dec 1984	Pettet (memo): Alpha, Cutter, Armour, Immuno, Hyland all offering heated products (Immuno Kryobulin was dry heated at 60°C for 12 hour).
20 Dec 1984	JKS (memo): proposed wording for HT2 heated factor VIII – "We have ... heated the concentrate under conditions which will probably kill the virus which transmits AIDS and may well prevent or reduce the transmission of Non-A, Non-B hepatitis ... Until a 'second generation' concentrate is available to everyone in 1985, we think this is the safest concentrate ... which we can offer you".
22 Dec 1984	Lancet: First generation heated commercial concentrate had transmitted NANB hepatitis.
24 Jan 1985	TJS to HCDs: HT2 heated concentrate generally available now; HT3 heated 8Y will be available from June 1985.
Feb 1985	*** First issues of heated (HT2) factor VIII
Feb 1985	*** Trial issues of heated (HT3) factor VIII
28 Feb 1985	TJS to DH (Duncan): letter setting out timetable for product availability, changeover arrangements and proposed licensing schedule for establishment of heat treatment for factor VIII and factor IX.
28 Mar 1985	*** Only heated (HT2 or HT3) factor VIII issued from PFL (Oxford) after this date
02 May 1985	*** Only heated (HT2 or HT3) factor VIII issued from BPL (Elstree) after this date
13 May 1985	*** No unheated factor IX issued from PFL (Oxford) after this date
July 1985	Fact sheet to HCDs and RTDs on BPL 8Y: "Clinical trials at six haemophilia centres are in progress ... several patients have safely passed the point at which first evidence of NANBH virus transmission would normally occur with unheated factor VIII."
08 Jul 1985	*** First issues of heated (HT3) factor IX
18 Sep 1985	*** All factor VIII issued after this date was heated using HT3 conditions
02 Oct 1985	*** All factor IX issued after this date was heated using HT3 conditions
02 Oct 1985	*** No unheated factor IX issued from BPL (Elstree) after this date

Chronology of events with relevance to "self-sufficiency", hepatitis C transmission and the establishment of terminal dry heat-treatment for UK coagulation factor concentrates

Table 1. Annual consumption of factor VIII in UK (including N.I.) in Million International Units (Miu)

Source: Paragraph 31 of the Re-Amended Main Statement Of Claim in the HIV Haemophilia Litigation. This cites a range of sources, some primary, some secondary; the figures were not challenged in any of the central defendants' defences. I don't have the original sources (typically Haemophilia Centre Directors' Annual Statistics), but the supply figures from BPL (which run by financial, rather than calendar year) are broadly consistent (see Table 2 below). A figure abstracted from the BPL annual report for 1996/7 (appended as Fig 1) is supportive.

Year	Total Miu factor VIII used (includes cryoprecipitate)	NHS Miu factor VIII	Comm. Miu factor VIII
1969	6.945	1.025	0
1970	8.189	0.884	0
1971	11.823	3.071	0
1972	11.039	1.939	0.095
1973	15.829	2.481	0.875
1974	20.548	2.732	2.681
1975	24.886	3.085	5.152
1976	33.716	6.915	11.069
1977	43.193	12.949 (increase reflects David Owen spend at BPL)	15.017
1978	45.050	14.600	19.273
1979	50.716	15.092	26.178
1980	57.271	14.364	34.749
1981	65.700	22.472 (increase reflects "stop gap" spend at BPL)	35.5
1982	73.732	22.892	45.644
1983	71.008	30.018	26.217
1984	79.910	40.192	34.003
1985	77.344	23.097 (decrease reflects introduction of HT3 at BPL)	50.902
1986	88.491	31.483	53.754
1987	87.857	25.982	59.186

Table 2. Factor VIII issued by BPL in Million International Units (Miu)

Source: BPL annual reports for these years (BPL GMP archive box 819, location no 251).
HT3 = terminal heat-treatment of the freeze-dried product at 80°C for 72 hours

Year	Factor VIII issued by BPL (Miu)
1981/2	21.53
1982/3	22.10
1983/4	27.08
1984/5	27.95
1985/6	8.00 (unheated, intermediate purity concentrate) 17.55 (HT3 heated factor VIII type 8Y)
1986/7	21.87 (all HT3 from now on)
1987/8	24.06
1988/9	52.75