Introduction of dry-heated concentrates of F.VIII and F.IX in England.

Recent testimony suggests that the Inquiry may not have a clear picture of these events in England, and has not called any other witness who might be better placed to explain. I therefore offer the Inquiry a description of the BPL/PFL products of interest, and an account of how they were brought into use.

I have not included an account of the formalities of licensing and clinical trial of BPL's heated products, or of recall of superseded products. I believe that, in those quite extraordinary times, BPL and MCA were in frequent discussion and that all procedures were transparent and compliant with contemporary regulatory practice. However, I was not closely enough involved in these formalities to offer further written or oral testimony on this area.

8CRV/HL
These are virtually the same "intermediate-purity" F.VIII concentrate, 8CRV made at PFL, Oxford and HL at BPL, Elstree, between about 1978/9 and 1985. They are basically large-pool cryoprecipitate from which some of the less soluble impurities have been removed. The Specific Activity is of the order of 0.5-1.0 IU F.VIII/mg protein, and the potency is about 17 IU/ml. It redissolves in about 5 minutes.
This product was not designed for dry heating, but a survey of recent batches in the second half of 1983 showed that all batches survived fairly well (i.e., remained within product specification) after heating at 60°C for 24 hours ("HT1"); and most batches withstood 70°C for 24 hours ("HT2"). There were penalties in yield and re-solution time, but these could be tolerated while better solutions were found.
The nearest PFC equivalent would be "NY".

8Y
This is a cryoprecipitate extract, more extensively depleted of fibrinogen, fibronectin and other redundant plasma proteins by two precipitation steps (without chromatographic purification). The Specific Activity is of the order of 5-10 IU F.VIII/mg protein, and the potency is about 25 IU/ml. It redissolves very rapidly within less than a minute.
This product was formulated for dry heating from the start, and was never infused in unheated form. The conditions ("HT3") were 80°C for 72 hours.
The nearest PFC equivalent would be Z8, although earlier versions of the latter were heated almost as severely as 8Y.

[I have commented elsewhere on the intuitive view that, e.g., "70°C is only marginally warmer than 60°C", repeated by some witnesses. Dr.Foster would be well placed to offer the Inquiry a short note on the dynamics of protein denaturation, if he has not already done so.]

9A
This is simply a dry-heated (HT3) version of the Factor II,IX,X concentrate (DE) manufactured at PFL from 1972-1985, and latterly at BPL as well. For optimal dry-heating, antithrombin and heparin were added to the formulation (the precise reasons are not of general interest). Both DE and 9A redissolve quite rapidly.
The nearest PFC equivalent would be DEFIX. In fact, because PFC and PFL collaborated on the development of DEFIX/DE in the early 1970s, there was very little difference between the two products.

Introduction of heated 8CRV/HL

Clinical trial for safety and efficacy: Early 1984 [PEN 017 1782]
Clinical trial for virus safety: Early 1984 [PEN 017 1782]
First issued via RTCs for general use: January 1985.

It must be appreciated that the batches of HT1-heated 8CRV infused in "early 1984" were unusual, in that they had been made from a 100kg pool of plasma, obtained by repeated plasmapheresis of a small number of donors who had earlier given at least 4 blood donations "without overt evidence of heptitis in the recipients" (the most that could be said at the time). The plasma had also been quarantined, I believe for at least 3 months, and would have been discarded had the donor shown signs of illness in that period. Although I cannot at this distance be exact, typically the 100kg pool may have contained 10 donations from each of about 20 "Green 4" donors. The publication, delayed until 1986, makes several points which remain valid today. As one of the authors, I am prepared to field any further questions on this small study. JKS Note 5 in B3 includes some additional interpretation of its lack of impact on opinion in England.

Drs. Colvin and Machin were among the most active and communicative of haemophilia physicians at this time and, although BPL held out no claim or suggestion whatsoever that these batches might not transmit "blood-borne viruses", it seems likely that this anecdotal "success", evident by mid-1984, became quite common knowledge. In the following period up until general release in January 1985, had any clinician asked for a supply on the same "Named Patient" conditions agreed by Drs.Colvin and Machin, BPL would have provided it without any absolute obligation to follow up for NANBH transmission. In the likely circumstances that the patient had not received concentrate before, the clinician would have been given the Oxford protocol for the study of hepatitis transmision and invited to keep me informed of follow-up. No such request was made, to my knowledge.

Samples of all batches of 8CRV and HL in stock or quarantine were trial-heated from November 1983. Batches shown not to withstand HT2 were heated by HT1. Stocks having been built up, the heated forms were issued, essentially simultaneously to every RTC, for general use in January 1984. There was no obligation to follow-up for hepatitis transmission, and I imagine that, with the promise of 8Y quite explicit by now, some clinicians would have delayed non-urgent interventions in mildly-affected patients.
Some clinicians continued to prefer unheated HL, which would have been requested from their RTC and issued at the latter's discretion. No unheated HL was issued from BPL after 2 May 1984.

Introduction of 8Y

Clinical trial for safety and efficacy: March 1985
Clinical trial for virus safety: from April 1985
First issued via RTCs for general use: September 1985

Between March and September 1985, HCDs were aware that 8Y was available for clinical trial, using the Oxford protocol. However, by this time many of the suitable adult PUPs and in England had been hoovered up by one commercial trial or another and were now infected. If a patient presenting himself at a HC was thought to have received very little or no treatment before, but circumstances were such that this could not be immediately

documented, 8Y was not withheld. All patients submitted in good faith continued to be supplied with 8Y until general release in September. From September, BPL allocated supplies directly to RTCs, who became responsible for onward allocation to HCs. Clinicians submitting suitable patients into trial after September would have been encouraged to ask for special trial supplies via Oxford PFL, where I liaised frequently with Dr.Rizza and was unofficial Trial Gofer. The aim was to ensure that a good spread of batches went into trial.

Introduction of 9A

Clinical trial for safety and efficacy: July 1985
Clinical trial for virus safety: (probably) July 1985
First issued via RTCs for general use: September/October 1985. No unheated DE was issued by BPL to RTCs after 02 October 1985.

The Inquiry has ample evidence that SNBTS very generously offered to give BPL equal shares in the laborious "Dog DIC" model, which we considered to be the only satisfactory way of predicting thrombogenicity in patients. This meant that first issues of HT3-heated 9A in England and the corresponding PFC concentrate in Scotland were essentially synchronised. We were painfully aware during the spring and summer of 1985 that some clinicians who had never observed significant thrombogenicity in their patients would gladly have used 9A without waiting for completion of the animal work, relying on the best *in vitro* tests. However, both Services stuck to the original policy.
No unheated F.IX was issued by BPL to the RTCs after 2 October 1985.

Although they draw on sources which I trust, I cannot provide primary documentation of the events presented here. **This account should be understood as my subjective "opinion", and should not be used more widely without independent verification.**

James K.Smith 21 October 2011