

Witness Name: Dr Terence J Snape

Statement No.: WITN3431034

Exhibits: WITN3431035

Dated: 3 May 2023

INFECTED BLOOD INQUIRY

SECOND WRITTEN STATEMENT OF DR TERENCE JOSEPH (TERRY) SNAPE

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This statement is true to the best of my knowledge, information and belief now. However, it is important to recognise that I am endeavouring to recall events which occurred many years ago and inevitably there is information that I can no longer recollect. This further statement should also be read in conjunction with my witness statement to the Inquiry dated 8 February 2022, which in particular gives a full history of my qualifications and experience

[WITN3431001]. I gave oral evidence to the Inquiry based on that witness statement on Tuesday 29 and Wednesday 30 March 2022 [INQY1000199, INQY1000200].

I provide this statement on behalf of the Department of Health and Social Care (DHSC) in response to the request under Rule 9 of the Inquiry Rules 2006 dated 1 March 2023.

I, Dr Terence Joseph Snape, will say as follows:

Section 1: Introduction

1. I refer to paragraphs 1 to 4 of my earlier witness statement dated 8 February 2022 [WITN3431001] which set out my personal information and my qualifications. Paragraphs 5 to 24 of the same statement set out my work experience.

Section 2: Response to Criticism by Witness W2368

A. Factor VIII concentrates involving purification using monoclonal antibodies (MAb)

General Background Information

2. I have been asked to respond to assertions made within the “taintedblood.info Accusations Document” [WITN2368023], which are repeated in the written statement of witness W2368 [WITN2368019].
3. I have reviewed the documents on the basis of statements as made, but it is clear that there are fundamental misunderstandings about the Lister Institute of Preventive Medicine, about the Blood Products Laboratory (BPL), and about BPL’s products and capabilities. I have attempted to clarify those misunderstandings as they arise.
4. In this statement, I have restricted my comments to statements made in respect of what the Accusations Document refers to as “monoclonal-derived Factor

VIII". I do not believe that I have sufficient expertise in the field of recombinant product manufacture to comment with any confidence on that area. At no time before I took early retirement from BPL in September 2000 was BPL involved in recombinant research or manufacture. This statement focuses only on aspects of factor VIII manufacture by MAb-purification which I consider to be within my knowledge and experience.

5. First, it is important to understand that so-called "monoclonal-derived Factor VIII" products are still human plasma products, with all the strengths and weaknesses of products derived from human plasma. As such, they are as likely to be infected with blood-borne contaminants like hepatitis viruses and HIV as any other plasma-derived product. The monoclonal antibody involved, typically murine (mouse) antibody to factor VIII, is bound to a solid matrix, and is used to bind and capture the factor VIII in an early purification step. The factor VIII is recovered from the solid matrix by chaotropic column elution and is then subjected to further purification.
6. This technique allows a target molecule (in this case human factor VIII:C) to be separated from other plasma proteins, by capturing the factor VIII:C onto mouse monoclonal antibody to human factor VIII:C that has been previously bound to a solid column matrix material. After washing the column to remove unwanted plasma proteins, the factor VIII:C is recovered from the column by treating the column with a reagent that breaks the bond (hence the term "chaotropic") between the mouse MAb that remains securely bound to the column matrix, and the factor VIII:C which can be collected as it emerges from the column. Depending on the efficiency of washing of the column before the factor VIII:C is recovered, a degree of virus elimination is achieved but the column washing and elution alone cannot be relied upon to produce a virus-safe product. A virus inactivation or virus elimination step would always follow, downstream of the elution of factor VIII:C from the column.
7. It is especially important to avoid confusing factor VIII concentrates purified by matrix-bound (mouse) factor VIII antibodies, where the MAb is simply a process agent, with true therapeutic MAb products manufactured by the hybridoma technique well-summarised in the review "*Development of therapeutic antibodies for the treatment of diseases*", by Ruei-Min Lu *et al*, in the Journal of Biomedical Science (2020), 27:1 [WITN3431035]. True therapeutic MAb

products manufactured by the hybridoma technique are injected or infused as part of a targeted clinical regimen for specific treatment of a disease. The mouse MAb used in the factor VIII:C purification scheme is never injected into a patient – it remains bound to the column matrix.

8. Factor VIII concentrates prepared from human plasma, and purified using monoclonal antibodies (MAb), are subjected to one or more virus inactivation steps.
9. Table 1 of the UKHCDO “*Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders*”, Haemophilia (1997), 3, 63-67, (see page 2 of [BART0000875]) summarises the plasma-derived and recombinant coagulation factor concentrates available at the time, and provides a useful summary of the manufacturing methods, virus inactivation procedures incorporated and product characteristics. The later World Federation of Hemophilia (WFH “*Registry of clotting factor concentrates, January 2006*”, see [WITN3431012], provides more extensive updated information.

BPL Background Information

10. Whilst BPL was developing and improving methodology for purification of factor VIII concentrates in the 1980s our focus was primarily on four areas of concern:
 - a. Process yield to maximise the output of product for clinical use;
 - a. Safety and efficacy, in particular virus safety with respect to hepatitis and AIDS viruses;
 - b. Product characteristics that would determine patient acceptability – potency, specific activity, storage conditions, ease of resolution, comfort on injection;
 - c. Maximising Good Manufacturing Process (GMP) within the constraints of the old manufacturing unit (B25) and planning for the transition to the new manufacturing unit (B27), with all the potential in that unit for scale-up and GMP improvements.

11. These concerns were well-satisfied by the 8Y process established in 1985: even allowing for terminal HT3 heat treatment in the sealed final product vial, yield was better than previous expectation; over time virus safety was firmly established in clinical trial; the product was readily soluble and acceptable for use both in the clinic and for home therapy; the 8Y product contained both factor VIII:C and VIII:vWF, so was suitable for treatment of both Haemophilia A and von Willebrand's disease; terminal HT3 in the sealed final product vial maintained virus safety even in the substandard manufacturing environment of B25.

12. By comparison, products like Baxter's Hemofil-M and Armour's Monoclate P, purified using matrix-bound (mouse) factor VIII antibodies, contained only factor VIII:C and were not suitable for the treatment of von Willebrand's disease. Like all products derived from human plasma, they had the potential to transmit blood-borne viruses and incorporated validated virus inactivation steps.

13. After 1986, when the 8Y process and product were established in use at BPL, other factors came into play:

a. As more MAb-purified products became available, marketing pressure to supply a more highly purified (higher specific activity) product increased;

b. Developing ideas on improvements in virus safety -

1. As alternative virus inactivation techniques were demonstrated to be effective against hepatitis viruses and HIV, the thinking of the manufacturers in collaboration with the EU regulatory agencies, began to lean in favour of multiple, orthogonal, virus inactivation or virus elimination steps (dependent on different mechanisms of action), for individual products;

2. Since most virus inactivation techniques were performed "in process" (pasteurisation at 60°C, solvent detergent VI, virus filtration) it became increasingly important to create a manufacturing process flow, and a facility layout, that could be

relied upon to prevent later downstream re-infection by virus after the only/each virus inactivation step was completed (a complication avoided by virus inactivation in the sealed final product container using terminal HT3).

- c. Whilst BPL's new B27 facility had been considered "state of the art" during facility design and construction, by 1987 it was clear that facility layout modifications would be necessary in coagulation factor processing areas, if BPL was to embrace these developing ideas on virus safety.

14. By 1987 it was agreed that BPL should extend its product portfolio to include specific activity factor VIII including MAb-purification and a complementary "state of the art" virus inactivation procedure (the product would later be launched alongside 8Y and would not replace it). Since the time required for process development, scale up and implementation was likely to be unacceptably long, it was agreed that existing technology would be licensed in from another company such as Baxter or Armour. (BPL had a leaning towards a product with an SD virus inactivation step, since we had plans to add a similar virus inactivation step to our Intravenous Immunoglobulin process that was under development at the time.)

15. Baxter's Hemofil M product was a Mab-purified product that included virus inactivation by a solvent detergent (SD) step. Previous liaisons with Baxter Healthcare had been effective, and the effectiveness of virus inactivation by solvent detergent had already been established. It was determined that BPL would seek a licence agreement with Baxter to use the technology licensed for Hemofil M. I was asked to lead a technology review visit to Baxter's plant in Glendale, CA, with an experienced team of BPL and PFL (Plasma Fractionation Laboratory) scientists. The technology was found to be satisfactory both in terms MAb purification of factor VIII:C, and in terms of virus inactivation by SD. My recommendation was that licensing should go ahead, and this was accepted by the BPL Executive, and by CBLA.

16. It was clear that facility modification would be required in the coagulation factor production suite in B27, to establish a facility layout consistent with the new thinking on the avoidance of virus cross-contamination post in process virus inactivation, but the delay to processing of the licensed-in process was considered unacceptable by BPL's CEO (Bernard Crowley), in respect of service to BPL's customers. I was asked to develop and manage a contract manufacturing programme with another Baxter process licensee (Kabi Pharmacia, Stockholm, Sweden) to bring the new product to market in an acceptably shortened time. I acted as BPL's "man in plant" in Stockholm during the first three runs during an 18-month period of manufacture of product from BPL's UK plasma. The product, styled "Replenate", was granted a UK product licence in March 1989.

17. Replenate included BPL human albumin solution as stabiliser – it was otherwise virtually homogenous factor VIII:C. Replenate contained no factor VIII:vWf, but the availability of BPL's 8Y concentrate for treatment of von Willebrand's disease patients made this less significant.

18. BPL introduced a chromatographically purified factor VIII:vWf concentrate styled "Optivate", as an alternative to 8Y, in the late 1990s. The product was subjected to two orthogonal virus inactivation steps, SD in process and HT3 in the final closed contained.

The "taintedblood.info Accusations Document"

19. In response to paragraph 1 of [WITN2368023] page 5,

"We accuse the Government and the Department of Health of FAILING TO LEARN LESSONS in not rapidly introducing monoclonal-derived Factor VIII at BPL Elstree when it was considered and allowed for in the plans for BPL in 1985/6 and that even now, the safest recombinant Factor VIII products are not being made available to all adult haemophiliacs within the UK, and that the same mistakes are being repeated: in placing cost concerns over and above patient safety."

20. This reflects lack of scientific understanding about MAb-purified factor VIII concentrates. Mouse monoclonal factor VIII antibody (MAb), bound to a chromatographic column matrix, is used in a purification step. The factor VIII product so purified is still a human plasma factor VIII product. Such products contain less plasma protein than conventionally purified factor VIII concentrates, but the MAb-purification step does not remove or inactivate blood-borne viruses, and the product is no safer in respect of virus risk than any other factor VIII concentrate derived from human plasma. All MAb-purified factor VIII concentrates were stabilised by the addition of human albumin - see [BART0000875 page 2] and [WITN3431012], the later World Federation of Hemophilia (WFH “Registry of clotting factor concentrates, January 2006” [WITN3431012] for evidence of this.

21. In my opinion, there were no safety consequences of the timing of adoption of MAb-purified concentrates by BPL. The record of virus safety of 8Y and 9A products over the 30+ years that they were manufactured and sold was maintained, with no recorded infections in that time as far as I am aware. They served UK haemophiliacs well, alongside the MAb-purified Replenate, Replenine (BPL’s chromatographically purified factor IX concentrate, incorporating an effective virus filtration step for virus removal), and Optivate products, offering virus safe clinical choice options.

22. In response to lines 6-13 of [WITN2368023] page 26,

“We believe that the technology for monoclonal-derived Factor VIII existed from as early as 1984. We ACCUSE the Department of Health and BPL of failing to learn any lessons from the years of hepatitis in the 1970s and from AIDS in the early 1980s. In failing to initiate and scale up the production of genetically engineered Factor VIII from circa 1986, or certainly within 5 years of this date, to allow for research and development, we allege that not enough was done to protect the haemophiliac community from the threat of further blood-borne pathogens – in particular the failure to introduce non-human-derived Factor VIII with haste.”

23. This again reflects an apparent lack of scientific understanding about MAb-purified factor VIII concentrates. They are not “genetically engineered”

products; the mouse monoclonal factor VIII antibody is not the product, or incorporated into the product, it is simply a component part of a purification step. It does not contribute to product virus safety, and virus inactivation or virus elimination (removal) steps are still a mandatory requirement.

24. BPL had no remit at any time for the development or manufacture of recombinant products as an alternative to products derived from human plasma.

25. In response to lines 15-23 of [WITN2368023] page 26,

"In a Sunday Times article in September 2001, Alan Milburn said that "where the system fails the lessons need to be learned." (Source: The Sunday Times, 30 September 2001.) In failing to learn these lessons, we find that batches of 8Y Factor VIII [FHC0289] manufactured from vCJD-implicated donations dating back to May 1990, (some 4 years after BPL had made plans to allow for monoclonal) are being traced in an Patient Notification Exercise initiated by The Health Protection Agency, Colindale [sic] as of September 2004. We believe that the possible exposure of haemophiliacs to this "theoretical" risk could most certainly have been AVOIDED if the Department of Health had ensured that monoclonal-derived Factor VIII has been developed at BPL from 1985 onwards."

26. This again reflects an apparent lack of understanding about MAb-purified factor VIII concentrates. As Table 1 of the UKHCDO "Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders" [BART0000875 page 2] makes clear, all MAb-purified factor VIII concentrates are strictly plasma-derived products, and all are stabilised with human albumin solution. In the case of BPL products, the human albumin would have been derived from the same UK plasma as the MAb-purified factor VIII concentrate, indeed by choice from the same plasma start pool to minimise exposure to donations from only one plasma pool.

27. In respect of the theoretical risk of transmission of vCJD, to the extent that such a risk existed, it would have applied to any factor VIII concentrate

manufactured from UK plasma, regardless of manufacturing method, whether conventionally purified, or MAb-purified with added human albumin stabiliser.

28. In response to lines 13-17 of [WITN2368023] page 27,

“Due to the failure to rapidly introduce monoclonal-derived Factor VIII at BPL Elstree, when it was considered and allowed for in 1985/6 and due to the fact that even to date, the safest recombinant Factor VIII products are not being made available to all adult haemophiliacs in the UK, we ACCUSE the Government and the Department of Health of FAILING TO LEARN LESSONS and placing cost concerns above patient safety.”

29. This again reflects lack of apparent understanding of MAb-purified factor VIII concentrates. MAb-purified factor VIII concentrates offer no exceptional benefits in respect of virus safety – they are still plasma products. Furthermore, recombinant factor VIII concentrates stabilised with human plasma albumin still carry the same actual virus risk, and the same theoretical vCJD risk, as factor VIII concentrates manufactured from human plasma.

Statement of Truth

The facts stated in this written statement are true to the best of my knowledge and belief now and without the benefit of any disclosure or access to documents concerning this issue beyond the documents mentioned herein and what is publicly available, for example, through publication on the Inquiry website. I have not had specifically drawn to my attention any of the latter.

GRO-C

Signed:

Dated: ... 3 May 2023

EXHIBIT TABLE TO SECOND WRITTEN STATEMENT OF DR TERENCE JOSEPH
(TERRY) SNAPE

Date	Notes/Description	Exhibit Number
2020	"Development of therapeutic antibodies for the treatment of diseases", by Ruei-Min Lu et al, in the Journal of Biomedical Science (2020), 27:1	WITN3431035
1997	"Guidelines on Therapeutic products to treat haemophiliacs and other hereditary coagulation disorders", Haemophilia (1997), 3, 63-77	BART0000875
January 2006	"Registry of Clotting Factor Concentrates", Carol K Kasper and Mark Brooker World Federation of Haemophilia, Montreal	WITN3431012