Witness Name: Sarah Middleton
Statement No.: WITN5666001
Exhibits: None
Dated:14.4.2021

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF SARAH MIDDLETON

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 15 March 2021.

I, Sarah Middleton, will say as follows: -

Section 1: Introduction

Please set out your name, address, date of birth and professional qualifications.

1. Sarah Middleton
   GRO-C Cumbria GRO-C
   DOB GRO-C 1947
   BSc Biochemistry University of St. Andrews. 1966-1969

Please set out your employment history, including the various roles and responsibilities that you have held throughout your career and the dates when you held them.

2. **1969-1976 Edinburgh Protein Fractionation Centre: Biochemist**
    - Purification of Factor IX, for human plasma using ion exchange resin.
    - Purification of Factor VIII, from human blood using purified cryoprecipitate fraction.
    - Clearance of Hepatitis B from Factor IX concentrate using polyethylene glycol precipitation.
    - Evaluation of Plasma Fractionation using solid phase polyelectrolyte based on Ethylene Maleic anhydride (EMA PE).

1976-1979 Department of Medicine University of Glasgow: Biochemist

- Left PFC for personal reasons continued to work on thrombogenicity of Factor IX concentrates.

1979-1987 Speywood Laboratories Ltd: Chief Scientist

- Development of EMA PE for purification of a concentrate of Porcine Factor VIII
- Application of EMA PE to purification of Human Factor VIII in collaboration with Bioproducts Laboratory Elstree and French Blood Service, Orsay.
- Participation in purification of Human Factor VIII to yield protein for sequencing Factor VIII

1987-1996 Delta Biotechnology Ltd: Development of Recombinant Human Albumin in yeast:

- Director of Quality Assurance, Clinical and Regulatory Affairs.
- Project Director- Development of an Ultrasound contrast agent using spray dried albumin.

1996- 2001 – Andaris Ltd: Director of Targeted Therapeutics

- Development of a novel Platelet Substitute.
- Development of novel topical Haemostat

2001- 2016 Founded Haemostatix Ltd: CEO and CTO

- Development of a novel substitute for Platelet Transfusion: Synthocytes
- Development of a topical haemostat for surgical use: PeproStat

Please set out your membership, past or present, of any committees, associations, parties, societies or groups relevant to the Inquiry's Terms of Reference, including the dates of your membership and the nature of your involvement.

3. No relevant Societies

Please confirm whether you have provided evidence to, or have been involved in, any other inquiries, investigations, criminal or civil litigation in relation to the human immunodeficiency virus ("HIV") and/or hepatitis B virus ("HBV") and/or hepatitis C virus ("HCV") infections and/or variant Creutzfeldt-Jakob disease ("vCJD") in blood and/or blood products. Please provide details of your involvement and copies of any statements or reports that you provided.

4. Interviewed with respect to US class action Infectivity of Blood Products sometime on 1990s. No documentation either prepared or received.

Section 2: Speywood Laboratories

A. Distribution of Koate and Humanate 1976-1981

Please describe Speywood Laboratories' distribution of the Factor VIII products, Koate and Humanate, from 1976 to 1981

5. Speywood operated from an office in Nottingham, with laboratories based in Wrexham in North Wales; for this reason, when I joined the Company, I had no specific knowledge of the distribution of Human Factor VIII concentrates.

To the best of your knowledge, during that period of time, what perception of the risk of transmitting hepatitis:
a) Was held about those products specifically, within the company?

6. I would assume that the potential risk of transmission of Hepatitis B was known with respect to Koate and Humanate. However, in these early days there was a strong belief of needing Factor VIII to stop bleeds, and there were no virus safe Factor VIII concentrates available.

To the best of your knowledge, during that period of time, what perception of the risk of transmitting hepatitis:

b) Was held about factor products in general, within the wider scientific community?

7. Knowledge of the potential for transmission of Hepatitis B with factor fractions was generally known but, as stated above the need for Factor VIII and Factor IX to stop bleeds was likely to have been the overriding factor. While there was clearly a need to try to remove virus, the technology needed to be developed, it was known for example that albumin could be pasteurised, Factor VIII and Factor IX were regarded as unstable proteins which it was believed would be difficult to heat treat.

B. Polyelectrolyte fractionation and highly purified human Factor VIII (Mono VIII:C)

Please describe your role in polyelectrolyte fractionation research in the early 1970s, with reference to your work at the Protein Fractionation Centre with Dr James Smith and at New York University with Dr J Alan Johnson. See PRSE0003349, section 2, paragraphs p-s.

8. Dr Alan Johnson NYU was seeking to work with a Plasma Fractionator to develop a new plasma fractionation technology, using a solid phase polyelectrolyte (EMA PE) manufactured by Monsanto Inc. It was envisaged that the EMA PE could be used fractionate albumin, immune globulins, Factor VIII and Factor IX fractions. (PRSE0003349).

My role was technology transfer initially working with Dr Johnson's group in his laboratory for a short time. At the time I recall there were problems recovering Factor VIII from the EMA PE and at that time I evaluated clearance of Hepatitis

B virus from a Gamma Globulin fraction using the EMA PE. I am not sure whether this was ever published.

9. When I returned to PFC, I carried out work to demonstrate using EMA PE for recovery of albumin and gamma globulin. No methods developed for factor VIII or FIX concentrates at this point.

10. Additional work with some relevance was that in collaboration with Dr Alan Johnson, a method was worked out for further purification of Factor IX using Polyethylene glycol, in an attempt to precipitate out Hepatitis B virus. (PRSE0003799, PRSE0002353).

11. I left PFC and subsequently learnt that the PEG method was used at PFC to prepare a Factor IX concentrate (Supernine), a product which was never licensed. (PRSE0003349)

To the best of your knowledge, to what extent was knowledge of the risk of transmission of hepatitis and/or other viral infections a driver for research into polyelectrolyte fractionation methods, by Speywood Laboratories and by other researchers?

12. In the first instance the driver for Speywood Laboratories was for developing the EMA PE to produce Porcine Factor VIII with increased purity. Previous methods to produce Porcine Factor for the treatment of patients with inhibitors to Human Factor VIII, had resulted in a product that caused platelet aggregation in recipient patients. It was believed that the platelet aggregation was caused by a contaminating protein, which could be removed using the EMA PE. I do not recall whether researchers, other than Johnson's group at this stage were looking at using EMA PE to eliminate virus.

Please describe the polyelectrolyte fractionation research conducted by Speywood Laboratories:

a) Setting out your role and making reference to any collaborative work with any other organisations or researchers, including Blood Products

Laboratory (BPL) and the Royal Free Hospital.

13. The EMA PE, of which I had previous experience, must have been modified to enable Factor VIII to be eluted from the resin. I assume this would have been a reduction in percentage of the active groups to produce the resin designated PE5. I worked with PE5 to produce a high purity porcine Factor VIII.

14. I developed a production scale process using PE5 to recover Porcine factor VIII from a cold precipitate fraction (cryoprecipitate) of Porcine plasma. BPL became interested in the development of a more purified Human Factor VIII, using the PE5. Initially I don't think there was evidence of clearance of virus using this method, however it could have been hypothesised that this might be the case.

15. I was seconded to BPL in April 1980 and provided with laboratory space and reagents. The objective was to try to develop the method for purification of Human Factor VIII initially from cryoprecipitate but also from plasma. Despite my attempting to optimise the method, the yields of Factor VIII were not satisfactory one reason was that the protein was readily activated by thrombin if all other clotting factors could not be removed. The yield of Factor VIII was all important, as fresh frozen plasma was a finite source of Factor VIII, and supply which was blood donor dependent could have limited the amount of Factor VIII available. (BPLL0016007003)

16. Purely for research purposes a batch of Human Factor VIII was prepared using PE 5 for the purposes of a small clinical trial. The results showed that Factor VIIIC circulated in the presence of the so called Factor VIII related antigen, but in patients with Von Willebrand's disease (lacking the antigen) the circulation time was limited. (BPLL0016007_26)

17. In April 1981 I was seconded to the French National Blood Laboratory (CNTS) at Orsay, outside Paris. There I worked closely with Professor JP Allain, to try to prepare Human Factor VIII, using PE E5. The objective was to achieve a 30% yield in a final freeze- dried product. The results were rather variable as had been

experienced at BPL, the project lasted 2-3 months, and I do not recall whether any Factor VIII was ever prepared for Clinical trial at CNTS. (BPL006007_019)

18. Together with Dr Tuddenham and his team at the Royal Free Hospital, with the addition of powerful proteolytic inhibitors, the PE5 was used as the first step in the process for purification of Human factor VIII, with a view to achieving pure protein for sequencing. (HSOC0022968)

Please describe the polyelectrolyte fractionation research conducted by Speywood Laboratories:

b) Assessing the effectiveness, or potential effectiveness, of the polyelectrolyte fractionation method as developed by Speywood Laboratories in reducing the risk of transmission of hepatitis. See BPLL0016007_026.

19. A small-scale experiment was performed to look at clearance of Hepatitis virus. This work was performed with Professor Howard Thomas, in his laboratory at the Royal Free Hospital and I believe was independent of BPL. The results indicated that Hepatitis B was not absorbed to the PE 5 and not present in the Factor VIII eluted from the PE 5. (IPSN0000408_009, IPSN0000589)

Please describe the nature of the then Department of Health and Social Security/Department of Industry/the Government's involvement in the polyelectrolyte fractionation research, including financing.

20. Whilst there is evidence of grant funding, I suspect from the Welsh Development Agency, I do not recall this precisely, but was aware that Speywood had limited finances. I do not believe BPL supplied any finance but supplied me with laboratory space, reagents and cryoprecipitate. (IPSN0000232_001, DHSC0003936_027)

Please describe the events that precipitated the end of the collaborative work between BPL and Speywood.

21. I cannot recall what events precipitated the end of the collaboration between BPL and Speywood, but it's possible that BPL did not consider the PE E5 could be used to produce a viable Factor VIII product because of the low and variable yield.

To the best of your knowledge, why did Speywood's polyelectrolyte fractionation research not produce a commercial highly purified human Factor VIII or Factor IX product. See IPSN0000257_059, IPSN0000259_036 and IPSN0000021.

22. My experience with the use of EMA-PE for the recovery of Factor IX, was that Factor IX could already be produced using another anion exchange resin, the EMA-PE did not offer any advantages. As stated above, PFC, applied polyethylene glycol precipitation to their Factor IX product (DEFIX) produced using DEAE cellulose, to produce a product called Supernine which was used in some Factor IX deficient patients (PRSE0003799, PRSE0002353). Due to relatively low number of Factor IX deficient patients, and the fact that Factor IX could be recovered directly from plasma (as opposed to a cryoprecipitate fraction) yield of Factor IX was less of an issue. As stated previously (Supernine), a PEG precipitated FIX product was never licensed (PRSE0003349).

23. In 1980 the Speywood business plan, based on the success with Porcine Factor VIII, anticipated the success of using PE5 for the production of a highly purified Factor VIII. However subsequently the PE-E5 did not produce a consistently viable yield of Human Factor VIII. This might have been due to proteolytic activity which was destroying the Factor VIII activity, which could not be realistically prevented in the preparation of a therapeutic Factor VIII. (IPSN0000257_059, IPSN0000259_036)

24. In the Plan prepared in 1983 the original plan was condemned as unrealistic, an indication of the clash between the entrepreneurial and conventional approach to the development of novel Biopharmaceutical products in the UK. (IPSN0000021)

To the best of your knowledge, why were polyelectrolyte fractionation

processes not more widely adopted by UK public fractionators or international commercial fractionators in the 1980s.

25. Since 1940s almost all plasma fractionation was carried out using the Cohn process, which was based on ethanol precipitation. As such all processing had to be carried out at +5C or less to prevent protein denaturation but with the advantage of limiting bacterial growth during processing. Considerable investment had been made in a chilled processing plant, with appropriate Manufacturing and Product Licenses. Cohn Fractionation was developed in the first instance to produce albumin, and to a lesser extent immunoglobulin, subsequently coagulation factors needed to be recovered before the addition of ethanol. Certainly with respect to albumin and immunoglobulins, following investment in the cold process, it was unlikely that a new unvalidated fractionation process was going to produce an advantage, and it would have meant all product licenses would have had to have been resubmitted.

26. As stated previously Factor IX was already being produced using an ion exchange resin. Attempts to produce Human Factor VIII using PE E5 did not result in a satisfactory yield and Companies were starting to look at heat treatment to reduce virus contamination.

C. Recombinant Factor VIII

Please describe the recombinant Factor VIII research conducted by Speywood Laboratories, setting out your role and making reference to any collaborative work with any other organisations or researchers, including:

a) The initial 1981 UK-based research programme.

27. My role in the recombinant Factor VIII programme was only in terms of purification of Factor VIII using the PE E5. Professor Tuddenham had developed a purification process based on PE E5 as the first step to adsorb Factor VIII from cryoprecipitate. Subsequently the eluted Factor VIII was captured and eluted from at least one immobilised monoclonal antibody. As stated previously the purification process was carried out in the presence of powerful protease inhibitors.

28. Subsequently as I recall the protein was supplied to Dr Mike Waterfield, at ICRF and Professor George Brownlee at the University of Oxford for sequencing. Dr Waterfield was only able to put limited resource into sequencing, for Professor George Brownlee, apparently funding became an issue.

29. Dr Cox, University of Oxford, was looking to express the Factor VIII gene in yeast, maybe with hind-site this was never going to be effective, Factor VIII is a very large glycosylated protein.

Please describe the recombinant Factor VIII research conducted by Speywood Laboratories, setting out your role and making reference to any collaborative work with any other organisations or researchers, including:

b) The 1982 partnership with Professor Edward Tuddenham at the Royal Free Hospital and Genentech.

See HSOC0022968 and IPSN0000024.

30. From my recollection, and probably with hindsight the UK programme, other than the work carried out by Dr Tuddenham, was not going to be useful in development of the recombinant protein. It was certainly not going to be competitive with companies with the expertise and finance such as Genentech Inc.

To the best of your knowledge, why was the decision made to renegotiate Speywood Laboratories' agreement with Genentech, and in particular why was the prospect of manufacturing recombinant Factor VIII in the UK not pursued? See IPSN0000426_036, IPSN0000414_001 and IPSN0000442_042.

31. The agreement with Genentech was set up by David Heath together with Dr Tuddenham. I recall that David Heath was sufficiently astute to specify, that should production need to be carried out using mammalian cell culture, then Speywood would receive the right to manufacture recombinant Factor VIII in the UK.

32. David Heath was an entrepreneurial business man, he was very astute, but not strong on the management front. He expected those about him to drive forward his ideas, with the exception of Dr Tuddenham's team not always successfully.

33. David Heath clearly had the vision to see the potential for the recombinant Factor VIII, and also was able to determine that Genentech Inc, had the resource and expertise to do this. However, money in Speywood was an issue, and there was clearly a clash between David's vision, and the more risk averse individuals who believed that Speywood should become profit making before indulging in what was regarded as "Blue sky "research. It was presumably because of this approach that the decision was made to trade off the manufacturing rights for recombinant Factor VIII in exchange for market territories.

D. Financing of research and development

To the best of your knowledge, please comment on how Speywood's financial difficulties impacted its research and development programmes, with reference to:

a) The sources of funding that were pursued.

b) The role of British Technology Group and Prutec.

c) The outcomes of the highly purified Factor VIII and recombinant Factor VIII programmes.

See IPSN0000426_036.

34. The development of a recombinant Factor VIII a project initiated by David Heath was regarded as very high risk. At the time very few if any recombinant proteins were being developed in the UK and the structure of Factor VIII protein was not known. Present in plasma at very low levels it was estimated that 2kg of recombinant protein would be sufficient to supply the world market for Factor VIII.

35. Factor VIII derived from blood was a specialist area very different from conventional pharmaceuticals in terms of marketing. Speywood Laboratories, had limited finances and it is my belief that British Technology Group and Prutec were uncomfortable with David Heath's approach, they being too risk averse and

consequently requiring unrealistic very short-term profits. This was the culture of Venture capital at the time.

36. Unfortunately, in order to attract funding there was a tendency to underfund project proposals with over optimistic milestones which were not met. Only because of Genentech in the US, was the programme to be successful. (IPS0000426_036, IPSN0000442_042)

E. Porcine Factor VIII - Hyate:C

Please describe the porcine Factor VIII research and product development conducted by Speywood Laboratories, setting out your role and making reference to any collaborative work with any other organisations or researchers.

37. Due to my experience with Alan Johnson's programme I was responsible initially for developing the Hyate:C process and analysis. In 1980-1981 I was seconded to other laboratories BPL and CNTS, to work on Human factor VIII, and had little involvement in plans to build a manufacturing facility for producing Hyate:C. Working with Porcine abattoir blood, this in itself being a challenge for a regulatory authority. (IPSN000232_001, DHSC0003936_27, IPSN0000378_001)

38. Clearly by 1984 the focus was on selling Speywood, with the emphasis on sales of Hyate:C, I left the Company just prior to the Company being taken over by Porton International.

To the best of your knowledge, why were indications for use of Hyate:C in the 1980s not expanded beyond inhibitor patients.

39. The product proved to be very successful for the treatment of patients with an inhibitor to Human factor VIII. However in spite of ambitions to use the product in non -inhibitor patients the risk of developing antibodies to the porcine Factor VIII with the potential for cross reactivity with human protein was regarded as a

limitation to its use and certainly in patients in which there was no inhibitor present. (IPSN000528, IPSN0000133_0133, IPSN0000057_071)

Section 3: Other Issues

40. From 1969-1987 I was involved with development of clotting factor concentrates for the treatment of Haemophilia A (Factor VIII deficiency) and Haemophilia B (Factor IX deficiency). My first task at PFC was with Dr Jim Smith to make a concentrated fraction of the proteins, for patient treatments. Prior to this, plasma and single donor cryoprecipitate were the only available treatments, patients at this stage often suffering chronic problems due to bleeding into the joints. Availability of Factor concentrates was a very significant improvement in treatment.

41. Subsequently of course virus contamination, resulting from the use of large pools of donor blood became an issue. Furthermore development of sufficiently sensitive assays for contaminating viruses needed to be developed.

42. Clearly as soon as the virus contamination became apparent, then methods, were initiated for removing viruses. Such work required parallel development of sensitive assays at the time.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed GRO-C

Dated 14/04/2021