Witness Name: Cees Th. Smit Sibinga
Statement No.: WITN6412001
Exhibits:WITN6412002 - 004
Dated: 07 October 2021

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF CEES TH. SMIT SIBINGA

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 25 May 2021.

I, Professor Cees Th. Smit Sibinga, MD, PhD, FRCP Edin, FRCPath, will say as follows: -

Section 1: Background and Professional History

1. My qualifications and experience are set out in **Exhibit WITN6412002.**

2. I have been involved in a 1998 Civil litigation in Groningen in relation to HIV infection of a Haemophilia A patient, who was infected by needle sharing and use of a commercial concentrate injected in Luxemburg during a holiday. My involvement was two-fold: firstly as a haemophilia treatment expert, and secondly as a responsible producer of small pool (units of one to six donations) wet cryoprecipitate and later the small pool (12-24 units) freeze dried and heat treated cryoprecipitate.

Section 2: Blood and Blood Products in the Netherlands 1970-1991:

Knowledge of risks of transmission of HBV, HIV AND HCV- blood products

3. Hepatitis B (HBV) transmission became known globally in the late 1960s, before testing was routinely introduced. That was during my residency (1966-1970) at the University Medical Centre of Groningen. Initially gel immunoelectrophoresis was used for testing, but this was later followed by a radioactive isotope test (RIA).

4. Human Immunodeficiency Virus (HIV) transmission risk became known soon after the discovery and outbreak of HIV in the early 1980s. In particular haemophilia patients (in the USA, UK) became infected through the use of large pool commercial clotting factor concentrates. That was during my regional blood bank employment in Groningen where I held the position of Medical Director from 1976 (until 2001).

5. Hepatitis C (HCV) transmission became understood when the virus was discovered in the late 1980s, early 1990s. Before that period we knew about the risks of transmission of non-A non-B hepatitis (NANB, later known as HCV)- the information came to life during my residency in Groningen (1960s).

6. The Dutch Haemophilia Treaters (Paediatricians and Haematologists) were united in an informal consortium that met at regular intervals at the National Haemophilia Centre in Huizen (van Crefeld clinic) to discuss treatment issues and the need to change policies to prevent transmissible infections. HBV was not so much a problem, but non-A non-B (HCV) was, and particularly HIV transmission in the early days when testing was not yet available at the many small hospital-based blood banks, although there was a well-recognized risk.

7. The Dutch blood bank directors [a mix of medical (largely general, microbiologists and a few clinical specialists, and pharmaceutically qualified (hospital pharmacists) people and one veterinarian] met regularly to exchange ideas, information and practices including in the 1980s regarding the HIV/AIDS policy and strategies.

8. Internationally, the annual Groningen Symposia on Blood Transfusion which I started in 1976 and lasted until 2004 (upon my retirement from the position of Medical Director) provided in a structured and scientific way information on current development on risks of infection through the use of blood products and plasma derived medicinal products (PDMPs). The faculties of these symposia consisted of a carefully selected number of international experts, including Dutch and foreign (UK, USA, France, Scandinavia, Germany, Switzerland, Italy) experts, and were attended by almost all Dutch blood bank senior staff and a mass of international colleagues from all over the world. I can recall the selection of British experts invited to attend: among others, Prof. J.D. Cash, Prof. P.L. Mollison, C.M. Lockwood, Prof. J.O. Forfar, J.W. Lockyer, M.M. Kerr, T.L. Turner, N.R.C. Robertson, C.A, Holman, M. Brozovic, P. Jones, J.L. Prothero, W.L. Marsh, R.J. Crawford, W.L. Ford, J.M. Goldman, R.F.M Wood, B.P. Griffith, H.H. Gunson, J.K. Smith, C.V. Prowse, P.R. Foster, S.M. Middleton, P.B.A. Kernoff, P.S. Skinner, B. Brozovic, D. Voak, K. High, T.J. Hamblin, J.A.J. Barbara, R.V. McIntosh, T.W. Barrowcliffe, C.R.M. Hay, W. Wagstaff, S.J. Urbaniak, C.A. Ludlam, P.L. Yap, E.J. Lee, D.B.L. McClelland, I.R. Peake, D.J. Anstee, D.E. Onions, M.L. Kavanagh, M.L. Turner, A.J. Barrett, S.R. Solomon.

9. Since 1977, the science has been documented in proceedings. These proceedings were initially published locally in The Netherlands (1977, 1978 and 1979) but since 1980 by Martinus Nijhoff Publishers, Kluwer Academic Publishers and Springer. The curricula were comprehensive, always ending with a clinical session and were focused on new developments and the horizon of science. A major driving motive was contributing to science-based development of transfusion medicine including the emergence and discovery of the risks of infection and immunologic effects through the use of blood products in the Netherlands and beyond, in both a national and international context.

10. The growing library of proceedings of the annual international symposia in Groningen became a source and reference for many blood bank professionals, nationally and internationally.

Risks of infection- domestic and imported products

11. There were differences in opinions and practices in The Netherlands between 1970 and 1991 on risks of infection through the use of domestic and imported products, because of the fragmentation of the blood supply.

12. The Groningen regional blood bank was more advanced (AABB associate institutional member since 1979 and accredited since 1981), introduced a quality assurance system and practiced a policy of more careful donor selection, standardized processing and testing, and had developed a strong clinical interface focused on patient safety and efficacy of physiologically potent blood products.

13. All (100%) collected blood was processed into its components. Our domestic products, in particular the cryoprecipitate, was preferred by the haemophilia treating clinicians (Paediatricians and Haematologists) over the available commercial concentrates. Cryoprecipitate was preferred because of traceability. This was because of the small pool of known and well-selected donors and the quality testing in our own Blood Centre Laboratory. This changed in the second half of the 1980s when heat treated and monoclonal products became available. The reason for this change was because we were developing a freeze dry and heat treatment procedure for our local small pool cryoprecipitate when the HIV/AIDS pandemic broke out but that was not yet ready for clinical use. However, we had access (our international network) to the early Hyland heat treated product and later to recombinant Factor VIII concentrate.

Risk reduction measures

14. In 1983, the Federation of Dutch Red Cross Blood Banks was created in order to harmonize policies and practices of the then 23 local and regional blood banks. During the meetings I had my share in the discussions, discussing the gaps and problems present and emerging at the national level. The

Federation met four times per year (all blood banks were represented by their director and a board member) which I had attended systematically. During the meetings I had my share in the discussions and decision-making especially in matters of quality, standardization, inspection and accreditation, haemovigilance, and prevention and mitigation of risks of blood transfusion.

15. At these meetings, whilst representing the Groningen regional blood bank (AABB accredited since 1981) and following the AABB Standards for Blood Banks and Transfusion Services at that time, I continuously stressed the importance of uniformity through national standards and a national Inspection and Accreditation system. As a result, the Federation of Dutch Red Cross Blood Banks requested me to organize and implement such a system, which I did. As of 1990, a national Inspection and Accreditation programme became operational of which I was appointed as the first national coordinator.

16. Regarding risk reduction, the Groningen regional blood bank practised small pool principles for cryoprecipitate (one to four donations). The University Hospital Pharmacy started producing wet frozen small pool cryoprecipitate as early as 1967 – glass bottles (open), no quality control, pooling in a laminar flow hood (LFH) which was in a basement room with an open window. The LFH was switched on just before the pooling started, with no control over particle density. Since May 1976, when I started the new Regional Blood Centre, we changed this poor practice to cGMP principles in multiple closed bag systems, all wet cryoprecipitate that was mechanically snap frozen at -50°C and stored at the same low temperature, well below the eutectic point of cryoprecipitate. Before clinical use the frozen packs were thawed (in an overwrap) in a water bath with circulating disinfected water at 37°C and transfused.

17. The Groningen regional blood bank started the development of heat treatment in 1985 in close collaboration with the Dutch RIVM (the Dutch CDC), the Scottish National Fractionation Centre (Dr. Peter Foster) and the University of Groningen Department of Biochemistry (Professor Max Gruber). The technology which was developed became operational in 1988. However, as a

national policy (implemented in 1990) the government ordered a stop of the cryoprecipitate production and treatment of haemophilia patients with the domestic small pool cryoprecipitate, leading to a blockade of our local freeze dried heat treated small pool cryoprecipitate production for the northern haemophilia group of patients. The stop of the cryoprecipitate production was ordered for precautionary reasons. The blood supply in those days was still highly fragmented and not all in the country were of acceptable operational quality.

18. Regarding donor selection, before May 1976, potential donors were massively called for selection during early evenings which was pretty primitive, and weeks to months later called for blood donation. That was changed as of May 1976 when I started with the new Regional Blood Centre for two provinces in the northern part of the country- Groningen and Drenthe. Selection then was done individually following a written donor selection form, with informed consent from the donor and a signature of the selecting personnel. Selection of the donor was done immediately before the actual donation. We followed the WHO and AABB recommendations in this donor selection process.

19. In 1984 we started with focused donor information on the risks of HIV transmission and personal risk behaviour. The donor questionnaire was redesigned with a series of risk behaviour questions, donor attendants were trained, and donors were motivated to confidentially self-exclude.

20. On the hospital side, we introduced the principles of lookback in case of a potentially infectious donor. Issued products from previous donations were traced back for patient safety reasons as well as for donor exclusion. This lookback was formally introduced by the Ministry of Health in 1985 as a mandatory procedure in relation to HIV.

Preferred haemophilia treatment approach

21. In general, home treatment started in Groningen around 1970 using frozen cryoprecipitate. Family doctors were trained on how to store, thaw and infuse

cryoprecipitate. When high purity commercial products came on the market, home treatment was continued using these concentrates. When commercial heat treatment was introduced and registered as a viral load reducing/inactivating treatment of freeze dried concentrates, products from Baxter and Armour were used for home treatment of adult patients. The paediatric patients (so called pups) were treated with our domestic cryoprecipitate, which was improved using heparin as an anticoagulant. In the beginning, this was frozen cryoprecipitate, thawed for infusion. Then came our improved small pool 'super cryoprecipitate', freeze dried and later heat treated.

22. In 1979 we, the Dutch Haemophilia Treaters, the Dutch Society of Haemophiliacs- Northern Division and my Regional Blood Centre, organized an international workshop on haemophilia in Groningen discussing 'home-treatment for haemophilia: perspectives and limitations'. Logistic support was provided by the Hyland Therapeutic Division of Travenol Laboratories Ltd. The use of cryoprecipitate at home was discussed at these proceedings with the patients and the Northern branch of the National Society of Haemophilia Patients (NVHP). We discussed the technical and comfort of life details – no travel, back to work/school, less loss of time before treatment. We all agreed to this change in treatment logistics especially for the prophylaxis. Family doctors were trained and supplied. The approach was studied and copied by the Irish Dublin Haemophilia Treatment Centre (Dr. Ian Temperley). The proceedings provide some good answers to the Inquiry questions.

23. Home treatment was not affected by the HIV/AIDS outbreak. The contact with the two manufacturers was intensified and detailed production information came along with each batch we received, well documented to be able to trace back in case of a suspected adverse event or infection. The Groningen Haemophilia Centre and Regional Blood Centre served as a model and reference, both nationally and increasingly internationally to which the annual international symposia and the published proceedings contributed substantially.

24. For various and obvious reasons e.g., quality of treatment (patient care), standardized production/manufacturing of products ('super cryoprecipitate') and the evidence-based and educational approach, the blood bank became in 1993 a formal World Hemophilia Federation collaborating and training centre (HTC). The same year also, WHO selected the Blood Centre as the first Dutch formal collaborating centre for blood transfusion. These assignments were important because they were a positive sign of recognition boosting the morale of all involved, and provided us with a wealth of information, besides the ongoing annual international symposia.

Section 3: Cryoprecipitate

25. In the 1970s, an international debate started on the optimal use of human blood and plasma for clinical haemotherapy purposes (component therapy). Pharmaceutical industries had developed more advanced technologies to recover and purify Factor VIII starting from the Cohn fractionation principle. However, the yield was extremely low, requiring large pools of plasma to be fractionated. To gain access to large quantities of plasma, commercial (paid) plasma collection using machine apheresis was initiated in the US and Europe. Key questions to be asked and answered in the perspective of self-sufficiency (blood and blood products including plasma derived medicinal product e.g., albumin, clotting factors, immunoglobulins) of a nation, were:

    a. What is the number of haemophilia patients in the population?
    b. What is the minimum effective dose necessary for haemostatic effects?
    c. What type of concentrates should be used; their yield from plasma and their costs (affordability)?

Development of super cryoprecipitate

26. Cryoprecipitate (the fraction of cold insoluble globulins or CIGs) remained the mainstay in haemostatic therapy in haemophiliacs in the Netherlands (type A, Factor VIII or anti-haemophilic factor/AHF deficiency) because of its relative high yield (around 30-40%), its ease of preparation and its low cost

(affordability). However, the purity (Factor VIII over Total Protein) is low compared to the commercial fractionation product. The recovery of FVIII from plasma depends on a series of conditions: anticoagulant and preservative used to collect blood and/or plasma; the time between collection and processing; the method of separation of plasma after centrifugation; the temperature conditions of freezing; the temperature conditions of storage; the thawing condition. Each of these conditions should be optimal and standardized, adhering to written up-to-date evidence-based protocols.

27. We, the Research Laboratory of the Groningen Regional Blood Centre, initiated in the 1970s and 1980s a project based on methods and technologies that showed consistently improved results in final yield and purity of Factor VIII in each of the listed steps of cryoprecipitate preparation, which was published in the international peer reviewed literature and presented at international and national scientific meetings (symposia, congresses).

28. In terms of our approach, research was done stepwise leading to a prototype of 'high yield' intermediate purity cryoprecipitate. Our findings are set out below:

    a. We discovered that collecting blood and plasma in heparin instead of citrate and the use of phosphate and dextrose instead of the original acidified dextrose preservative had a significant improvement in Factor VIII recovery;
    b. The plasma is squeezed off into one of two tubing connected satellite bags allowing a small amount of plasma to enter the connecting tubing (tail) which is then clamped-off;
    c. Snap freezing the plasma in a circulating dry ice methanol freezing bath (-50 to -70°C) showed a minimal loss of Factor VIII after storage well below the eutectic point of plasma (-23°C) at temperatures below -50°C;
    d. Thawing method was changed using a circulating water (melting ice) bath at 0-4°C. The plasma bag is at the long side folded over by two elastic bands to allow a constant pressure while syphoning the plasma

over in the empty satellite bag till about 30 ml of precipitate is left in the plasma bag;

e. The precipitate is then re-snap frozen and stored (see step C);
f. Additionally, standardized Factor VIII assay using plasma and cryoprecipitate reference samples.

29. The final recovery of this method was consistently 70-80%. Over time, we improved on the details, developing an upscaling for clinical use.

30. The next step was the development of a freeze-drying procedure. In 1981 we started the development of a freeze-drying method for the advanced cryoprecipitate. The method became operational by 1983.

31. In 1985 we started the research and development of a heat treatment method of the freeze-dried small pool super cryoprecipitate which was finalized in 1987 and in 1988 and 1989 clinically evaluated in paediatric patients. There were no adverse events reported and the clinical recovery and half-life of Factor VIII did not differ from commercial high purity products.

32. The heat treatment procedure had a minimum loss of Factor VIII using low concentration (2%) sucrose and heating (68°C) for 48 hours in the freeze-dried state was adopted. The vials of freeze dried and heat-treated cryoprecipitate contained between 280 and 390 IU Factor VIII dissolved in 10ml sterile distilled water. The contents were derived from pools of 12 to 24 blood donations. We calculated that about 25-30% of all whole blood collections would be processed into cryoprecipitate (local FVIII product) leaving 50-55% fresh plasma for fractionation and 15-20% for platelet production.

33. During the second half of the 1970s and in the 1980s, the developments were exposed to international peer review through presentations at symposia and congresses and publishing in international peer reviewed journals. In particular, in 1981 a special workshop on 'Development systems for efficient separation of Factor VIII from human fresh frozen plasma' was conducted in

Groningen. Proceedings were published (1982, ISBN 90-6626-007-6) edited by R.S. Lane (Elstree, UK), G.A. Rock (Ottawa, CA) and me.

34. Given the significant improvement of yield and purity of the super cryoprecipitate (small pool, freeze dried and heat treated) we aimed for scaling up in order to accommodate our haemophilia patients. However, because of the commercial production and marketing of heat treated (Hemofil T®) and monoclonal Factor VIII (Hemofil M®), the haemophilia treaters decided to change policy (reducing infection risks) and started using monoclonal products for haemophilia treatment. The production of small pool super cryoprecipitate, freeze dried and heat treated was continued for use in traumatology, surgery and obstetrics.

Section 4: Annual Symposium on Blood Transfusion - Groningen Meetings:

Summary of annual symposium about blood transfusion- 1976 to 1991

35. The scientific annual symposia was spread over three days and were well attended, in particular by the Dutch blood bank and transfusion community, bringing top of the bill and cutting-edge science presented by well-recognized, international expert scientists, without the need to travel large distances. They were highly appreciated nationally and internationally and contributed to the development of transfusion medicine vein-to-vein in The Netherlands and far beyond in the world. The annual symposia were conducted between 1976 and 2004 – 28 all together in a row. The Proceedings, with peer-reviewed manuscripts of the presentations and recorded and edited discussions, have shown to be precious resources of transfusion medicine science and its development over almost three decades. A chronology of the themes discussed and chairs over these 28 years is attached for your convenience and information. (**Exhibit WITN6412003**)

36. All annual symposia focussed not only on state of the art knowledge but in particular on what is on the horizon. The blood supply and transfusion practices have long been in a Cinderella position where the science was

heavily skewed towards the laboratory bench and test tube, rather than focusing on patient needs and treatment. The series of symposia I organized followed two alternating thematic main streams of knowledge, bringing the principles of knowledge economy in practice:

a. the operational aspects and approaches;
b. the immunological aspects and potential.

37. Each symposium highlighted the clinical application and benefits to patient treatment and care. By exploring the scientific and operational horizon, quite often brand new developments, not yet earlier published or presented, came to life during these symposia and the lively discussions. Often challenging and tickling questions were asked, leading to lively responses and exchanges of ideas and scientific philosophies. The details that came to the surface during these discussions were captured and published as an integral part of these scientific transfusion medicine events.

38. In 1983, the late Professor H.O. Nieweg, clinical haematologist at the University of Groningen Medical Centre and in charge of the Haemophilia Centre, attended a symposium on haemophilia care in the USA, where he met Dr. B.J. Gerety from the then US Office of Biologics Research and Review, Bethesda, MD. During this symposium, Dr. Shanbrom reported the successful effects of heat treatment of commercial Factor VIII concentrates on Non-A Non-B hepatitis in Chimpanzees. Upon Professor Nieweg's return, he informed me and discussed the pros and cons of using this commercial heat-treated product for home treatment of the adult haemophilia patients and asked me to order the product. He started, soon after his return, and after careful consultation of the haemophilia treaters in the northern Netherlands, the patients and the Medical Advisory Board of my blood bank, with heat-treated Factor VIII concentrate from Baxter. Among this cohort, we have not seen any transmission since then.

39. In 1984, in the presentation and following discussions during the ninth symposium by Dr. B.J. Gerety and J.M. Jason from the CDC, Atlanta, GA. Dr.

Gerety reported on the application of heat (60°C for 10 hours) to eliminate HBV and the then Non-A Non-B agent (HCV).

40. As usual, the information was picked up by few attendees, even after the proceedings were published after 9 months. However, we used the information as a legitimate starting point for our own heat treatment development as described above. Even the leadership of the Dutch Red Cross Central Laboratory for Blood Transfusion did not express interest, but exposed their criticism of our research efforts. The information (immediate and through the proceedings (see list of references- **Exhibit WITN6412003** and **Exhibit WITN6412004**) was used for local development and improvement of blood bank and transfusion operations and practices. Individually there is always the need for an open-mindedness and receptibility to perceive messages such that they will be digested and translated intellectually to generate action. Not every attendee came with sufficient intellectual development to be able to transform the information into action, besides the environmental barriers (e.g., position, operational climate, local circumstances and state of development). The series of books (proceedings) is still actively used in many developing situations. I experience that as a gift as they are highly appreciated by each and every colleague in the low- and middle- income countries (LMICs) and have spread all over the world.

41. The symposia of 1982, 1993, 1995, 1997 and 1998 brought new concepts in quality management to the notice and contributed to implementation in a number of prominent blood centres in Scandinavia, mainland Europe (e.g., France, Italy, Austria, Germany, Ireland) and also the UK, Brazil, South Africa.

42. Specific new developments presented and discussed were e.g. apheresis technology; cryopreservation of platelets and stem cells; bacterial surveillance; error policy and management; rDNA technology to engineer proteins like Factor VIII; heat treatment and pathogen reduction; minimal lesion in haemato-oncology; artificial intelligence and smart card application in donor management; immunoaffinity technology for Factor VIII purification; ECMO in neonatology; vitrification of organs (ice-free preservation); impact of

biotechnology, growth factors and bioengineering; immune targeting and the conditioning of lymphocytes; potential of gene therapy and cellular engineering; evidence based transfusion practice and alternative approaches; early development of Patient Blood Management (PBM) and principles of haemovigilance; risk management and new test technologies (NAT). Selected attendees from a variety of countries took the messages back home and used the proceedings (published with inclusion of the edited discussion) as a reference and 'guideline' for science-based development.

43. Since 1997 almost all symposia were formally supported and endorsed by WHO, EU, Council of Europe and International Society of Blood Transfusion (ISBT). As of 1994 the symposia were CME and CPD approved, which served as a proof of quality and attracted more attendees.

Section 5: Work in Edinburgh

44. Following my appointment at the end of 1975 as a medical director of a new-to-establish regional blood centre for two Provinces (Groningen and Drenthe) in the north of the Netherlands, I realized that I was not really equipped to run such a regional centre, being educated as a clinical haematologist. I was supposed to start my new career in May 1976 and decided to have myself educated and trained in blood banking and blood transfusion by three good colleagues in the UK (Edinburgh), USA (Albany) and Strasbourg (France). All three were running a regional blood centre of the economy of scale of what I was charged and intended to establish in Groningen, serving 13 hospitals (2 tertiary and 11 secondary/referral).

45. In the beginning of 1976, I spent 6 weeks in Edinburgh at the Edinburgh and Southeast Scotland Blood Bank by invitation of the late Dr. John D. Cash (medical director), whom I knew from the scientific field of blood coagulation and microcirculation. We were close friends. He provided me with a tailor-made education and training in management and operations of a regional blood centre vein-to-vein and from the lowest to the highest rank. Through Dr. Cash I came in contact with the Royal College of Physicians of Edinburgh.

Over the decades we kept a close personal and professional contact, as I did with the other two mentors – the late Dr. A.F.H. Britten (Albany upstate New York, USA) and Dr. Jean-Paul Casenave (Strasbourg, France).

46. All three were not only good blood bank managers but even more excellent and innovative thinkers and scientists. Through them and their attitudes I developed from the beginning research and education as paramount elements for improvement.

47. Key principles have always been team work, curiosity, an open mind, evidence, quality and building a science oriented network, thinking and practising 'out of the box'.

Statement of Truth

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

Signed GRO-C

Dated 07 October 2021