SCHIFF

STATEMENT OF EXPERT EVIDENCE

A. Dr. Peter Schiff,
Executive Director, Blood Products Division,
Commonwealth Serum Laboratories,
45 Poplar Road,
Parkville.

Bachelor of Medicine, Bachelor of Science in Medicine, Doctor of Philosophy in Biochemistry and Fellow of the Australasian Colleges of Pathologists and Physicians.

Employed at Commonwealth Serum Laboratories in the Blood Products Division since 1966 with a special interest in haematology, especially in the clinical use of plasma derived blood products.

B. SUBSTANCE OF EVIDENCE

The Production of Factor VIII

1. CSL receives frozen plasma from the Red Cross throughout Australia. The frozen plasma is thawed and pooled into a large container.

2. In 1980, approximately 150 litres of plasma was used per production run for Factor VIII. In 1985, this was increased to approximately 300 litres and in 1989, to approximately 600 litres.

3. On average, it requires approximately five

donations to produce 1 litre. Accordingly in 1989, a production run of 600 litres could have used up to 2500 to 3000 donations.

4. Once pooled, the plasma is then slow thawed at approximately 0 degrees centigrade. This allows the Factor VIII to be concentrated in the cryoprecipitate.

Factor VIII Production in 1985

5. In early 1985, the Margolis method was the method then used to produce Factor VIII. The Margolis method consists of FVIII in the cryoprecipitate being filtered through controlled pore glass. This involves cryoprecipitate being filtered through a tube containing glass beads which have the effect of separating the Factor VIII from the cryoprecipitate and other impurities in the cryoprecipitate.

6. The concentrate is then put through a sterilizing filtration membrane and then put into sterilized containers. The material is then freeze dried and then heated in dry air ovens for 72 hours at 60 degrees centigrade.

7. The finished product is then quality control

tested for impurities, sterility, potency and purity.

Factor VIII Production Between 1980 and 1983

8. The method used prior to the Margolis method was the Johnson-Wickerhauser method as modified by Smith.

9. Under this method, a tris buffer solution is used to extract the cryoprecipitate. The Factor VIII is solubilized into the tris buffer. The tris buffer that now contains the dissolved Factor VIII is then put through a second cold precipitation process to remove impurities.

10. The Factor VIII that is contained in the tris buffer solution is absorbed onto aluminium hydroxide. This is then passed through sterilizing filter membranes and dispensed into the final containers, freeze dried and then sealed for dispatch.

The State of Knowledge in CSL about AIDS between 1980 to 1984

11. I first became aware of reports of some strange new disease as yet unidentified in approximately March of 1982. This was at a meeting of the Australian Society for Infectious Diseases at which

an American expert in infectious diseases raised a number of cases concerning homosexual men, who had contracted some infectious disease as yet unidentified. This expert did not know the cause of the disease nor the method of transmission. At this time, this expert suspected that the disease was transmittable between people, however, he did not have any information as to the method of transmission.

12. In July 1982, an article was published in the Morbidity and Mortality Weekly Report which first described the association of haemophilia and AIDS. This publication was made in the United States. This article was significant in that it was the first published article which suggested that AIDS may be transmitted through blood or blood products. This article would have been received by CSL sometime in August 1982 and would have been circulated amongst certain members of staff. The contents of the article did not cause any particular alarm at CSL, because staff at CSL did not believe that AIDS was a problem as yet identified in Australia.

13. CSL then received a further article from the Morbidity and Mortality Weekly Report dated 4 March 1983. This article would have been received sometime in late March or early April. This article is headed "Prevention of Acquired Immune Deficiency

Syndrome: Report of Inter-Agency Recommendations". Page 102 recommends that the following actions be taken:

(a) That as a temporary measure, members of groups at increased risk of AIDS should refrain from donating plasma and/or blood.

(b) Centres for blood donation should inform potential donors of this recommendation.

(c) The Food and Drug Administration (FDA) is noted as preparing new recommendations for manufacturers of plasma derivatives and for establishments collecting plasma or blood.

(d) That studies should be conducted to evaluate screening procedures for their effectiveness in identifying and excluding plasma and blood with a high probability of transmitting AIDS. These procedures should include specific laboratory tests as well as careful histories and physical examinations of donors.

(e) That physicians should adhere strictly to

medical indications for transfusions and autologous blood transfusions are encouraged. The final recommendation of the article is that work should continue towards development of safer blood products for use by haemophilia patients.

(f) The article noted that the National Haemophilia Foundation has made specific recommendations for management of patients with haemophilia and these recommendations were not spelt out in the article; only referred to in Reference Number 17 of the article.

(g) The article then concludes by stating that as long as the cause of AIDS remains unknown, the ability to understand the natural history of AIDS and to undertake preventative methods is somewhat compromised.

14. To the best of my knowledge, this article was not discussed at any meetings at CSL nor any action taken that specifically related to the recommendations of the article. Reason: The occurrence of AIDS in recipients of blood or blood products had not been described in Australia.

15. On 27 May 1983, the Red Cross Working Party on Factor VIII and Factor IX Concentrates recommends that Blood Transfusion Services not collect or use blood from persons with symptoms of AIDS. This presumably was implemented by the various Red Cross Divisions, but I am unaware of the date(s) on which this action commenced. At this meeting, the sterilization of Factor VIII and Factor IX concentrates was discussed; this was mainly in the context of sterilization for hepatitis. Dr. Margolis noted that approximately 50 per cent of the activity of the concentrates was lost by the Hyland sterilization process.

16. In relation to AIDS, the Working Party noted that the number of people contracting AIDS was likely to increase rapidly. The Committee noted various copies of memoranda to manufacturers of plasma products and collectors of blood emanating from the FDA in the United States. The meeting also referred to a letter from the Department of Health. From these documents, it was decided that the Working Party propose that the Blood Transfusion Services should not collect or use blood from persons with symptoms and signs suggestive of AIDS nor from sexually active homosexual or bisexual men with multiple partners nor from present or past abusers of intravenous drugs, nor from sexual partners of persons in the above categories.

Again, I have no knowledge of when these recommendations were put into effect by the Red Cross Divisions. Until specific laboratory tests for AIDS became available, the Working Party consider that the above measures should be taken to protect recipients of blood and blood products.

17. In a news release by the National Health and Medical Research Council dated 9 June 1983, the following paragraph appears:

> "Unlike the US, there have been no cases reported in recipients of blood or blood products. There is little likelihood of spread by this means to Australia and within it as we rely entirely on voluntary systems of blood donation and do not have the need of many countries to import a range of blood products. Steps have already been taken to exclude potential blood donors who may constitute a risk".

18. This new release simply underlines the belief of CSL staff at the time that because of Australia's isolated position and given Australia's system of voluntary blood donation, there was a reduced likelihood of the spread of AIDS.

19. By recommendation dated 14 January 1983, the National Haemophilia Foundation set out a number of recommendations to prevent AIDS in patients with

haemophilia. The recommendations for physicians treating patients with haemophilia included the use of cryoprecipitate to be used in preference to other forms of treatment including patients with clinically mild haemophilia who require infrequent treatment. Cryoprecipitate was to be preferred over Factor VIII for haemophilia A patients. In relation to recommendations to Factor VIII concentrate manufacturers, the Foundation recommends that serious efforts should be made to exclude donors that might transmit AIDS. These recommendations would include: identification by direct questioning of high risk groups, evaluation and implementation of surrogate laboratory testing that would identify individuals at high risk of AIDS transmission and finally, manufacturers of Factor VIII should cease using plasma obtained from donor centres that draw from population groups in which there is a significant AIDS incidence. The latter did not appear to be relevant to CSL at that time, since in January 1983, only one or two AIDS cases had been identified in Australia and there was no evidence of any risk to the blood supply. There were various other minor recommendations to do with the processing of plasma and the production of Factor VIII concentrate. However, there were no suggestions of any tests or screening mechanisms being available. One recommendation suggested that efforts should be continued to expedite the

development of a processing method that will inactivate the AIDS virus potentially present in Factor VIII concentrates. No such process was apparently yet available.

20. These recommendations were repeated in a Haemophilia Information Exchange AIDS Update Medical Bulletin No. 9 which referred to recommendations dated 22 October 1983.

21. In relation to both of the above recommendations, CSL did not institute any new testing or screening procedures. These procedures were already in place as a result of previous meetings and related mainly to the screening of blood donors by the Blood Transfusion Services.

22. By newsletter dated 2 December 1983, the Morbidity and Mortality Weekly Report stated that although the aetiology of AIDS remains unknown, the epidemiologic evidence suggests that it can be spread by blood or blood products.

23. In a meeting of the Blood Transfusion Service Executive Sub-Committee in Canberra on 23 to 24 February, it was noted that pilot tests were to be conducted on Factor VIII concentrate to reduce the risk of hepatitis. This involved heating the Factor VIII concentrate. This heating presently

results in a 40% loss of Factor VIII activity and yield.

24. Montagnier's group in Paris described a retrovirus associated with AIDS which they termed LAV (lymphadenopathy-associated virus) in late 1983. In a statement by the Secretary of Health and Human Services in the United States dated 23 April 1984, it was announced that a probable cause of AIDS had been found and that a blood test for the AIDS virus could be expected to be available in approximately six months. It was hoped that this test would ensure that blood from transfusions was free from the AIDS virus.

25. In Science Volume 224 published 4 May 1984, four papers were published describing the discovery and isolation of a virus believed to be responsible for the cause of AIDS and designated HTLV-III.

26. By letter dated 11 October 1984, I described my visit to the Centers for Disease Control in Atlanta in the United States. The Center was having some success with the heat treatment of Factor VIII concentrate in apparently inactivating the AIDS virus. Apparently, the virus is very sensitive to heat. I arranged for some CSL product to be sent to Atlanta for testing under this method.

27. On 18 October 1984, a meeting of the National Blood Transfusion Committee's AIDS Working Group decided that the sterilization of Factor VIII concentrate should be considered an urgent matter and a decision was made that CSL should introduce heat sterilization as a matter of urgency.

28. In the Morbidity and Mortality Weekly Report dated 26 October 1984, it was noted that the National Haemophilia Foundation in the United States recommended that heat treated coagulation concentrates should be used in preference to non heat treated concentrates with the understanding that protection against AIDS is not yet proven with such a method.

29. In a report of the Department of Health on heat treatment of Factor VIII dated 2 November 1984, it was recommended that heat treatment of Factor VIII concentrate be carried out at 60 degrees centigrade for 72 hours and implemented immediately. Stocks of the lower purity Factor VIII concentrate were to be withdrawn for heat treatment. Production of standard Factor VIII concentrate was terminated at 2 November 1984 and all remaining existing stocks at CSL were withdrawn from issue pending further studies. With immediate effect, i.e. November 1984 AHF (Fibrinogen-poor) became the routine issue product, heated prior to issue as described above.

Because it was impossible to meet total demand with new product alone, due to yield losses and lead times, Standard AHF was returned to CSL and heated under varying conditions compatible with the ability of individual batches to be redissolved subsequently. Where this was successful, the material was reissued for clinical use to supplement supplies of AHF (Fibrinogen-poor). This practice ended in February 1985. I believe that CSL was one of the first manufacturers of AHF in the world to introduce a heat treatment of its product.

30. It is to be noted that heat treatment of Factor VIII concentrate was not a viable alternative until such time as the Margolis method of producing Factor VIII was perfected. This was because impurities in the Factor VIII concentrate produced by the prior method made it insoluble after freeze drying and heating.

31. A telephone conversation with Dr. Aronson, formerly with the Division of Blood and Blood Products, Bureau of Biologics, Washington provided the following information. The date of the conversation was 12 July 1989. Hyland was the first of the American Fractionators granted a licence by the FDA to heat treat Factor VIII concentrate. This was in February or March 1983.

The intention of the heat treatment was to reduce the risk of hepatitis transmissions. The other manufacturers in the United States had similar heat treating processes in place by early 1984. Heat sensitivity of the HIV virus was not demonstrated until mid 1984 in the United States and not published until early 1985. It was not until the end of May 1985 that the Bureau of Biologics required that Factor VIII concentrate be heated. Between March 1983 and March 1985, there was a mixture of heated and unheated Factor VIII concentrate available on the American market. The heated product was less attractive because it was more expensive and had a lower yield.

32. CSL commenced studies of heating to reduce the risk of hepatitis transmission in August 1983 and reported to the BTS Executive Sub-Committee on Factor VIII in February 1984. That report noted that yield by heating was reduced by approximately 40%.

33. CSL maintained a liaison with overseas manufacturers and kept abreast of overseas developments. It was one of the first AHF manufacturers to routinely screen for AIDS antibodies and one of the first AHF manufacturers to heat treat its product as aforesaid.

Testing for AIDS

34. Testing kits approved by the FDA were not approved by nor available from the FDA until February 1985 in the United States. Approved tests were not available in Australia until early April 1985. The test kits were imported on behalf of the Commonwealth Government and were distributed to Blood Transfusion Services throughout the States. The CSL was in addition, supplied with test kits which were used to test pools of plasma and also test during the manufacturing process and the final (issue) stage of various blood products. The test kits were used by the Blood Transfusion Services to test individual donations of blood or blood products.

35. From about October or November 1984, Professor Gust had access to some experimental test materials. However, these were not approved tests nor was the testing material widely available.

Ex 223 3

CURRICULUM VITAE

1. PERSONAL DETAILS

Name : Peter SCHIFF

Date of Birth : GRO-C 1935

Marital Status : Married

Family : One son, aged 27 years, two daughters aged 27 and 21

Home address : GRO-C Australia.
Tel : GRO-C

Business address : C/- Commonwealth Serum Laboratories
45 Poplar Road
PARKVILLE. 3052. Australia.
Tel : GRO-C

2. QUALIFICATIONS

B.Sc (Med) in Pathology, Sydney University	1957
M.B.,B.S. Hons II, Sydney University	1959
Passed United States ECFMG Examination	1964
Ph.D in Biochemistry, Australian National University (ANU)	1965
Fellowship, Royal College of Pathologists of Australasia (FRCPA)	1973
Membership, Royal Australasian College of Physicians (MRACP)	1975
Fellowship, Royal Australasian College of Physicians (FRACP)	1978

3. CURRENT EMPLOYER

Commonwealth Serum Laboratories (CSL)
45 Poplar Road
PARKVILLE. 3052. Australia.

4. POSITIONS HELD

(a) Before joining CSL :

(i)	Junior Resident Medical Officer)Royal Prince	1959
(ii)	Senior Resident Medical Officer)Alfred Hospital, Sydney	1960
(iii)	Research Scholar, ANU	1961-64
(iv)	Professorial Medical Registrar, Sydney Hospital	Feb-Aug 1965

(b) Since joining CSL :

(i)	Medical Officer, Research Division	1965-66
(ii)	Clinical Assistant, Royal Melbourne Hospital	1965-70
(iii)	Chief of Research	1966-74
(iv)	Research & Development Director	1975-
(v)	Executive Director, Blood Products Division	1987-

5. EXTERNAL ASSOCIATIONS

(a) As CSL representative :

(i) Member of the National Blood Transfusion Committee since 1966
(ii) Member of the Human Pituitary Advisory Committee since 1973
(iii) Member of the Commonwealth AIDS Task Force, 1984–87.

(b) Otherwise, Member of :

(i) International Society of Blood Transfusion
(ii) Australasian Society of Blood Transfusion (President 1974–76)
(iii) International Society of Haematology
(iv) Haematology Society of Australia
(v) American Association of Blood Banks
(vi) International Society on Thrombosis and Haemostasis
(vii) Transplantation Society of Australia and New Zealand.

6. PUBLICATIONS

Author of 48 papers and communications that have been published in the scientific literature, mainly relation to the use of blood products (see list attached).

7. DESCRIPTION OF PRESENT DUTIES

CSL is a manufacturer and distributor of biological pharmaceutical products for use in human and veterinary medicine. As R&D Director I am responsible for a staff of some 150, of whom approximately 50% are research scientists, the remainder being support staff. Subject disciplines covered by the Division include Immunochemistry, Immunohaematology, Bacteriology, Bioengineering, Venoms Research, Virology and Pharmacology. Medical and veterinary consultants, drug registration and the library are also under my control.

My clinical interests are mainly haematological, in particular the clinical use of blood and its components. CSL operates the only plasma fractionation plant in the South-West Pacific Region, and I represent the Laboratories on the Red Cross National Blood Transfusion Committee, and advisory committee on blood policy to the Federal and State Governments. I also liaise with clinicians and patient-interest groups, e.g. haemophilia societies, on the clinical use of fractions such as plasma volume expanders, coagulation factors and immunoglobulins.

CSL strives to be at the forefront of technology in the biological sciences. To this end we have recently strengthened our fermentation group and taken steps to establish groups with expert knowledge in peptide synthesis/immunology and in genetic engineering. All these activities are encompassed within the scope of my responsibilities.

To keep abreast of developments in other countries, I travel abroad at least annually to attend international conferences and for discussions with scientists working in related fields. I have presented papers at the World Federation and Haemophilia Congress in New York in 1977, and in 1982 was invited to participate as a teacher in a WHO Training Course for blood bankers in Peking.

8. EXTRACURRICULAR ACTIVITIES

My relaxations include philately, reading, and jogging. I have been an active member of B'nai B'rith, an international Jewish service organization, since 1960 and have served three terms as President of my Lodge. I am presently in my fourth year as Co-Chairman of the Australian Associatiion for the Weizmann Institute of Science.

Attch.

DR PETER SCHIFF - LIST OF PUBLICATIONS

1. Schiff P, Warren BA.
Scalene node biopsy: a survey of 250 biopsies performed at post mortem.
B.Sc.(Med.) thesis (pathology), Sydney University, 1956.

2. Warren BA, Schiff P.
Sarcoid-like lesions in lymph nodes draining malignant neoplasms.
B.Sc.(Med.) thesis (pathology), Sydney University, 1956.

3. Schiff P, Warren BA.
Scalene node biopsy: its value as a diagnostic aid in chest diseases. Dis Chest 1957, 32:198.

4. Hagerman DD, Rosenberg H, Ennor AH, Schiff P, Inove S.
The isolation and properties of chicken kidney serine ethanolamine phosphate phosphodiesterase.
J Biol Chem 1965 240: 1108.

5. Thomson E, Macdonald RH, Mathieson B, Stening SEL, Macknight E, Schiff P, Hay J, Morris JP, Minognue N, Archer G.
Prevention of Rh-haemolytic disease.
Med J Aust 1967 2: 261.

6. Duxbury AE, Schiff P.
The use of gamma globulin in prevention of diseases.
Med J Aust 1967 1: 246.

7. Castaldi PA, Somer JB, Schiff P, Blackburn CRB.
Concentrated Factor VIII in the management of haemophilia A and von Willebrand's disease.
Med J Aust 1967 2: 481.

8. Schiff P, Sutherland SK, Lane WR.
Human gamma globulin for intravenous administration: preparation, testing and properties.
Proc Aust Soc Med Res 1967 2: 120.

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The preparation, testing and properties of human gamma globulin for intravenous administration.
Aust Paediat J 1968 4: 121.

10. Schiff P, Warburtob MF.
A rapid method for the measurement of rubella antibody titres in plasma.
Proc Aust Soc Med Res 1967 2: 126.

11. Wells JV, Penny R, Schiff P.
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Proc Aust Soc Med Res 1967 2: 123.

12. Baxter EH, Mars AGM, Schiff P, Lane WR.
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Proc Aust Soc Med Res 1968 2: 197.

13. McKenzie IFC, Morris PJ, Schiff P, de Gabriele G.
Anti-lymphocytic serum preparation and in vitro testing.
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Med J Aust 1969 1: 1035.

16. Schiff P.
The immunology of Rh-haemolytic disease: a review.
Med J Aust 1969 2: 915.

17. Schiff P.
The preparation and properties of a prothrombin complex (PPSB).
Med J Aust 1969 2: 1001.

18. Trinc JC, Schiff P.
Deadly sea wasp.
Sea Frontiers 1970 16: 32.

19. Schiff P.
Are gamma globulins of placental origin equivalent to gamma globulins of plasmatic origin?
Vox Sang 1971 20: 92.

20. Schiff P.
The use of gamma globulin for passive protection against infectious hepatitis.
Med J Aust 1970 2: 338.

21. Schiff P.
Anti-Rh(D) gamma globulin.
Aust J Med Tech 1971 2: 21.

22. Harrison HA, Torda TA, Schiff P.
Hypotensive effects of stable plasma protein solution (SPPS): a preliminary communication.
Med J Aust 1971 2: 1308.

23. Shaw AE, Schiff P, Castaldi PA.
Hepatitis following the use of fibrinogen.
Med J Aust 1971 2: 1308.

24. Case J, Schiff P, Walsh J.
Blood group antibodies in human immune serum globulin.
New Engl J Med 1972 287: 359.

25. Schiff P.
VI The development of plasma derivatives in Australia.
Vox Sang 1972 23: 38.

26. Schiff P.
Clinical uses of human blood fractions.
Med J Aust 1973 1: 22.

27. Schiff P.
Modern trends in immunization.
Med J Aust 1973 1: 551.

28. Schiff P.
Prophylaxis against serum hepatitis.
Bull Postgrad Comm Med Uni Sydney (Suppl) 1973 29: 94.

29. Schiff P (Ed).
The role of plasma volume expanders in the treatment of hypovolaemic shock.
Australian Society of Blood Transfusion, Symposium 1973.

30. Schiff P.
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31. Schiff P.
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33. Schiff P.
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Aust Prescriber 1976 1: 38-40.

34. Schiff P.
Can a national all voluntary blood transfusion serviced by adequate blood component therapy cover actual and future needs of albumin? (International Forum).
Vox Sang 1976 31: 236-8.

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Plasma protein fractions.
Bull Postgrad Comm Med Uni Syd 1976 31:338-41.

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Albumin-containing plasma volume expanders.
Aust NZ J Surg 1977 47: 783-6.

37. Schiff P.
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Proc Aust Soc Blood Transf Symp 1979 35-8.

38. Cossart Y, Gust I, Schiff P.
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Med J Aust 1982 1: 407-8.

39. Schiff P.
Stable plasma protein solution.
Med J Aust 1982 1: 493.

40. Schiff P.
CSL's fractionation program in 'Strategies for the procurement and use of Factor VIII for the 1980s'.
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Aust NZ J Med 1987 17(Suppl 2): 528.

43. Schiff P.
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44. Schiff P.
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45. Thomas KB, McGrath K, Fung L, Herrington RW, Schiff P.
Factor VIII concentrates prepared from heparinised plasma (Abstract).
Aust NZ J Med 1987 17(Suppl 2): 546.

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Recovery of FVIII from blood stored overnight at 4°C for 12-15 hours (Abstract).
Aust NZ J Med 1987 17(Suppl 2): 546.

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48. Thomas KB, McGrath KM, Taylor M, Young IF, Herrington RW, Schiff P.
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49. Roberton DM, Hosking CS, Efthimiou U, Wright S, Upton H, Colgan T, Hartman L, Schiff P.
Decreased incidence of adverse infusion reactions in hypogammaglobulinaemic children receiving low pH intravenous immunoglobulin.
Aust NZ J Med 1987 17: 495-500.