SCOTTISH EXECUTIVE

Health Department

HEPATITIS C AND HEAT TREATMENT OF BLOOD PRODUCTS FOR HAEMOPHILIACS IN THE MID 1980s

October 2000

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REPORT ON HEPATITIS C AND THE HEAT TREATMENT OF BLOOD PRODUCTS FOR HAEMOPHILIACS IN THE MID-1980S

SUMMARY

Remit

- to examine evidence about the introduction of heat treatment in Scotland for Factor VIII in the mid 1980s, to assess whether patients in Scotland with haemophilia were exposed to the risks of the hepatitis C virus longer than they should have been, given the state of knowledge at the time;

- to examine evidence about the information given to patients with haemophilia in the 1980s about the risks of contracting the hepatitis C virus from blood products.

Findings

- the Scottish National Blood Transfusion Service were around 18 months behind the Bio Products Laboratory in England in producing a heat–treated product which was subsequently found to have eliminated the hepatitis C virus;

- there were understandable technical reasons why this was the case:
  - there was no test to identify the presence of the virus, so scientists could not be sure that any particular heat treatment had actually worked until they reviewed the effects of the resultant products on patients;
  - the heating process could easily render blood products unusable, and different types of heating and freeze-drying processes and equipment had to be tried in order to obtain a usable product;

- once SNBTS had managed to develop a suitable heat-treated product, they were quickly able to produce sufficient for domestic demand;

- no evidence of any policy by Haemophilia Centre Directors deliberately to mislead patients about the risks of hepatitis.

CHRONOLOGY

A full chronology of events is given as Annex A to the Report. The key dates are as follows:

Late 1983 – SNBTS prepare batch of pasteurised Factor VIII for clinical evaluation

January 1984 - First patient in clinical evaluation for SNBTS pasteurised Factor VIII suffers adverse reaction, and trial is abandoned.

1984 - The Plasma Fractionation Laboratory (PFL) in Oxford (a pilot plant laboratory for Bio Products Laboratory in Elstree) managed to dry heat a Factor VIII product to 80°C for 72 hours. It was expected that this would give greater protection against HIV. There was no indication whether this temperature would have an effect on the agent responsible for Non A Non B hepatitis (NANBH) – not at that time recognised as hepatitis C. The Scottish National Blood Transfusion Service (SNBTS) decided to keep trying to develop pasteurisation.

December 1984 - SNBTS were able to heat treat a year's supply of Factor VIII at sufficient temperatures to render it HIV-safe.

September 1985 - BPL heat treating all of its Factor VIII at 80°C for 72 hours. This accounted for 25% of the requirement in England and Wales.

August 1986 - SNBTS produced the first trial batches of their new Factor VIII product heat treated to 80°C for 72 hours.

September 1986 - A BPL/PFL preliminary report was published which indicated that heat treatment of Factor VIII at 80°C for 72 hours might prevent the transmission of NANBH.

March 1987 - The clinical trial of the SNBTS Factor VIII product (heat treated at 80°C for 72 hours) was completed.

April 1987 - SNBTS Factor VIII product (heat treated at 80°C for 72 hours) was available for clinical use.

October 1988 - The full results of a study were published in the *Lancet* showing that heat treatment of Factor VIII at 80°C for 72 hours was effective against NANBH.

1989 - Hepatitis C virus finally isolated and identified.

1993 - Results published confirming the clinical safety of both SNBTS and BPL products as regards HCV transmission.

HEPATITIS C AND HEAT TREATMENT OF BLOOD PRODUCTS FOR HAEMOPHILIACS IN THE MID 1980s

Introduction

1. In the late summer of 1999, the Minister for Health and Community Care, Susan Deacon MSP, gave Scottish Executive officials the task of ascertaining the facts surrounding the heat treatment of blood products for haemophiliacs in the mid 1980s. The remit for this exercise was as follows:

- to examine evidence about the introduction of heat treatment in Scotland for Factor VIII in the mid 1980s, to assess whether patients in Scotland with haemophilia were exposed to the risks of the hepatitis C virus longer than they should have been, given the state of knowledge at the time;

- to examine evidence about the information given to patients with haemophilia in the 1980s about the risks of contracting the hepatitis C virus from blood products.

2. Assertions came to Ms Deacon's attention in late summer 1999 that a hepatitis C inactivated Factor VIII product had become available in England in 1985 through the Bio Products Laboratory (BPL), whereas it had taken until late 1987 for the Scottish National Blood Transfusion Service (SNBTS) to produce a comparable product in Scotland. The assertions led to concern that Factor VIII users in Scotland might therefore have been at risk longer than they should have been. This was the subject of media debate and of calls from MSPs to look at the matter. In early August 1999, the Minister asked officials to begin the factfinding exercise which is the subject of this report, and she invited the Haemophilia Society to meet her so she could hear their concerns first-hand. This meeting took place on 14 September 1999.

3. In this exercise, we have tried to ascertain and present the facts about what happened, based on the evidence we have received from interested parties. This exercise is not an attempt to approve, blame or justify. Nor is it an attempt to apply hindsight and set out in detail what might have been done instead.

Methodology

4. We have examined written submissions from the Scottish National Blood Transfusion Service (Reference A), from the Haemophilia Society (Reference B), and from individual haemophiliacs and their families (Reference C). We have met with the Haemophilia Society and with current Scottish Directors of Haemophilia Centres. We have assessed the information given to us and its relevance to this exercise. We have gone back to the relevant people with further questions arising from what we have read in their submissions. We believe we have pulled together a comprehensive view of the issues.

5. We have drawn substantively on the content of the submissions we received, and throughout this report we have marked any reference to those documents. In the interests of openness, these papers are available for viewing (apart from most of those

from individual haemophiliacs: we sought permission to make them publicly available but, understandably, many correspondents felt unable to grant it). The volume of the material gathered together is considerable. However, we are making copies of the main submissions written for this exercise available to SNBTS, the Haemophilia Society and to the Directors of Haemophilia Centres. A copy will also be placed in the Scottish Parliament Information Centre for MSPs, and in the Scottish Executive Library at Saughton House, Broomhouse Drive, Edinburgh EH11 3XD for members of the public. If other copies of the main submissions are requested they will be provided on payment of a fee of £13.50 to cover copying costs. (The report itself will be provided free of charge.)

6. The events in question took place so long ago that we have found it difficult to access relevant information from our own files. Some of them had been destroyed, presumably during routine procedures for the review and disposal of files. We used the files and information still available to us, and asked the Department of Health to give us any further relevant information.

Background on the Hepatitis C Virus

7. Hepatitis C (HCV) is a blood borne virus, first isolated and fully identified in 1989. Knowledge about this virus had been developing since the mid 1970s, when the scientific community began to comment on asymptomatic liver disease in haemophiliacs treated with blood products. Although the disease could be classified as hepatitis, being an inflammation of the liver, it was not identifiably the result of either the hepatitis A virus or the hepatitis B virus. The condition became known as Non-A Non-B Hepatitis (NANBH) until the isolation of the virus in 1989. Knowledge about hepatitis viruses is still evolving, and several further types have since been identified.

8. From reading the scientific literature in the late 1970s and early 1980s included with SNBTS's submission, it is apparent that there was no real consensus on the progression of any disease caused by the hepatitis C virus (as we now know it) at the time. Current best estimates are that around 80% of those infected by hepatitis C will become chronic carriers of the virus; around 20% of people with chronic hepatitis C infection will develop progressive liver disease resulting in cirrhosis and, in approximately 5% of cases, primary liver cancer, over a period of 20-30 years. Hepatitis C can be transmitted from person to person through the cross-contamination of blood (for example, through the sharing of needles) and, less commonly, can be sexually transmitted.

Background on Haemophilia

9. There are around 400 haemophiliacs living in Scotland. There are 2 types of haemophilia – Haemophilia A and Haemophilia B. This report concerns blood products for the treatment of haemophilia A. Haemophilia A is a genetically inherited bleeding disorder which results from lack of the coagulation Factor VIII in the blood. In patients with this deficiency, any episode of bleeding is abnormally prolonged and potentially fatal. The product of choice for treating Haemophilia A is Factor VIII concentrate, which until recently was produced solely from human plasma. (It can now be produced bio-synthetically, using genetic engineering.) Manufacturing pools for plasma products such as Factor VIII consist of donations from thousands of

individuals. If just one of the donations used in the manufacturing pool for Factor VIII is infected with hepatitis C, there is a risk to the whole batch made from that pool, and to all recipients of that batch of blood products. It is possible nowadays to identify the presence of the virus in pools or in individual donations. Up to around 1989-90, it was not possible to do so with any certainty, as the virus had not then been isolated.

Effect of HCV on Haemophiliacs

10. Throughout the mid to late 1970s, scientific papers noted the occurrence of hepatitis and liver function abnormalities in haemophiliacs, and postulated that they might be related to treatment with blood products, particularly concentrates of Factors VIII and IX (the latter used to treat Haemophilia B), because the large donor pools used to produce these products would increase the risk of any hepatitis virus (and indeed any virus) present in individual donations.

11. It is generally accepted that a number of haemophiliacs in Scotland (as in other countries) were infected with hepatitis C through blood products. Figures provided by the Scottish Haemophilia Centre Directors show that:

- 15 HIV-negative haemophilia patients have died of liver disease in Scotland in the last 15 years; [1]
- of the haemophilia patients who were first treated with a blood product during the period in question in this paper (September 1985 – December 1987), the majority have tested HCV negative, but a small number[2] have tested HCV positive, and the status of a small number is unknown. Not all of the HCV-positive group amongst these patients were treated with SNBTS-produced Factor VIII concentrate during the period in question – some of them were treated with cryoprecipitate. Current Haemophilia Centre Directors told us that it was their policy to contact all haemophilia patients on their registers who may have been exposed to HCV risk, and to offer testing, after testing became routinely available in 1993-94. Reasons for not being able to confirm the HCV status of some patients might include them not having wanted to take the test, or having moved outwith Scotland.

12. During this exercise, we received 28 letters from individual haemophiliacs, and 15 letters from friends and families of haemophiliacs, describing the effects of the hepatitis C virus on their lives. Some of the letters deal with the health problems encountered by sufferers. Most people who mentioned treatment said it had been unsuccessful. Three people mentioned funding problems with treatment. Many writers felt that haemophiliacs had not been adequately warned of the risks of infection from blood products, and that they had received inadequate advice and support. Some correspondents were the parents of haemophiliac children; they described how they felt after having consented to treatment which resulted in their child becoming infected. Many correspondents expressed great disappointment that

[1] The figure excludes patients who were also HIV positive, since HIV of itself causes immunosuppression which renders individuals susceptible to illnesses which they would otherwise be able to combat. The figure, however, includes individuals whose deaths from liver disease may not have involved Hepatitis C: for example, cirrhosis of the liver from another cause.

[2] Fewer than 10; more detailed information is withheld in the interests of confidentiality.

no apology had ever been offered to them. A few correspondents said that there had been a delay in their being informed that they were infected with HCV. A number of correspondents also mentioned the effect on their families. Some families had to cope with seeing a loved one suffer, physically and emotionally. Other families were financially disadvantaged because partners were unable to take up paid employment since they were caring for a hepatitis C positive relative. Sufferers said they had worried about the risk of infecting their loved ones. Some correspondents mentioned in addition the social stigma of hepatitis C; they did not want their neighbours to know they were infected. Others pointed out that people infected with hepatitis C may have difficulty in obtaining a mortgage or personal insurance, or may be subjected to increased payments.

Development of Heat Treated Products

13. The following paragraphs set out the background and events as presented to us by the various interests involved in this exercise. They relate progress towards a Factor VIII product successfully heat-treated to inactivate HCV, which we now know was the principal cause of NANBH. (In a minority of NANBH cases, other viruses were responsible.) We have also produced a timeline, to be easy to read but still comprehensive - see Annex A.

14. The scientific community world-wide shares information through the publication of papers. Papers are subject to a process of peer review before they are published. Sometimes, information is shared at conferences before a paper has been published.

15. In considering progress towards successful heat treatment to inactivate the causative agent of NANBH, it is worth noting that there are two basic types of heat treatment:

i) wet-heating to a certain temperature, otherwise known as pasteurisation;

ii) dry-heating, which involves freeze-drying a product, then subjecting the dried product to heat. The product is reconstituted with water for use.

16. In both types of heat treatment, crucial factors are the temperature and length of time for which the product is heated. It was apparent to us from the contents of the published scientific papers included with SNBTS's submission that subjecting Factor VIII to heat treatment was a far from straightforward matter. Improperly controlled heating of plasma proteins can cause them, in lay terms, to cook; this changes their nature and spoils the product for human use. An additional technical complication arose from the view that the purification of Factor VIII (separation of the Factor VIII component from other material in plasma) was important in working out the process of heat treatment.

17. In 1980, German scientists working for Behringwerke published a report which suggested that pasteurising Factor VIII at 60°C for 10 hours removed the risk of hepatitis B, but that further proof was needed to confirm whether this process was also suitable for inactivating the agent responsible for NANBH (SNBTS submission, ref 36.) Behringwerke obtained a US patent for the process of stabilising Factor VIII in pasteurisation in 1981. Yields from this process were acknowledged to be low –

less than 25% of SNBTS's own production yield of Factor VIII. (The product subsequently proved still to be associated with NANBH transmission, albeit at reduced levels). SNBTS research on pasteurisation also began in 1981.

18. In 1982, US scientists at an International Society of Haematology Congress reported that Factor VIII could be heated to 80º C for 10 hours but the resultant product was visibly less soluble than products in clinical use. Furthermore, it was unknown whether this heat treatment actually inactivated the relevant viruses. Chimpanzee studies were planned. (*SNBTS: Ref A1 paper 27*).

19. Current Haemophilia Centre Directors have recalled that in 1983, Scotland was approaching self-sufficiency in SNBTS Factor VIII and IX, in accordance with Scottish Health Service Policy that Scotland should be self-supporting in blood products including the routine use of SNBTS Factor VIII and IX concentrates for the treatment of haemophiliacs.

20. In 1983, SNBTS learned that two commercial firms were investigating dry heat treatment of Factor VIII at 60°C. SNBTS carried out preliminary studies on dry heat treatment of their own Factor VIII product NY in November 1983, and found that it could indeed be heated in this way, but with a lower degree of virus inactivation than they had already obtained in their studies on pasteurisation. They proceeded to clinical trial of a pasteurised product, but the first patient suffered an adverse reaction and the trial was abandoned.

21. In late 1983, HIV was isolated as a blood-borne virus. It was first cultured for research in March 1984. The focus on heat treatment shifted towards the optimal method to eradicate HIV, since this was now recognised as the biggest threat to haemophiliacs. SNBTS decided to explore further the options available should HIV be found to be sensitive to dry heat treatment. They made further measurements of the behaviour of their Factor VIII product NY when subjected to heat treatment, which were completed in October 1984.

22. In April 1984, Bayer (USA) published a patented method for the pasteurisation of Factor VIII. SNBTS noted that the Plasma Fractionation Laboratory (PFL) in Oxford, which was a pilot plant laboratory for BPL, in 1984 managed to dry-heat an experimental preparation of Factor VIII product (known as 8Y) to 80°C for 72 hours. It was expected that this would provide greater protection against HIV. SNBTS noted that this product was 10 times more purified than SNBTS's own Factor VIII NY product, which was believed to be the reason why the heat treatment was successful, without spoiling of the product. At that time there was no indication whether this degree of heat treatment would have any effect on hepatitis viruses (and since the causative agent of NANBH had not been isolated, it could not be tested for directly).

23. In November 1984, SNBTS learned of reports that HIV was sensitive to 68°C dry heat for 1 hour. In December 1984 they were able to heat-treat a year's supply of the Factor VIII product NY at 68°C for 2 hours, thus rendering it HIV-safe. In January 1985 they were able to begin dry heat treatment at this temperature for 24 hours, and in the same month SNBTS put into action a process to specify and procure a high accuracy treatment cabinet (basically a kind of oven) to a similar specification to that used by PFL. The first of these cabinets was obtained and put into use in July

1985. By July 1986, SNBTS had enough stocks of Factor VIII NY to stop production but still maintain sufficient supplies to the health service, so they could concentrate on trialling other types of heat treatment.

24. Meanwhile, in March 1985, PFL at Oxford were heat-treating all of their Factor VIII – some at 80°C. In May 1985 Bio Products Laboratory (BPL) in Elstree were doing the same. By September 1985, all PFL/BPL Factor VIII was being heat treated at 80°C for 72 hours. This amounted to a quarter of the requirement in England and Wales for Factor VIII.

25. SNBTS meanwhile were also attempting to develop the technical processes which would produce a Factor VIII product able to withstand dry heat at 80°C without spoiling. In Autumn 1985, they developed a more highly-purified Factor VIII, but it was unable to withstand heat treatment at 80°C. They therefore concluded that it must be the process of freeze-drying which was crucial when it came to the tolerance of the product to dry heat, rather than higher levels of purity. In February 1986, SNBTS management endorsed the approach of their scientists to concentrate on 80°C dry heat.

26. In August 1986, SNBTS produced the first trial batches of their new Factor VIII product - called Z8 - treated at 80°C for 72 hours. In September 1986 came a preliminary report that treatment of the BPL Factor VIII product 8Y at 80°C for 72 hours might prevent the transmission of NANBH (*SNBTS Ref A1 paper 53*). SNBTS undertook a clinical trial of their own Factor VIII product Z8 in March 1987. In April 1987 they made it available for routine clinical use.

27. The first production of 80°C dry-heated Factor VIII 8Y in England was March 1985. A preliminary clinical report issued in September 1986 suggested that 80°C dry heat treatment was indeed effective against NANBH. The scientists involved would doubtless have been reasonably confident before then that they were at least heading in the right direction, but they could not know for sure that this form of heat treatment would be effective until after the product had been in clinical use. The full results of this trial were not published until October 1988; SNBTS Factor VIII product Z8 had been in routine clinical use from April 1987. SNBTS say that in 1987 they supplied 89% of Scotland's needs with Z8. In 1988, they were able to supply all of Scotland's needs with Z8. In contrast, they estimate that outwith Scotland over half the UK's Factor VIII concentrate requirement in 1988 was still being supplied with products being heat treated at 60-68°C.

28. After the HCV virus was isolated and identified in 1989, results were published in 1993 confirming the clinical safety of both 8Y and Z8 as regards HCV transmission.

Treatment

29. The second part of the remit of this exercise concerns the treatment of haemophiliac patients, and whether they were given sufficient information about the risks of using Factor VIII.

30. It should be repeated in this context that not all patients treated during the time in question were given SNBTS-produced Factor VIII. Some were given commercial products or cryoprecipitate (see paragraph 11 above).

31. Current Haemophilia Centre Directors recalled that hepatitis and abnormal liver function were well-known risks of Factor VIII and IX concentrates since their introduction in the mid 1970s. They believed that these risks were well-known to the scientific community, concentrates manufacturers, health departments and health boards, healthcare professionals, patients and relevant patient societies including the UK Haemophilia Society and its Scottish branch. They gave their opinion that the risk of hepatitis was a major, widely-publicised factor in pressure from the UK Haemophilia Society on UK Health Departments to progress self-sufficiency in the UK through production of concentrates from UK donor plasma through SNBTS and BPL. They believed that patients and parents were informed of the risk of hepatitis as part of general education on haemophilia and its treatments, including:

- use of educational material, including that produced by the UK Haemophilia Society;
- education for patients and carers about home treatment with factor concentrates (they sent us an excerpt from a document called "Haemophilia Home Therapy" (*Reference D*), produced in 1980 by Peter Jones, at the time Director of the Newcastle Haemophilia Reference Centre, which contains relevant reference to hepatitis);
- hepatitis warning signs and cross-infection precautions, in haemophilia centre treatment areas;
- national and local meetings of the UK Haemophilia Society.

32. We have seen a copy of the product insert leaflet included with SNBTS Factor VIII product NY (*reference E*). It carried a warning that the product could not be assumed to be virus-free. This document is headed "Human Antihaemophilic Factor – Factor VIII concentrate – HT (Lyophilised)", is dated 5/4/85 and carries the product licence number. It states that "the product has been heat treated at 68°C for twenty-four hours in the dried state but it cannot be assumed that the product is non-infective". It mentions among possible side-effects "the general complications of hepatitis". Patients treating themselves would have been able to refer to this leaflet, since it was packaged with each vial of the product intended for self-administration. However, not every person who takes a medicine at home is guaranteed to read or completely understand the product insert.

33. We have also found some examples of guidance available to clinicians.

In June 1983, the UK Haemophilia Centre Directors Organisation (UKHCDO) wrote to Haemophilia Directors about the risk of AIDS (*reference F*), and set out some recommendations for treatment, including the use of DDAVP [the drug Desmopressin Acetate] in treating mild Haemophilia A and von Willebrand's disease. In December 1984, the UKHCDO issued an "AIDS Advisory Document" (*reference G*), which mentioned that dry heat treatment of Factor VIII at 68°C inactivated the AIDS virus, but noted in passing that it was unlikely that the process would completely inactivate Non A Non B Hepatitis. In its Recommendations, it noted that "concentrate is still needed; bleeding is the commonest cause of disability and death ."

There is also relevant material in the 1984 revision of Notes on Transfusion (*reference H*), issued by the DHSS, the Welsh Office and the Scottish Home and Health Department, intended for use by medical staff of hospitals. It describes some of the principles of practice of transfusion with blood and blood products, as well as suggested procedures. This document notes the phenomenon of post-transfusion hepatitis, saying that until suitable tests were available to identify the viruses concerned, there would continue to be a risk associated with the use of blood and blood products.

34. We are extremely grateful to current Haemophilia Centre Directors in Scotland, who met with us to discuss these issues. They felt that from the mid 1970s there had been a widespread awareness of the risks of contracting hepatitis. They recalled a generally-held perception in clinical circles until the late 1980s that NANBH was a mild non-progressive condition. From the mid 1970s, they said, patients were increasingly keen to be prescribed concentrate to allow them to treat themselves at home. Current Haemophilia Directors are obviously unable to speak for their predecessors, but they expressed the view on their own behalf that it was for the individual clinician to recommend a course of action to a particular patient, based on the clinician's assessment of benefits and risks of a particular product. They said their own practice was to give patients and parents current information on the benefits and risks of treatments at their clinic review visits.

35. Current Haemophilia Directors recalled that while there was an awareness of the risks of hepatitis, the main concern in the mid 1980s had been HIV. They said that they believed Haemophilia Centre Directors had at that time given patients advice on avoiding "risk" behaviour to prevent the spread of blood-borne viruses, including use of circulars and publications by the Haemophilia Society and others. We have obtained a copy of one of these: "AIDS and the Blood: A Practical Guide" (*reference I*), written by Dr Peter Jones and distributed by the Haemophilia Society. It contains advice about safe behaviour and advice to patients (and parents of young patients) about examining the possibility of modifying their treatment. It also sets out some of the issues surrounding the heat treatment of blood products, as understood at the time. Current Haemophilia Centre Directors recalled that they or their predecessor directors had liaised with the Scottish Office and SNBTS on the development of new products though not, they said, in a formal advisory capacity.

36. We also asked the Haemophilia Centre Directors to comment on the view that mild haemophilia sufferers might have been put at unnecessary risk through treatment with Factor VIII concentrate, when safer alternatives might have been available. They recalled that different treatments such as cryoprecipitate or desmopressin had indeed been available for so-called "mild" haemophiliacs. These alternatives could themselves produce severe adverse effects (e.g. anaphylactic reactions or thrombosis), so their use had to be a matter of clinical judgement in each case. The Directors took issue with the view that mild haemophiliacs need not be considered clinically serious cases – they explained that although mild haemophiliacs do not suffer spontaneous bleeds, they bleed seriously if subjected to trauma. In such circumstances, their situation can no longer be considered mild and use of factor concentrates would be necessary. There was still a severe risk of death or disability if the bleeding was not

stopped quickly and in many cases mild haemophiliacs presented with late bleeds which involved more treatment.

37. On the issue of testing, current Haemophilia Centre directors were quite clear that their general policy was to inform patients previously treated with blood products that they were being tested for hepatitis viruses and that results would normally be discussed at their next review appointment, as with all test results.

Complaints about individual treatment

38. Some correspondents have raised the issue that they are dissatisfied with the treatment they received at the time, and suggest it did not meet with the clinical policy on testing outlined above, but they understand they cannot now make a complaint through NHS complaints procedures for various reasons. This seems an appropriate place to clarify the current complaints procedure. The Scottish Executive's leaflet on The NHS Complaints Procedure makes clear that

"Usually the NHS will only investigate complaints that are either

Made within 6 months of the event; or
Made within 6 months of you realising that you have something to complain about as long as that is not more than 12 months after the event. These time limits may be waived if there are good reasons why you could not complain sooner."

The Directions to NHS Trusts, Health Boards and Special Health Boards on complaints procedures state that where a complaint is not made during the period specified it shall be referred to the complaints officer and if he is of the opinion that -

> (a) having regard to all the circumstances of the case, it would have been unreasonable for the complainant to make the complaint within that period; and
>
> (b) notwithstanding the time that has elapsed since the date on which the matter which is the subject of the complaint occurred, it is still possible to investigate the complaint properly,

the complaint shall be treated as though it had been received within the time limit.

The complaints system does not deal with events about which the complainant is already taking legal action.

Conclusion

39. The facts strongly suggest that SNBTS made very reasonable progress in developing products with reduced viral risk, relative to activity elsewhere. We accept that they were not the first. Scientific knowledge and technical expertise in this area were developing rapidly during the period in question, spurred on by the drive to eliminate HIV. It is worth remembering that commercial products available during the time in question were not proven to be HCV-safe (and many were subsequently withdrawn). We accept SNBTS's assertion that they were able to provide sufficient

hepatitis C inactivated Factor VIII to cover the needs of all haemophiliac patients in Scotland by 1988 – we know of no other country which could make the same claim.

40. In relation to information given to patients about the risks involved with their treatment, we accept that knowledge of the effects of HCV would have been limited. We accept that clinicians would have had available to them information about the general risks of blood-borne disease, including hepatitis, and that they would have been able to pass this information on to patients. We accept that it would be good practice to offer people a test for HCV when it became available and to discuss the result with them. We have seen no evidence that clinicians had a policy to test without informing patients. Whether these policies may have failed in the case of any individual patient is outwith the scope of this exercise; we have outlined the complaints procedure in this report and we also note that some patients have started legal proceedings.

HAEMOPHILIACS AND HEPATITIS C

TIMELINE

When	Scotland	England	Scientific Literature
1975			Paper by Italian scientists describes "Asymptomatic liver disease in haemophiliacs", asserts Factor VIII/IX possibly responsible because of large donor pools; also that available methods for universal donor screening unlikely to eliminate risk. (SNBTS ref. 11[3])
June 1978			US paper comments that liver abnormalities in haemophiliacs probably related to treatment with blood products and incidence of HBV. (ref. 13)
Sept 1978			*Lancet* paper identifies factor-concentrate replacement therapy as probably related to high incidence of chronic liver disease among haemophiliacs. (ref. 12)
1980			German scientists for Behringwerke publish report which suggests that pasteurising Factor

[3] Subsequent references in this section are all to papers included with the SNBTS submission

			VIII at 60°C for 10 hours frees it from hepatitis B risk – says further clinical proof needed for NANBH. (ref. 36)
September 1981	SNBTS begins its own research on pasteurisation.		
October 1981			Behringwerke get US patent for process to stabilise Factor VIII in pasteurisation (heat-treatment of liquid to 60º C). Although HBV was removed through this process, unclear at time whether this was because of purification or heat-treatment. Yields low – less than 25% of SNBTS's own production process of Factor VIII.
August 1982			US scientists at International Society of Haematology Congress report Factor VIII can be heated to 80º C but it was visibly less soluble than products in clinical use and it was unknown whether this heat treatment inactivated the relevant viruses. Chimpanzee studies were planned. (ref. 27)
September 1982			Italian scientists suggest non-A non-B chronic hepatitis is non-progressive. (ref. 14)
1982			Abstract in *Hepatology* suggests insidious progression of NANBH.

1982			US: 3 haemophiliacs develop new illness, which subsequently becomes known as AIDS.
1983			Further cases of this illness in recipients of Factor VIII.
1983			Manchester scientists suggest that liver biopsy on haemophiliacs not justified by incidence of liver damage (especially in the absence of proven therapy). Suggests liver disease in haemophiliacs an "overstated problem". (ref. 15)
1983	Scotland self-sufficient in SNBTS Factor VIII NY.		
Late 1983	SNBTS prepare batch of pasteurised Factor VIII for clinical evaluation.		HIV first isolated.
January 1984	First patient suffers adverse reaction, clinical study abandoned, and R&D programme revised.		
March 1984			HIV first cultured for research.
April 1984			Bayer (USA) publish patented method for pasteurisation of Factor VIII.
June 1984	SNBTS collaborate with US's Alan Johnston on purification for pasteurisation process, in hope that it would improve pasteurisation and perhaps allow greater heat to be applied.		
October 1984	Samples from haemophiliacs at Edinburgh		

	Centre tested using new HIV screening test. SNBTS informed that a number who had only ever received SNBTS products (i.e. none from abroad) are HIV+, indicating contamination of Scottish blood supply.		
November 1984			International Committee on Thrombosis and Hemostasis, concerned at the lack of a uniform approach in studies, draws up a protocol for evaluating the risk of hepatitis transmission by new products.
1984	SNBTS decide to keep trying to develop pasteurisation.	PFL Oxford manage to dry-heat a Factor VIII product ("8Y") to 80°C for 72 hours. Expected to provide greater protection against HIV. 10-times more purified than SNBTS NY product -–believed by SNBTS to make the difference. No indication whether 80°C treatment would have an effect on hepatitis viruses. Production of 8Y undertaken with early model of freeze-drier, which was later recognised as crucial in the process. (ref para 7.14 of SNBTS submission)	Clinical studies suggest pasteurisation at 60°C for 10 hrs might be effective against hepatitis viruses (ref. 47).
August 1984 & July			US scientists doing chimpanzee studies claim

1985			reduction of hepatitis infectivity following dry heat treatment to 60º C. (ref. 30,31)
Oct-Dec 1984	PFC production suspended during planned upgrade of facilities.		
November 1984	SNBTS scientists learn results of US work, that dry heat treatment at 68º C for one hour inactivates HIV. They already know that NY can withstand this level of heat for 2 hours. Decide to dry heat-treat existing stocks of NY.		
December 1984	All stocks of NY issued by PFC from now on – 12 months' supply – have been dry heat-treated to 68º C for 2 hours – HIV-safe.		
January 1985	SNBTS put into production their developed process to dry-heat Factor VIII to 68º C for 24 hours.		
January 1985	SNBTS order specialised heat treatment oven to specification similar to that used by PFL.		
March 1985		All PFL (Oxford) Factor VIII Heat treated – some at 80°C	
May 1985		All BPL (Elstree) Factor VIII heat treated – some at 80°C	
July 1985	SNBTS receive specialised oven (see above) and put to use.		*Lancet* article and letter suggests that clinical data from humans do not bear out the results of

			chimpanzee studies.
September 1985		All PFL/BPL Factor VIII (up to 40% of England and Wales requirement) heat treated at 80°C.	
1985			US paper suggests "no indication to alter current therapy patterns because of concern over plasma product-related liver disease", but also points out that some studies suggest more insidious nature of disease than previously thought. (ref. 16)
1985			*Lancet* article by Sheffield scientists concludes chronic persistent hepatitis in haemophiliacs not as benign as hitherto supposed; an "understated problem"; suggests NANBH mainly responsible (ref. 17)
Autumn 1985	SNBTS develop highly-purified Factor VIII, but it does not stand up to dry heat at 80°C – NY samples included as control *do* withstand. They conclude that it is the process of freeze-drying which is important rather than purity, when it comes to tolerance of dry heat. Decide to concentrate on 80°C dry treatment of Factor VIII to increase safety margin for HIV (as this was the overriding concern at the time).		

October 1985	Clinical trial and introduction of Factor IX product DEFIX dry-heated to 80º C for 72 hours. (Safety studies had been needed prior to this due to risks of thrombosis).		
Feb 1986	SNBTS management endorse strategy concentrating on 80º C dry heat (see Autumn 1985).		
August 1986	SNBTS produce first full-scale production trial batches of Factor VIII product Z8 (heated at 80°C for 72 hrs).		
September 1986		PFL/BPL report preliminary clinical data showing their 80° C dry-heat 8Y reduced risk of hepatitis transmission, and suggest fuller study be carried out. (ref. 53)	
December 1986	Z8 issued for clinical trials.		
April 1987	Z8 made available for routine clinical use.		
April 1987			Clinical studies redone to fit in with ICTH protocol suggest pasteurisation at 60°C for 10 hours effective. (ref. 48)
1988			French study of 60-68°C dry-heated products suggests heating at this level reduces NANBV contamination by 75%
1988	Look-back study shows that NY heat-treated in		

	November 1984 and Jan/Feb 1985 had been prepared using HIV-infected donations, and that HIV virus had not been transmitted – thus demonstrating efficacy of the process as far as HIV was concerned.		
May 1988			US patent granted to Alan Johnson for purification process
October 1988			Paper published in *Lancet* suggests 8Y (heated at 80°C for 72 hours) free from NANBH C risk (ref 60).
1989			Hepatitis C DNA code isolated (ref. 18)
1990			Letter published in *Lancet* suggests 8Y does not transmit hepatitis C risk (ref 61) and undertakes to continue to follow relevant patients.
1992			Paper by Finnish scientists reports that 68°C/72h dry-heated product had been in use in Finland 1985-1991, but the risk of contracting HCV with that product was now seen to be appreciable, before the advent of screening blood-donors for HCV.
November 1992			Report from UK scientists suggests that haemophiliacs exposed only to “super dry-heated

			concentrates" (for 72h at 80° C) presented no evidence of HCV infection. (ref. 63)
December 1992			Report on behalf of UK Haemophilia Centre directors confirms that 8Y treatment (dry heat at 80°C for 72 hours) seems to reduce risk of HCV transmission from 90% to 0-11%. (ref 62)
May 1993			Study by Haemophilia directors provides additional evidence that dry heat treatment for 72h at 80°C is effective in preventing HIV and HCV transmission (ref. 64)
January 1994			Paper by Italian scientists suggest heat-treated products (pasteurised or dry-heat treated at 68°C for 72h) effective in reducing risk of transmission of hepatitis C, and looks forward to even more effective virucidal treatment. (ref. 67)