Done 17

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23 March 2000

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HAEMOPHILIA AND HEPATITIS C

1. Apologies for overrunning your deadline for comments on the draft report. Attached are some suggested amendments which I would be more than happy to discuss. I think the structure of the report is fine, but like John and Lynda would welcome a table summarising the section on Development of Heat Treated Products. I have tried to clarify the text, but even so I think it makes rather difficult reading, particularly for those who are coming new to the issue. Some form of table would therefore be helpful, and I recall that BPL had produced a tabulated chronology of their product development during the period in question. I think we may have discussed inserting relevant SNBTS product developments into this chronology, and you may wish to include something along these lines in the report.

2. In paragraph 8 I have stuck to describing haemophilia resulting from **Factor VIII deficiency** (Haemophilia A) since the investigation revolves round Factor VIII production in Scotland. However, I would welcome views on whether we should/need to allude to Haemophilia B which of course results from Factor IX deficiency - if only to show we are aware that the term haemophilia covers both of these entities!

3. Paragraph 10 will obviously have to be redrafted in the light of the letters from Philip Cachia, firming up on the numbers.

4. As far as the Conclusion is concerned, I agree with John that this should be made more definite. I think it would be useful in this paragraph to refer to the fact that comparable developments in the commercial sector usually take significantly longer than SNBTS's development of Z8. SNBTS allude to a fairly powerful example in this context in paragraph 5.6 of their submission to us, in which they state "We are aware of one major USA manufacturer (Bayer) who took 7 years to develop a process for the pasteurisation of Factor VIII, which they later abandoned". This example, and that of the difficulties experienced by Behringwerke, referred to in the report, might usefully be alluded to in the Conclusion.

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5. Finally, as far as financial help is concerned you will need no reminding that DH are very nervous about this. Mike McGovern made a point of bringing the issue up with me during a recent unrelated telephone conversation, during which I reassured him that we recognised that compensation in this area would set a very difficult precedent for the Government, given the many claims for compensation that it receives.

GRO-C

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23 March 2000

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

Introduction/Summary

1. [To be completed.]

Purpose of Exercise

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

- to examine evidence about the introduction of heat treatment in Scotland for Factor VIII in the mid 1980s, to assess whether or not 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.

3. This exercise is not an attempt to apply hindsight and set out in detail what ~~should~~ have been done at the time; nor is it an attempt to apportion blame. ~~We~~ have tried to ascertain and present the facts about what happened, based on the evidence we have received from interested parties.

Methodology

4. We have examined written submissions from the Scottish National Blood Transfusion Service, from the Haemophilia Society, and from individual haemophiliacs and their families. ~~We have met with the current Scottish Directors of Haemophilia Centres~~. 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, and throughout this report we have marked references ~~in italics within brackets~~. In accordance with the Scottish Executive's policy on open Government, 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 felt unable to grant it). The volume of the material gathered together precludes widespread indiscriminate photocopying. However, we are making copies of the submissions written for this exercise available to SNBTS, the Haemophilia Society and to the Directors of Haemophilia Centres, and we shall consider requests from other people.

Background on the Hepatitis C Virus

6. Hepatitis C is a blood borne virus, isolated and 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. 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~~in development~~, and has now reached the stage where Hepatitis viruses D, E and G have been identified.

7. From reading the scientific literature in the late 1970s and early 1980s, it is apparent that there was no real consensus on the progression of any disease caused by the Hepatitis C virus at the time (*reference SNBTS submission papers x – x*). 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~~ and, in approximately 5% of cases, primary liver cancer over a period of 20-30 years.

Background on Haemophilia

8. Haemophilia is a genetically inherited bleeding disorder which results from lack of the coagulation factor Factor VIII in the blood. In patients with this deficiency, any episode of bleeding is abnormally prolonged and potentially fatal. Haemophiliacs therefore require treatment with blood products to replace the missing coagulation factor. The product of choice is Factor VIII concentrate, produced from plasma. Manufacturing pools for plasma products such as Factor VIII consist of donations from tens of 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. ~~disease whereby the person affected lacks coagulant factor in the blood. Unless this deficiency is remedied, any episode of bleeding is serious and may be potentially fatal. Haemophiliacs are treated with products to help their blood coagulate. Among these products is Factor VIII, which is produced from blood plasma. If one of the blood donors whose blood plasma is used in a 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 the recipients of that batch. Manufacturing pools for plasma products consist of donations from tens of thousands of donations of individual people.~~

Effect of HCV on Haemophiliacs

9. Throughout the mid to late 1970s, scientific papers discussed liver function abnormalities in haemophiliacs, and postulated that they might be related to treatment with blood products, particularly Factors VIII and IX, because the large donor pools used to produce these products would increase the risk of any virus(es) present. ~~with Factor VIII/IX possibly responsible because the large donor pools needed to produce these products increased the risk~~.

10. It is generally accepted that haemophiliacs in Scotland were infected with Hepatitis C through blood products. ~~in this way~~. Figures provided by the Scottish Haemophilia Centre Directors show that [DN – to be redrafted in the light of Philip Cachia's communications]

252 haemophilia patients currently living in Scotland are Hepatitis C positive.
15 haemophilia patients have died of liver disease in Scotland since September 1985. This last figure does not include patients who were 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 have involved factors other than uncomplicated Hepatitis C infection; for example, cirrhosis of the liver due to alcohol abuse. ~~people to succumb to illnesses they would otherwise be able to avoid. It does however include people whose deaths involved factors other than straightforward Hepatitis C infection; for example, cirrhosis of the liver due to alcohol abuse.~~

11. 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. ~~Others point out that people infected with Hepatitis C are unable to obtain a mortgage or insurance, or are subjected to increased payments. 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, that they had received inadequate advice and support. Some correspondents were the parents of haemophiliac children~~, who were upset that a decision they had taken~~ without ~~apparently having been given all the relevant information,~~ resulted in their child becoming infected. Many correspondents expressed great disappointment that no apology had ever been offered to them. A few correspondents ~~alleged~~reported that there had been a delay in their being informed that they were infected with HCV. ~~Some~~ 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. ~~Some~~ Other families were financially disadvantaged because partners were unable to take up paid employment since they were caring for a Hepatitis C positive ~~sufferer~~ 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 point out that people infected with Hepatitis C are unable to obtain a mortgage or insurance, or are subjected to increased payments.

Development of Heat Treated Products

12. 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, ~~pre-publication~~, information is shared at conferences.

13. In considering progress towards successful heat treatment to ~~successfully~~ inactivate the causative agent of NANBH~~whatever agent was causing NANB~~, it is worth~~while~~ noting that there are two basic types of heat treatment:

~~I~~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.

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 papers published that subjecting F~~f~~actor VIII to heat treatment in an effort to eradicate contaminating viruses, was a far from straightforward matter ~~was not a straightforward matter~~. ~~In~~ An additional technical complication arose from recognition ~~of the need to~~ purify Factor VIII (separate the Factor VIII component from other material in plasma) ~~, it was thought that the purification of the product (the separation of the Factor VIII component from other material) was important.~~

14. In 1980, German scientists working for Behringwerke published a report which suggested that pastuerising Factor VIII at 60°C for 10 hours removed the risk of ~~freed it from~~ Hepatitis B ~~risk~~, but ~~said~~ that further proof was needed to confirm whether this process ~~it~~ 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 ~~of the~~ process were acknowledged to be low – less than 25% of SNBTS's own production yield ~~process~~ of Factor VIII. SNBTS research on pasteurisation also began in 1981. ~~also began its own research on pasteurisation in 1981.~~

15. In 1982, US scientists at International Society of Haematology Congress reported that Factor VIII could be heated to 80° 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. (*SNBTS paper ref. 27*).

16. The Department has seen supporting evidence from January 1983 that the SNBTS Protein Fractionation Centre (PFC) was going ahead with the development of a pasteurised heat treated product with the intention of reducing the risk of transmitting Hepatitis. (*Paper X: SNBTS Directors/Haemophilia Directors/Scottish Office meeting.*) In 1983, Scotland was self-sufficient in SNBTS Factor VIII ~~FVII~~ product, in accordance with Scottish Health Service policy that Scotland should ~~at that time to~~ be self-supporting in blood products. ~~There was some concern that commercial firms might pre-empt PFC by offering supplies of their own heat treated products for clinical trials. By 1985, focus on heat treatment had shifted to HIV, since this was now seen as the biggest threat~~.

17. In 1983, SNBTS learned that two commercial firms were investigating dry heat treatment of FVIII at 60°C. SNBTS carried out preliminary studies on dry heat treatment of their own 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 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.

18. In March 1984, HIV was isolated as a blood-borne virus. The focus on heat treatment therefore shifted towards the optimal method to eradicate HIV, since this was now recognised as the biggest threat to haemophiliacs. ~~On learning of this development, SNBTS~~ SNBTS therefore decided to explore further the options available should HIV be found to be sensitive to dry heat treatment. They made further measurements of ~~on~~ the behaviour of NY when subjected to ~~under~~ heat treatment, which were completed in October 1984.

19. In April 1984, Bayer (USA) published a patented method for the pasteurisation of FVIII [60°C for 10 hours – check]. PFL in Oxford in 1984 managed to dry-heat their own Factor VIII product (8Y) to 80°C for 72 hours. It was expected that this would provide greater protection against HIV. However. ~~This~~ this product was 10 times more purified than SNBTS's 8Y product, which SNBTS postulated might be the factor which allowed this treatment. At that time ~~There~~ there was no indication ~~at that time~~ whether ~~thus~~ 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).

20. 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 ~~their~~ Factor VIII product NY at 68°C for 2 hours, ~~to render~~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 [DN - What exactly does this mean?] 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, they had sufficient stocks to stop production but still maintain supplies, and go on to trial other types of heat treatment.

21. ~~In January 1985, SNBTS had put into action a process to specify and obtain a high accuracy treatment cabinet to a specification similar to that used by PFL. The first of these cabinets was obtained and put to use in July 1985.~~

22. Meanwhile, in March 1985, PFL were heat-treating all of their FVIII – some at 80°C. In May 1985 BPL were doing the same. By September 1985, all PFL/BPL Factor VIII, which amounted to a quarter of the requirement in England and Wales for Factor VIII, ~~FVIII – a quarter of the England and Wales requirement of Factor VIII –~~ was being heat treated at 80°C [check – for how long???]

23. In Autumn 1985, SNBTS developed a highly-purified ~~FACTOR~~ Factor VIII, but it was unable to withstand ~~did not stand up to~~ heat treatment at 80°C. They concluded that it was the process of freeze-drying which was crucial when it came to the tolerance of the product to dry heat. Scientists at SNBTS decide that they should concentrate on 80°C dry heat; this approach was endorsed by SNBTS management in February 1986.

24. In August 1986, SNBTS produced ~~their~~ the first trial batches of their new Factor VIII product - Z8 - ~~FVIII Z8,~~ treated at 80°C for 72 hours. In September 1986 came a preliminary report that treatment of the BPL product ~~FVIII~~ 8Y at 80°C for 72 hours might prevent the transmission of NANBH (*SNBTS paper ref 53*). SNBTS undertook ~~introduced~~ a clinical trial of ~~their new product~~ Z8, in March 1987. In April 1987 they made it available for routine clinical use. ~~Results confirming the efficacy of 80°C/72h heat treatment of 8Y were finally published in October 1988~~.

25. It seems important to note that while the first production of 8Y in England was March 1985, ~~earliest introduction of 8Y had been March 1985 in England,~~ there was no evidence that the 80°C/dry heat treatment ~~method~~ was indeed effective against NANBH until the preliminary clinical report was published in September 1986. The full results of this trial were not published until October 1988, by which time the SNBTS product Z8 had been in widepsread clinical use from April 1987. Scotland became sufficient in Z8 in 1987, the same year that the product was introduced. It would be difficult to construe from this chronology that there was ~~had been~~ undue delay in introducing an HCV safe product in Scotland..

26. ~~Scotland became self-sufficient in Z8 in 1987, the same year it was introduced.~~

27. After the HCV virus was isolated and identified in 1989, results were published confirming ~~on the~~ clinical safety of both 8Y and Z8 as regards ~~form~~ HCV transmission in 1993. ~~In October 1992, UK marketing authorisation had been withdrawn form the last heat treated but non HCV product.~~

Screening for HCV

28. [to be added once I have read Prof Cash's papers! – basically setting down what is known about ALT testing, when it was introduced, and whether it was considered in this country]

Government Policy

29. [To be added once I have got papers from DH]

Complaints about individual treatment

30. Some correspondents have raised the issue that they cannot make a complaint about the treatment they received at the time, since they were told that the time limit for making complaints is six months. 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."

In addition, it makes it clear that the complaints system cannot deal with events about which the complainant is already taking legal action. 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. So much time has now passed that complaints officers may well take the view that it would not be feasible to investigate this type of complaint. It is possible for Ministers to issue different directions to the NHS about conducting complaints procedures. However, it ought to be said that these procedures were designed for fast resolution of complaints; it is difficult to see how complaints about the availability of information could actually be resolved.

Conclusion

31. The episode of HCV infection of haemophiliacs is devastating for the individuals infected and their families, and is a matter for public distress and regret. While ~~Even though~~

the facts strongly suggest that ~~the people~~those involved in the manufacture of blood products made every effort to develop ~~safe~~ products free of viral risk, it is undeniable that these efforts took some time to come to fruition. However, to talk in terms of people being exposed "longer than they should have been" is not ~~appropriate~~accurate. [DN - to be expanded in the light of comment in covering minute]~~; it would be impossible to specify how long someone *should* have been exposed - unless this were to be no time at all. Scientific knowledge in this field was developing all the time, and it is impossible to say how much more quickly it *could* have developed under any given circumstance.~~

Scientific knowledge in this area was developing rapidly during the period in question. From the available evidence, SNBTS appear to have acted ~~as quickly as possible~~ reasonably under the circumstances to develop a Factor VIII product free of the risk of Hepatitis C.

as qu. as they could