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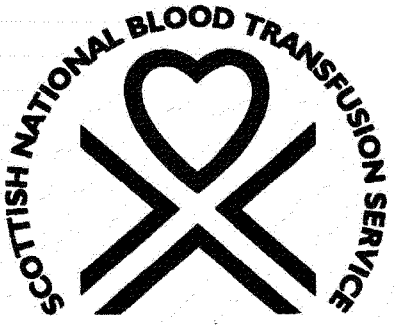

PENROSE INQUIRY

ACTIONS SURROUNDING FVIII BATCH 023110090 (NY 3-009)

GLOSSARY

antibody	A protein produced as part of the body's immune response to a 'foreign invader'. Depending on the infectious agent, antibodies may be effective at eliminating a 'foreign invader' (e.g. measles virus) or less effective (e.g. HIV, Hepatitis B and hepatitis C infection). A reactive antibody to a virus, such as hepatitis C virus, means that the person may at some stage have been infected with the virus. It does not necessarily indicate present infection
antigen	A 'foreign' substance that stimulates the formation of antibody, as part of the body's immune response. Tests that detect the antigen are more direct than those that detect antibodies and can detect infections earlier.
combi tests	An assay system which simultaneously tests for both antigen and its related antibody in the same assay.
EIA	Enzyme Immunoassay
factor II	Prothrombin. A blood coagulation factor present in DEFIX, an SNBTS coagulation factor concentrate that was used in the treatment of haemophilia B and other disorders of coagulation.
factor VIII	A blood coagulation factor which is lacking in people with haemophilia A. Factor VIII is a protein which is present in trace quantities in the plasma of normal people eg. accounting for about 6 parts per million (ppm) of the total protein present in normal human plasma.
factor IX	A blood coagulation factor present in DEFIX which is lacking in people with haemophilia B.
factor x	A blood coagulation factor present in DEFIX, an SNBTS coagulation factor concentrate used in the treatment of haemophilia B and other disorders of coagulation.
HIV	Human immunodeficiency virus - the blood borne virus which causes AIDS. There are different strains of the virus (i.e. HIV-1, HIV-2). HIV-1 was first isolated in 1983 and was proven to be the cause of AIDS in 1984. HIV-2 was discovered in 1986.
HTLV III	Former name for HIV
Immunoglobulin G (IgG)	Plasma proteins involved in fighting infections (commonly known as antibodies)
library samples	Archive samples stored usually frozen for protection
Logs	Logarithms, a number expressed to the base 10
NAT Testing	A test that detects the nucleic acid (or gene) (of a pathogen)
Plasma	The straw coloured liquid portion of blood. Contains proteins (e.g. albumin, antibodies, clotting factors) as well as hormones, fats and dissolved salts and gasses.
Polymerase chain reaction (PCR) assay	Sensitive analytical technology by which the genetic material of viruses can be detected directly.
RNA	Ribonucleic acid (acts as an intermediate between genes and proteins; or in some pathogens the stuff of genes themselves)

seroconversions	A response to an infection, usually occurring early in an infection, which denotes the point where an individual goes from having no antibody, to the formation of antibodies against the agent causing infection.
Western blot system	An analytical technique used to detect specific proteins in a sample, by separating them using electrophoresis and then transferring the dispersed proteins to a membrane where the target protein is detected using its specific antibody.

CONTENTS

1. Questions From Mr Tullis

The questions contained in an e-mail dated 26 February are as follows

*When it first came to light in the Autumn of 1984 that the group of patients at Edinburgh Royal Infirmary had been infected with HIV from a PFC product, a batch of Factor VIII concentrate (**023110090**) was strongly implicated. It was decided to identify all donors to the pool of plasma from which this batch had been manufactured and then quarantine all plasma subsequently donated by those donors. We need a step by step explanation of the records and the systems which enabled these steps to be taken. Where and in what form were the records which revealed:*

** The pool from which the batch had been manufactured*
** The identity of the donors contributing to that pool*
** The location of all other plasma from those donors.*
Was the infected donation or donations identified? Was the donor identified?
What, physically, happened to the plasma when it was quarantined?

The following elements of this paper are intended to address the specific questions from Mr Tullis and to provide some background information on the circumstances which led to this batch being considered to be a possible source of HIV infection in some haemophiliacs.

Note: the full batch number which appeared on the label was 023110090. However, for in house purposes this is condensed to NY 3-009 and this term is used in the rest of this paper, for ease of reading.

2. Timeline of Key Actions in Response to Finding of Infectivity

Information on HIV infection of haemophiliacs in Edinburgh first became known to the SNBTS in October 1984. This came from Dr Ludlam, Haemophilia Centre Director, Edinburgh Royal Infirmary, who had test results available from a development test for HIV (then called HTLV III) carried out in the laboratory of Dr Tedder in Middlesex Hospital Medical School. Data was initially available on 3 haemophiliacs, all of whom had received batch NY 3-009 and were positive for HTLV III [HIV]. On the basis of this initial report, a recall of batch NY 3-009 was carried out on 1 November 1984[1]. By mid November, data became available on 16 haemophiliacs, who had all apparently developed evidence of HIV infection during 1984. Batches received by these patients were identified by Dr Ludlam. Following a meeting held between Dr McClelland, Director South East Regional Transfusion Centre (SERTC), and Dr Ludlam, Dr Ludlam's findings were summarised and it was reported by Dr McClelland that 15 of these patients had received no commercial FVIII and the 16th had received commercial FVIII "...several years ago which can be discounted from the present problem". The review of the batches received showed that the 16 haemophiliacs had received a total of 33 batches of SNBTS FVIII over a period which could account for the development of their HIV infection. For each of these 33 batches, an analysis was performed of the number of the 16 haemophiliacs who had received each batch. The number of recipients of each batch varied between 2 and 15, i.e. no batch had been given to all 16 patients. However, batch NY 3-009 had been given to 15 of the patients at a time which was consistent with them developing the infection. In contrast, 2 separate batches had been given to 14 of the 16 patients, but following further investigation it was found that several of these patients had received the product after they had become infected.

On the basis that batch NY 3-009 was the most likely batch to have infected the majority of the patients, the earlier decision to recall it on 1 November 1984 was fully justified. Steel et al reported in the Lancet in 1988 that later monitoring revealed that a further 3 recipients

of the implicated batch developed antibody to HIV making a total of 18[2]. It is noteworthy, however, that Steel et al also reported that not all recipients of batch 3-009 developed evidence of HIV infection (14 out of 32 recipients remained uninfected). Although it has never been established conclusively that the batch was infective, the actions taken were made on the basis that this was a justifiable, though unproven, assumption. Following this decision, a number of actions were taken and these are summarised in Table 1.

The information that SNBTS FVIII had transmitted HIV was discussed at many meetings, both at key SNBTS Management meetings and at multidisciplinary meetings with other interested parties, e.g. Haemophilia Directors and Scottish Home & Health Department (SHHD). Dates of some of these meetings are also provided in Table 1.

3. History of Batch NY 3-009

The plasma used to make the batch was collected at each of the 5 SNBTS Centres (Aberdeen, Dundee, Edinburgh, Glasgow and Inverness). A weight of 940 kg of plasma was entered into production and this was derived from approximately 4,000 donations.

The manufacture of this batch was started on 7 November 1983 and a total of 1070 vials were cleared for issue on 10 February 1984. This 3 month period covered the time to manufacture, test and package the batch and this overall processing time was typical of product manufactured at that time.

Of the 1070 vials placed at issue, 1020 were sent to the SERTC on 23 February 1984. These vials would have been used to supply the Edinburgh Haemophilia Centre. The remaining 50 vials were supplied to the North East Regional Transfusion Centre (NERTC), where they would have been held for the treatment of haemophiliacs in Aberdeen.

The recall of batch NY 3-009 was initiated by telephone on 1 November 1984 and followed up in writing on 7 November[3]. None of the 1020 vials supplied to the Edinburgh centre were available for return, i.e. they had all been used to treat haemophiliacs. 41 of the 50 vials sent to Aberdeen were returned unused, and were held in quarantine at the Protein Fractionation Centre (PFC). These were used in the period 1984 to 1988 as the basis for carrying out studies of markers of infectivity. All remaining vials held at the PFC were discarded during a tidy up of the quarantine area in 1988, following a Medicines Control Agency (MCA) Inspector's request to tidy out the cold storage area. This meant that no further material was available for study in the period 1988 to 2008. When the Penrose Inquiry was announced, further investigations were made as to whether or not there were any vials from batch NY 3-009 still in existence within any of the clinical virology laboratories with which the SNBTS has collaborated over the years. One vial of batch NY 3-009 was discovered and has subsequently been investigated by the National Institute for Biological Standards and Control (NIBSC). The results of this investigation are noted below (section 7).

4. PFC Records

As a pharmaceutical manufacturer, the PFC was obliged to hold records of all manufacturing activities. Typical records and the form in which these were retained is summarised as follows.

4.1 Batch Manufacturing Record

All PFC products were manufactured in batches, each labelled with a unique batch number and expiry date. Key stages in batch manufacture and key quality control (QC) tests during manufacture and on the finished product were all recorded in this batch record. If the batch complied with the release criteria defined at the time, the

batch was approved for issue by the SNBTS QC Inspector following a final review of the batch record.

The batch record was retained in paper form throughout the shelf life of the product. Early batch records such as this one were subsequently converted into microfiche form to reduce storage requirements. These microfiches have been retained on a permanent basis. A paper copy of the batch record has since been recreated from the microfiche copy.

4.2 Issue History

At the same time as the QC Inspector approved the batch for release, he also approved the issue of the batch by signing a batch history record sheet which comprised of a single buff coloured stiffened paper record. This unique record sheet was used to record all product issued from the released batch. These record sheets have been retained on a permanent basis. The record sheet for batch NY 3-009 shows that 50 vials were sent to the NERTC on 22 February 1984, and the remaining 1020 were sent to the SERTC on 23 February 1984.

A copy of the original history sheet is available. Original history sheets have been retained and are still held in PFC records.

4.3 Plasma Records

At that time, all plasma for fractionation at PFC was collected as whole blood and the plasma separated from the red cells at the regional centre. The plasma was frozen as soon as possible after separation. Plasma was received from each of the 5 Scottish Centres in cardboard boxes which typically contained 12 frozen plasma donations. Each box was given a unique number at the centre of origin, and it was this box number which was recorded by the PFC staff on plasma traffic sheets. No records were kept at the PFC of the donation numbers of the individual donations contained in each box; instead this information was retained at each of the 5 centres so that a trace could later be carried out if required.

Individual boxes of plasma were bound in groups of 4 for storage purposes and given new identifiers (cold storage numbers) for each group of 4 [4 x 12 = 48 plasma donations]. These new identifiers were also recorded in the plasma traffic sheet along with the weights of the contents in kilograms (Kg). When required, a suitable weight of plasma was removed from storage. The cold storage numbers for each group of 4 boxes was recorded in the batch record. A total of 95 cold storage units were used to manufacture batch NY 3-009 and it is these numbers which are recorded in the batch record, with a total recorded weight of 1043 Kg (Note: this weight included packaging with an estimated weight of 103.1 Kg, giving a plasma weight of 940 Kg). This is equivalent to plasma from 4560 blood donations, a relatively small number by international standards.

When the decision was made to trace the individual donations used to make this batch, the process was fairly straightforward. The batch record was consulted to obtain the cold storage numbers. The plasma traffic sheets were then consulted and the individual box numbers obtained. Lists of box numbers were then compiled for each centre, and it was these lists which were supplied to the relevant centres in a series of letters dated 12 November 1984. Copies of the traffic sheets are available. The original traffic sheets were retained and are still held in external storage.

5. Records at Transfusion Centres

Each Centre held paper records which identified the contents of each box of plasma despatched to the PFC. When notified by the PFC of the box numbers included in batch NY 3-009, they could find the donation numbers of the implicated donations. From these numbers, they were able to identify the relevant donors from further paper records (this was all performed prior to computerisation of SNBTS donor records). Since the original donations were collected in autumn 1983 (entered into production at the PFC on 4 November 1983), it was likely that many of the donors would have given subsequent donations. These were also traced and provided the information used to quarantine subsequent plasma donations, either those held at the Regional Centres or subsequently sent to the PFC.

6. History of Quarantine of Donations

At a meeting of the SNBTS Co-ordinating Group on 6 November 1984, it was decided that the donations used to manufacture the batch should be traced and that relevant information should be provided to each Centre to enable them to perform this trace[4]. As stated in paragraph 4.3 above, the information on plasma box numbers was supplied to each Regional Transfusion Centre on 12 November 1984. This allowed each site to trace the constituent donations and, therefore, the donors could be identified. At a further meeting of the Co-ordinating Group on 20 November, it was decided that repeat donations from the donors should be followed up. The actions varied for the plasma and cellular components. For ease of understanding, these are described separately below.

6.1 Plasma Donations

It was decided at the Co-ordinating Group meeting on 20 November that plasma from these donors would be quarantined[5]. The minute states that "...PFC would quarantine any fresh plasma related to the donors whose donations had been pooled into the batch concerned". This quarantine would apply to all subsequent donations, and on this topic, the minute states that "...subsequent donations from the same donors have to be identified so that they can be separated, the cells discarded and the plasma quarantined." It is known that plasma from these donors held at the PFC was segregated physically to prevent it from entering into production.

Further discussions within SNBTS took place in January 1985. A written proposal to return the quarantined plasma to stock was made by the PFC Director on 8 January[6]. The principal justification for this proposal was that the FVIII product manufactured from these donations would be heat treated using a process with published capability to inactivate HIV. This proposal was agreed by the National Medical Director in mid January and confirmed in writing on 23 January 1985[7]. An instruction to remove the quarantine status from this plasma was issued to PFC Manufacturing Managers on 22 January 1985[8].

The period of plasma quarantine was therefore less than 3 months in total and was of a precautionary nature only, since it was never proven conclusively that the batch was infective, nor that any particular donor was implicated.

6.2 Cellular Components

At the Co-ordinating Group meeting on 20 November 1984, it was also agreed that red cells from donations collected from the donors should be discarded.

Consideration was given to testing samples from all 4,000 donors for evidence of HIV antibody. Samples were not retained from all of the donors, so testing all of the donors would not have been straightforward. Dr Tedder, of the Middlesex Hospital Medical School, was approached to test the samples available (around 60% of the total), but felt that this was not worthwhile unless the SNBTS could guarantee to supply samples from 99.5% of the donors.

However, this decision to discard the red cells was reversed on 3 December 1984, in a letter from the National Medical Director, based on issues relating to maintenance of the blood supply[9]. The letter suggested that, in view of the operational requirements of the service, all 4,000 donors should remain on service and their donations used to manufacture concentrated red cells and platelet concentrates. Plasma would remain in quarantine until further notice. The proposals from the National Medical Director were ratified at a meeting of the SNBTS Directors on 11 December 1984.

7. Further Testing of Batch NY 3-009 and Contributing Donors

Since the initial identification of batch NY 3-009 as possibly infected, a number of studies have been carried out to elucidate the possible involvement of this batch in cases of HIV transmission. A number of facts are known about this batch and are summarised as follows:

- a total of 32 patients received the batch, but only 18 (see section 2) were ultimately found to have evidence of HIV infection. This suggests that the batch was not as infective as some batches from US manufacturers which resulted in infection in up to 100% of recipients.

- the batch was tested over the period 1985 to 1986 in a number of laboratories for the presence of antibody to HIV, but none was ever found.

- when HIV screening was introduced by the SNBTS in October 1985, all donors found positive were studied and lookbacks were performed on previous donations. For some of these donations, it was possible to find library samples to test and positive donations were found which had been included in pools used to make individual batches. In addition, previous donations were traced for which no library samples were found, but which were considered to be potentially infective. These donations (both confirmed positive and potentially positive) were all traced and the findings are summarised in an internal report. (Appendix 1) None of these donations were used to make batch NY 3-009.

- as stated earlier, the bulk of the returned vials were discarded during a clear out in 1988, so it was not possible to use more recent techniques to test for infectivity as and when they were developed. However in 2008, a vial was discovered in a research lab in the University of Edinburgh. This vial was sent directly to an independent laboratory at the National Institute for Biological Standards and Control (NIBSC), where it was reconstituted and sub-samples were frozen to permit further analysis. Some of the sub-samples were tested in the expert virology laboratory within NIBSC. Samples were tested for the presence of antibody to HIV and for HIV RNA using the latest very sensitive methods. The results are summarised in a report from NIBSC (Appendix 2). With regard to antibody, a negative result was found in tests from 2 different manufacturers, with indeterminate results in a western blot system. Some more recent assays test simultaneously for antibody and antigen in a single assay system. Using these so-called combi tests, a negative result was found in one assay (Murex) but positive results were obtained in a second test (Genscreen). Negative results were obtained from a commercial

polymerase chain reaction (PCR) assay, whereas low levels of HIV RNA sequences were found using a sensitive in-house PCR test. The conclusion from these tests is that there is some evidence for very low levels of HIV markers in this batch, but this does not confirm infectivity. The material for batch NY 3-009 also tested positive for HCV [Hepatitis C] RNA showing that despite the unsuitable storage conditions nucleic acid tests were still effective. It was expected that batch NY 3-009 would contain HCV RNA because of the known epidemiology of HCV in Scotland then and now with almost 1% of the population being HCV positive, and 0.1% of new blood donors.

In conclusion, batch NY 3-009 has recently been shown to contain low levels of markers of HIV infection and could have been infective in 1984. However, due to the ambiguity of the test results, the infectivity of this batch has never been absolutely confirmed, nor has a specific infective donor been identified.

8. Introduction of Heat Treatment

It should be noted that the finding of HIV infection in Scottish haemophiliacs was unexpected, since until that time the belief was that the infection was largely confined to donors in the USA. The report of HIV infection in Scottish haemophiliacs in October 1984, coincided with the finding by workers in the USA, that HIV could be inactivated rapidly in freeze dried FVIII by heating the final dried vials at 60-68°C (reported by Dr Jason at a meeting in Groningen on 2 November 1984. This data was later published by McDougall et al in 1985[10]). This process was introduced by the PFC very quickly and after 10 December 1984 all FVIII issued by the SNBTS was heat treated, initially at 68°C for 2 hours. Unheated stocks of FVIII were recalled on 6 December 1984. Further developments allowed FVIII to be heated at 68°C for 24 hours. This process was available for FVIII prepared from January 1985, and this product was issued routinely from 4 September 1985.

The introduction of heat treatment was a very rapid process and had a number of effects:

- no cases of HIV have ever been reported in recipients of SNBTS heat treated FVIII. (Indeed, it is known that potentially infective donations from donors who were subsequently found to be HIV positive were included in some heat treated batches. The recipients of these batches were tested and no new infections arose in patients who were HIV negative prior to receipt).

- all plasma in stock in October 1984 when the first evidence of infection came to light was used in the manufacture of heat treated FVIII which was issued from 1985 onwards. This provided the basis for releasing the quarantined donations from the donors who had contributed to batch NY 3-009.

9. Conclusions

The main conclusions are as follows

9.1 The infectivity of the batch was deduced from epidemiological data available in 1984. It seems likely that this assumption was correct, but it has never been proven.

9.2 The actions taken at the time were well documented and most of the documentation is still available and described in this paper.

9.3 None of the donors whose plasma was used to make batch NY 3-009 was ever identified as being HIV positive

9.4 When the possible infectivity of batch NY 3-009 was discovered, a decision was taken to quarantine any further plasma donations from the same donors, pending investigation. This investigation did not identify an infective donor and the quarantine was ended when heat treatment at 68°C for 24 hours was ready to be introduced, i.e. all of the quarantined units of plasma were used to make product heated at 68°C for 24 hours, a process with published evidence of efficacy in inactivating HIV.

10 References

1. McClelland DBL, Memorandum to RJ Perry (Acting Director, PFC), 20 November 1984. Events leading up to the recall of Factor VIII Batch 023110090.

2. Steel et al (1988), HLA Haplotype A1 B8 DR3 as a Risk Factor for HIV-related Disease. Lancet, May 28 1988, 1185-8.

3. PFC records. Recall of Defective Product from RTCs by PFC. Batch NY3-009. Recall initiated by B Cuthbertson, 7 November 1984.

4. Perry RJ, Letter to the Regional Transfusion Directors, 12 November 1984.

5. SNBTS, Minutes of the SNBTS Co-ordinating Group Meeting held on 20 November 1984, Item 15.

6. Perry RJ, Letter to the National Medical Director (J D Cash), 8 January 1985.

7. Cash JD, Letter to RJ Perry (Acting Director, PFC), 23 January 1985.

8. Perry R, Memorandum to W Grant, A Dickson, 22 January 1985. Quarantine of plasma associated with FVIII batch no 3-009.

9. Cash JD, Letter to RJ Perry (Acting Director, PFC), 3 December 1984. Donors: Batch 023110090 Intermediate FVIII.

10. McDougall et al (1985). Thermal inactivation of the acquired immunodeficiency syndrome virus T-cell lymphotropic virus-III / lymphadenopathy-associated virus, with special reference to antihemophilic factor. Journal of Clinical Investigation 76, 875-7.

TABLE 1

NARRATIVE OF EVENTS SURROUNDING PFC FACTOR VIII BATCH NY 3-009 (NY3-009)

Date	Comment
c.June-October/1983	Collection of whole blood donations that provided plasma to 3-009.
04/11/ 1983 – 11/11/1983	NY batch 3-009 prepared at PFC; 1158 vials prepared.
10/02/1984	1070 vials inventoried and available for issue/release. [Others: 1 for library, 2 secondary rejects, 55 badly dried (primary rejects), 30 to QC].
22/02/1984	50 vials issued to Aberdeen.
23/02/1984	1020 vials issued to Edinburgh. Batch NY 3-009 transfused into patients between March and May 1984.
26/10/1984	Dr Ludlam informed Dr McClelland of initial concerns that PFC factor VIII had transmitted HIV to 3 haemophiliacs (all received NY batch 3-009, as well as other batches being involved).
01/11/1984	Dr McClelland contacted Bruce Cuthbertson (in Dr Perry's absence) describing seroconversion of 3 haemophiliacs treated with NY batch 3-009; BC contacted Dr Urbaniak (Aberdeen) requesting that NY batch 3-009 be recalled and quarantined.
02/11/1984	Recall of NY batch 3-009 initiated by PFC. 41 vials returned from Aberdeen (9/11/84), no vials from Edinburgh (form returned 20/11/84).
02/11/1984	Initial analysis by Dr. Ludlam showed one batch of PFC factor VIII was received by 15/16 of patients who seroconverted in 1984 and received (almost) exclusively PFC factor VIII.
02/11/1984	Dr Jason (Centers for Disease Control, USA) reports at Groningen conference that HIV is inactivated at 68°C, 4logs in 1 hour.
03/11/1984	Dr McClelland and Dr Boulton contacted all the Scottish Transfusion Centres and Northern Ireland Transfusion Centres to inform senior staff that NY batch 3-009 should be immediately recalled.
06/11/1984	Co-ordinating Group meeting. Dr McClelland gives update on findings of HIV infection in haemophiliacs.
07/11/1984-21/01/1985	The same plasma used to make NY 3-009 was also used to make a product (DEFIX) containing Factors II, IX and X, used principally for the treatment of haemophilia B. DEFIX, DE831, was recalled on 7 November. DEFIX issued to Glasgow, Edinburgh and Dundee, all used apart from 1 vial returned from Glasgow. No HIV infections reported in any recipient.
Week of 12/11/1984	Dr McClelland reports to the Scottish Regional Transfusion Directors (RTDs) that 16 patients seroconverted in 1984 who received exclusively PFC Factor VIII concentrate.
12/11/1984	Dr Perry (Director PFC) writes to each RTD detailing box numbers of plasma from their centre which contributed to the plasma pool.
15/11/1984	Dr McClelland issues letter to Dr Cash, summarising Dr Ludlam's data on Factor VIII batches used for the 16 HIV transmissions concluding that NY batch 3-009 is probably responsible for these seroconversions.
18/11/1984	Heat treatment at 68°C for 2 hours of all Factor VIII begins at PFC.
20/11/1984	Dr McClelland issues memo listing the events leading up to the recall of NY batch 3-009 to Dr Perry (cc Dr Cash).

Date	Comment
20/11/1984	Co-ordinating Group meeting, item 15: AIDS, Position of each centre with respect to tracing donors who contributed to NY3-009, identifying subsequent donations, discarding the red cells and quarantining the plasma recorded. Discussions on quarantining plasma and discarding red cells took place.
28/11/1984	Dr Perry writes to each RTD stating that all plasma delivered on or after 2 Nov 1984 is still in stock and has not been processed and in addition gives box numbers from their Centre received before 2 Nov which had not yet entered into the process. (19 from Dundee, 120 from Edinburgh, 1 from NI, 32 from Glasgow, 0 from Aberdeen and 0 from Inverness).
29/11/1984	Meeting of Haemophilia Directors and SHHD to discuss implications of recent finding of HTLV III antibodies in Scottish haemophiliacs.
03/12/1984	Letter from Dr Cash to Dr Perry advising that red cells and platelets from donors contributing to manufacture of batch do not need to be discarded.
06/12/1984	Letter from Dr Perry to RTDs: Arrangements made for first batches of heat treated (HT) FVIII to be dispatched to Belfast, Glasgow, Edinburgh, Inverness, Aberdeen and Dundee RTCs (~one months supply). Request from Dr Perry to RTDs to make arrangements for all unheated Factor VIII to be recalled as widely as possible.
10/12/1984	Sufficient heat-treated Factor VIII for all patients was distributed by SNBTS throughout Scotland and Northern Ireland.
11/12/1984	Meeting of SNBTS Directors: decision to discard red cells from subsequent donations of those who contributed plasma to the implicated batch was relaxed due to the possibility of considerable shortage over Christmas period. Donor samples kept. In West one donor identified who was homosexual and weakly positive for VD. Donor sample sent to Dr Tedder for testing. (This donor was subsequently found to be negative for antibody to HIV).
08/01/1985	Dr Perry writes to Dr Cash, asking that decision to quarantine plasma should be reversed as the PFC now has more rigorous heating conditions for FVIII.
22/01/1985	Memo from Dr Perry to PFC Manufacturing Managers instructing them to release all quarantined plasma for processing.
23/01/1985	Dr Cash writes to Dr Perry, cc all RTDs, confirming that all plasma being held in quarantine which relates to the implicated batch of FVIII should be released for fractionating.
19/02/1985	Co-ordinating Group meeting, item 9d: agreed that Centres holding plasma related to implicated batch could release it to the PFC. They would continue to hold samples.
03/08/1985	Publication in Lancet from Ludlam et al indicating that one batch of SNBTS Factor VIII had resulted in 15 haemophiliac patients acquiring antibodies to HTLV-III.
14/10/1985	Nationwide testing of blood donations for HIV antibody starts.
28/05/1988	Lancet publication from Steel et al indicating 'Of 32 patients exposed to a single batch of factor VIII contaminated with HIV, 18 became antibody positive'. Dose of vials in those that seroconverted ranged from 9-109 vials (8 of 9 patients who used 40 or more vials became infected, only 7 of 23 who used less seroconverted).

Date	Comment
1988	Inadvertent discard of remaining PFC vials of NY batch 3-009 following Medicines Inspector comment to tidy up cold room.
Dec 1990	Journal of Virology publication (Vol. 64 no. 12, Balfe et al) suggested that there may be three or more different HIV viruses involved in the HIV 'Edinburgh cohort' (6 patients having sequences with a very close relationship, and two patients more divergent).
14/04/2008	Dr Bienek (PFC) contacted Prof Simmonds inquiring as to whether or not he had ever tested any PFC Factor VIII for HIV in the early 1990s.
23/04/2008	Prof Simmonds replies that a vial matching that description had been found.
30/04/2008	Prof Simmonds indicated that he thinks that vial of NY 3-009 had been at room temperature for several years – now being placed in the fridge.
11/08/2008	Vial of NY 3-009 sent directly from Prof Simmonds lab to NIBSC for testing.
29/08/2008	Interim report received from NIBSC indicating that the material for batch NY 3-009 had tested positive for HCV RNA (20-50IU/mL [80-200ge/mL]); negative for HIV-1 RNA; negative in three different anti-HIV-1 and 2 test, indeterminate in one other anti-HIV 1+2 test and reactive in a fifth anti-HIV 1+2 test (repeatedly reactive).
31/03/2009	Final report received from NIBSC indicating that batch NY 3-009 had tested positive for HCV RNA, negative for HIV-1 RNA by NAT but positive for HIV-1 RNA by PCR at very low levels, negative in three different anti-HIV-1 and 2 tests, indeterminate in one other anti HIV 1+2 test but reactive in a 4th generation highly sensitive EIA for anti-HIV 1+2 (repeatedly reactive).

APPENDIX 1

COPY OF 1991 REPORT ON HIV INFECTIONS IN PFC PLASMA DONORS

HIV SEROCONVERSIONS RELATED TO SNBTS FVIII

1. INTRODUCTION

This updates an earlier (interim) report dated 28/6/86 which summarised available information on FVIII batches administered to 18 Scottish haemophiliacs believed to have seroconverted to HIV following receipt only of SNBTS FVIII. The contents of this report only relates to information received by the manufacturer (PFC). Other clinical information may be available from Regional Transfusion Directors or Haemophilia Directors.

2. SUMMARY OF DATA ON BATCHES ADMINISTERED

2.1 16 Haemophiliacs in the South-East of Scotland were found to have seroconverted to HIV at some stage during 1984. 15 of the 16 haemophiliacs received a common batch (023110090) and it has been concluded that this batch was infective.

2.2 Follow-up of West of Scotland haemophiliacs, has revealed two patients receiving SNBTS FVIII who seroconverted in 1984 and 1985 respectively.

PATIENT 1

Incomplete details available as no written report ever received from reporting clinician (Dr Maddock, GRI).

Sample	1.7.82	Negative
Sample	12.12.83	Positive

PATIENT 2

Seroconverted between 5.10.84 and 25.10.85. At least five years since previous Commercial FVIII.

2.3 The batches of product received by the South-East and West of Scotland seroconverters are summarised in Table 1. The following should be noted:

a. Neither of the West of Scotland patients received the batch (023110090) implicated in the South-East Scotland seroconversions.

b. No batch is common to the two West of Scotland seroconversions.

c. If SNBTS FVIII was responsible for each of the 18 seroconversions, then at least three infective batches must have been issued.

d. Seven batches were common to West of Scotland and South-East Scotland seroconversions. These batches were:

:/WS6/LETTERS/CUTHBERTSON/DML01011.91

	Batch	Number of Seroconversions	
	756	8/18	
	762	10/18	*
	780	2/18	
	784	13/18	
	797	10/18	*
	3-003	15/18	*
	3-016	4/18	
c.f.	3-009 (South-East Implicated batch)	15/18	*

The batches marked * were tested for HIV antibody using a sensitive variant of the Wellcozyme assay. No trace of antibody was found in any of these batches.

3. RETROSPECTIVE DETECTION OF HIV POSITIVE DONATIONS USED IN THE MANUFACTURE OF SNBTS FVIII

The introduction of HIV antibody testing led to the discovery of several donors who were HIV antibody positive. When positive, library samples of previous donations were also tested. Where HIV positive library samples were detected, the fate of the donation was traced.

3.1 Six batches of FVIII have been identified which were derived from confirmed HIV positive donations. These are listed in Table 2, only one of these batches was in the group of batches listed in Table 1 which had been potentially implicated in the seroconversions. This batch (No. 797) had been administered to 8 of the Edinburgh seroconversions and could have been implicated in their seroconversion. However, 19 patients in the West of Scotland received this batch. Of these, 12 were already HIV positive prior to receiving it. The remaining 6 recipients remained seronegative. It does not therefore, appear to be a good candidate batch for any of the Edinburgh seroconversions.

3.2 A further group of FVIII batches have been derived from donations for which there was no library sample remaining but where a subsequent donation was found HIV-antibody positive. It is likely that many of these donations were seronegative but their infectivity cannot be completely excluded. Of these 10 batches, only one (3-015) was included in Table 1. Whether this batch was genuinely infective cannot be concluded, although it should be noted that only 8 of the Edinburgh and neither of the Glasgow seroconverters received this batch.

3.3 Follow up of retrospective donor testing has not, therefore, been of any significant value in pinpointing the infective batches responsible for these 18 seroconversions.

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4. COMMENTS

At least 3 batches of SNBTS FVIII were infective and led to seroconversions to HIV in 18 recipients of SNBTS FVIII. The precise number of implicated batches may be defined more precisely as a result of PCR studies on the HIV isolated from these patients. Such studies are being carried out by other bodies at the present time.

One batch (3-009) remains the main candidate for 15 of the 18 seroconversions but the other candidate batches have not been identified.

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5/1/91

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TABLE 1

FVIII BATCHES OF PRODUCT RECEIVED IN 12 MONTH PERIOD BEFORE EARLIEST POSSIBLE TIME OF SEROCONVERSION

Batch	South-East (n = 16)	West (n = 2)	Total (n = 18)
666	0	1	1
681	0	1	1
682	0	1	1
692	0	1	1
699	0	1	1
700	3	0	3
708	2	0	2
711	8	0	8
715	0	1	1
721	6	0	6
724	9	0	9
727	5	0	5
728	8	0	8
733	8	0	8
746	7	0	7
749	0	1	1
750	6	0	6
756	7	1	8
757	0	1	1
759	0	1	1
762	9	1	10
766	0	1	1
768	12	0	12
773	10	0	10

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TABLE 1 CONTINUED

Batch	South-East (n = 16)	West (n = 2)	T (
775	0	1	1
776	5	0	5
780	1	1	2
781	6	0	6
782	0	1	1
784	12	1	1
785	0	1	1
786	5	0	5
787	8	0	8
791	13	0	1
797	9	1	1
799	11	0	1
800	5	0	5
802	10	0	1
803	0	1	1
3-003	14	1	1
3-004	0	1	1
3-005	0	1	1
3-010	2	0	2
3-013	0	1	1
3-014	6	0	6
3-015	8	0	8
3-016	3	1	4
3-017	14	0	1
3-019	10	0	1

TABLE 1 CONTINUED

Batch	South-East (n = 16)	West (n = 2)	Total (n = 18)
3-009	15	0	15
4-006	0	0	1
4-005-1*	0	0	1
4-022-1*	0	0	1
4-055-1*	0	0	1

NOTE: * = Heat Treated 2hrs at 68°C.

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TABLE 2

BATCHES OF FVIII DEFINITELY KNOWN TO HAVE INCLUDED AN HIV-POSITIVE DONATION

BATCH	PFV INCIDENT REFERENCE NUMBER	YEAR OF MANUFACTURE	HEAT TREATMENT CONDITIONS
797	7	1983	NONE
4-027-1	4	1984	68°C/2h
4-047-1	4	1984	68°C/2h
4-072-1	11	1984	68°C/2h
5-003	17	1985	68°C/24h
5-014	4	1985	68°C/24h

NOTE: All of the batches in this table were derived from donations retrospectively found to be HIV-antibody positive.

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BATCH	PFC INCIDENT REFERENCE NUMBER	YEAR OF MANUFACTURE	HEAT TREATMENT CONDITIONS
495	10	1979	NONE
540	10	1980	NONE
599	1	1981	NONE
657	1	1982	NONE
680	10	1982	NONE
702	1	1982	NONE
735	2	1982	NONE
3-015	2	1983	NONE
4-017	9	1984	NONE
5-003	17	1985	68°C/24h

NOTE: All of the batches in the table were derived fro donations for which there are no library samples but wh were found to be HIV-antibody positive on testin subsequent donations.

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APPENDIX 2

COPY OF REPORT FROM NIBSC

Blanche Lane
South Mimms
Potters Bar
Hertfordshire EN6 3QG
United Kingdom

TEST REPORT

TEST REPORT NUMBER:	BV013
SAMPLE TYPE: (nature of material)	Human Antihaemophilic Factor VIII lyophilised
LOT/BATCH/BULK NUMBER OR OTHER IDENTIFIER:	023110090 Expiry Nov 1985; Manufacturer SNBTS, PFC

CLIENT NAME: **SNBTS** NIBSC CONTRACT No: **N/A**

CLIENT ADDRESS: For attention of **Protein Fractionation Centre**
Attn Dr. Carol Bienek,
Virology Section Head
21 Ellen's Glen Road
Edinburgh EH17 7QT

TEST METHOD(S): **NAT for HCV, NAT for HIV-1, anti-HIV 1+2**

RELEVANT METHOD IDENTIFIER(S) (non-accredited tests are marked *, accredited tests may include those for which accreditation is claimed under the bounds of our flexible scope of accreditation): See page 2 and 3

DATE OF SAMPLE RECEIPT:

SAMPLE CONDITION ON RECEIPT:
Delete as appropriate:
Freeze dried/~~Frozen/Chilled~~/Room temperature
Samples suitable/~~unsuitable~~ for testing
Unsuitable for testing because: N/A

REPORT COMPLETED BY:

Signed: Name: Morag Ferguson Position: Laboratory Supervisor, Blood Virology Date 31 March 2009
(print name) (print job title)

REPORT AUTHORISED BY:
Signed: Name: Philip Minor Position: Head, Division of Virology Date 31 March 2009
(print name) (print job title)

National Institute for Biological Standards and Control
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A World Health Organization Laboratory for Biological Standards



APPENDIX 2 CONTINUED

COPY OF REPORT FROM NIBSC

TEST REPORT

TEST REPORT NUMBER:	BV013 SNBTS Human Antihaemophilic Factor VIII lyophilised sample 023110090

SNBTS Human Antihaemophilic Factor VIII lyophilised sample 023110090

Samples were tested according to NIBSC documented procedures as detailed below

Aliquots prepared 14 x 1050µl; 8 x 500µl; 1 x < 500µl.

Aliquots used in initial testing:	HIV 1 RNA	1 x 1050µl
	Anti-HIV 1+2	1 x 500µl
	HCV RNA	1 x 1050µl
Aliquots used in confirmatory testing:	HCV RNA	2 x 1050µl
	Anti-HIV 1	1 x 500µl
	HIV 1+2 RNA	1 x 1050µ

Aliquots remaining 10 x 1050µl; 6 x 500µl; 1 x < 500µl.

Test results

HCV RNA by NAT

Date of test	Test	Result
15August 2008	SOP Bloodvirol 21,22 and 19 Roche Cobas Monitor HCV PCR assay	HCV RNA positive, 'grey zone'
20 August 2008	SOP Bloodvirol 21,22 and 19	HCV RNA positive # In duplicate

values obtained correspond to HCV RNA at approximately 20-50IU/ml

REPORT AUTHORISED BY:
Signed: Name: Philip Minor Position: Head, Division of Virology Date 31 March 2009

(print name) (print job title)

NIBSC s/n 2604 UserRef. QA/Tem:QM001 Version: 3.00 Page 2 of 3

APPENDIX 2 CONTINUED

COPY OF REPORT FROM NIBSC

TEST REPORT

TEST REPORT NUMBER:	BV013 SNBTS Human Antihaemophilic Factor VIII lyophilised sample 023110090

HIV-1 RNA by NAT

Date of test	SOP	Result
14/15 August 2008	*Retro/SOPNAT1 Roche Cobas Monitor HIV-1 PCR assay	HIV-1 RNA negative In duplicate

*Sensitivity of assay approximately 50 copies/ml. Method not accredited to ISO17025 but procedures documented and used in the release of CE marked working standards.

Additional assays were conducted using in-house HIV-1 and HIV-2 PCR assays (non-accredited), an alternative extraction procedure and also using the nucleic acid extracted by Magnapure for the HCV RNA tests.

There is evidence for the detection, verified by cloning and sequencing, of HIV-1 RNA sequences in the sample, though at very low levels. The sequence identity studies indicate the sequences recovered to have close homology with North American HIV-1 clade B viruses circulating at least in the 1990s in the USA. Though the conclusion has to be viewed with some caution given that it is based on only 120bp of a highly conserved region of the HIV-1 genome.

Anti-HIV 1÷2

Date of test	SOP	Result
15 August 2008 + 21 August 2008	RET/SOP AE1 Genscreen Ultra Ag-Ab HIV EIA	Reactive in both assays
20 August 2008	RET/SOP AE2 Murex HIV-1.2.O EIA	Negative
15 August 2008	RET/SOPAE6 ImmunoComb HIV-1/2 BiSpot assay	Negative
20/21 August 2008	RET/SOPAI1 HIV Western blot 2.2	Indeterminate results with gag p24 and gag p17
19 August 2008	RET/SOPAE5* Innogenetics	Negative

*– non-accredited

REPORT AUTHORISED BY:
Signed: Name: Philip Minor Position: Head, Division of Virology Date 31 March 2009
(print name) (print job title)

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