

SUMMARY OF SNBTS RESPONSE TO HIV CONTAMINATION OF
PFC COAGULATION FACTORS

1. FVIII HEAT TREATMENT DEVELOPMENTS

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| Oct 1982 | - | In response to known hepatitis risk of FVIII concentrates, PFC initiated development programme for solution heating of FVIII (publications appended). BPL (Elstree) were exploring dry heat as an option on a collaborative basis with PFC. |
| 1983/1984 | - | International debate as to causative agent of AIDS. Consensus view that causative agent was an infectious agent (virus) emerged in mid-1984. |
| Oct 1984 | - | Report from SEBTS of seroconversion of haemophilic cohort. |
| Oct 1984 | - | SNBTS carried large stock of FVIII (unheated/12 months supply). PFC immediately examined tolerance of this material to withstand dry heat. Established that product would tolerate 68 °C/2hrs. |
| Oct 1984 | - | Present at conference (Groningen) where first virus inactivation results were announced (US) from CDC/Cutter study. Indicated that dry heat at 68 °/1hr inactivates approximately 4 logs virus. |
| Oct - Dec 1984 | - | Heat treatment and clinical trial of existing FVIII stocks. |
| Dec 1984 | - | Issue of heated FVIII to Haemophilia Centres/RTC's. |
| Jan 1985 | - | Recall of all FVIII stocks (RTC and Haemophilia Centres), heat treatment and re-issue on batch dedication basis. |
| Jan 1985 | - | New heating process developed (68 °/24hr) and implemented for all <u>new</u> batches of FVIII. |
| Jan 1985 - Autumn 1985 | - | Routine issues of 68 °/2hr product. |
| Autumn 1985 - Apr 1987 | - | Routine issue of 68 °/72hr product on batch dedication basis. |
| Mid 86 - Apr 87 | - | Development and manufacture of 3rd generation product 75 °/80 °/72hrs (Z8). |
| Apr 1987 - Present | - | Routine issue of Z8 on batch dedication basis. |

It is noteworthy that as a direct consequence of high stock levels in December 1984 it was possible to exchange and transfuse heated product into the supply system whilst maintaining supply. Also high stock levels and ability to implement a heating programme rapidly meant that product derived from plasma collected in 1983 was subjected to a significant heat treatment process. To my knowledge this was not accomplished elsewhere in the world. In England and Wales for instance, only product derived from plasma collected from early 1985 was subject to heat treatment.

2. FIX HEAT TREATMENT DEVELOPMENTS

- 1975-1982 - Explored possibility of polyethylene glycol (PEG) precipitation to reduce product thrombogenicity and increase virus safety.
- Oct 1982 - Initiated development programme for solution heating of FIX concentrates to inactivate virus contaminants.
- Oct 1984 - Initiated development work on dry heated product as preferred option to solution heating.
- Feb - Oct 1985 - Clinical evaluation and detailed study of product (heated) thrombogenicity. Commercial purchase of heat treated FIX.
- Oct 1985 - FIX (80 °/72hrs) issued for routine use.
- Oct 1985 - Present - FIX (80 °/72hrs) issued routinely throughout Scotland and Northern Ireland.

3. BATCH HISTORY OF FVIII BATCH NO 023110090 ASSOCIATED WITH HIV TRANSMISSION TO SHS HAEMOPHILIACS

This batch was associated with the transmission of HIV to approximately 15 Edinburgh Haemophiliacs. The details of these seroconversions have been extensively reported in the literature by Dr Ludlam.

FVIII Batch No 023110090 was manufactured in November 1983 from plasma collected in the Autumn 1983. Clearly this preceded the availability or introduction of plasma donation testing or product treatments to inactivate HIV (eg heat treatment) either in the UK or internationally.

Following the reports of product infectivity, attempts were made to identify the specific donation(s) which led to the product being infective. These were unsuccessful.

Attached is a summary of the action taken by Dr McClelland and Dr Cuthbertson to effect a batch recall after initial notification by Dr Ludlam of seroconversions.

Batch No 023110090 was in all other respects compliant with the product specification at that time and there were no notable events during the manufacturing process.

4. PACKAGE INSERTS - AIDS WARNINGS

At no time during the manufacture of non-heated products did we include a specific warning in our insert leaflets that FVIII (or FIX) carried a risk of HIV transmission. Reference to the possibility of hepatitis transmission has always been included, latterly updated to include HIV. I enclose the various texts used for inserts since 1983 and the chronological sequence of their introduction.

5. GENERAL CONCLUSIONS

- (i) PFC has been pursuing the development of virus inactivation procedures since before 1982.
- (ii) HIV was not established unequivocally as the causative agent of AIDS until at least mid-1984.
- (iii) SNBTS made heat treated FVIII available to all Haemophiliacs in December 1984.
- (iv) Heat treated imported products were not licenced (by DHSS) in the UK until February 1985 although limited material was available on a named patient basis before that time.
- (v) All plasma collected after 1983 (approximately) was processed to heated product.
- (vi) By all international standards, the SNBTS took prompt action to reduce the risk of HIV transmission to Haemophiliacs.
- (vii) Prior to 1985 the PFC did not include AIDS warnings in package inserts (or other formal product documentation) since there was no firm scientific evidence to support or justify such a warning.

DR R J PERRY
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HISTORY OF FACTOR VIII LEAFLETS

In 1983 the leaflet was coded as PFC 35B (A). A review of the leaflet text was initiated in April 1985. The PFC number had been changed to 55L. (B).

A further review was undertaken in March 1987 when the new product Z8 was introduced, the code number changing to 3L (C).

Last order PFC 35B made 14.3.84 (T0962/L).

First order PFC 55L made 13.6.85 (Y0228/678).

First order PFC 3L made 24.4.87 (B00309/678).

The first possible date the PFC 55L leaflet could have been used would be 31.7.85.

When the PFC 3L arrived the remaining PFC 55L were discontinued from use. This was 19.5.87.

Further Information Labels

The original labels were made using the Markem machine.

These were attached to the vials shoulders and cap. (A)

The purchase of the Zeta printer allowed the information to be printed on circular labels. These were affixed to the cap flip top. (B)

Since the start of heat treatment each vial has carried a heat treated sticker and the box outers have carried a similar statement on both box ends.

Initially the label said heat treated but in 1984 a standard label pattern was introduced with specific temperatures and times stated. (C & D)

The heat treatment operation is fully documented in Productions Monthly Report - 11/84 to 5/85.