SNBTS DOCUMENT REQUEST No:

2010/00039

Updated Statement, March 2011

RE: MR VICTOR TAMBURRINI

SPPS BATCH NUMBER 1194: Statement of Clarification

1. Introduction

In a letter dated 10 November 2010 to Dr Richard Soutar, Gemma Lovell of the Penrose Inquiry team requested clarification of an apparent inconsistency between the evidence contained in a letter dated 10 June 2008 from Dr Soutar to the Crown Office Procurator Fiscal Service (COPFS) in respect of the late Mr Tamburrini, and an expert report prepared for the COPFS by Professor JP Allain. As the SNBTS manufactured the product in question and better understands the procedures applied, it can offer clarification to the Public Inquiry.

This brief statement has been prepared by Dr R J Perry (former Director of the Protein Fractionation Centre) and Dr B Cuthbertson (SNBTS National Quality Director). The key conclusion is that the SNBTS can confirm that the product in question was pasteurised at 60°C for 10 hours as per the relevant British Pharmacopoeia monograph.

2. Nature of Discrepancy

In 2008 Professor J P Allain provided an expert report and Dr R Soutar provided a response on behalf of the SNBTS to the Procurator Fiscal concerning the manufacture of the batch of Stable Plasma Protein Solution (SPPS, Batch Number 1194) that had been administered to the late Mr Tamburrini in September 1984.

Dr Soutar had advised in his letter that "*...the file for serial batch no 1194 has been checked and contains a copy of the temperature/time chart for the*

pasteurisation process. This confirms that the batch was heated for 10 hours at 60°C and is duly signed by both operator and supervisor".

Professor Allain had similarly conveyed his view that the product batch was manufactured correctly, but in his submission he stated that "*...the batch was effectively submitted to 48 hours of incubation*" and that "*...the temperature reached by each vial was consistent with the intended 56°C*"

These two statements are clearly discrepant. The details quoted by Professor Allain do not refer to the pasteurisation of the albumin/SPPS but rather to the routine autoclave/steriliser validation test. The rest of this brief paper explains the background to heat treatment of this batch and how the mistake was made in interpreting the relevant detail in the complex batch record supplied to him.

3. Regulatory Advice on Heat Treatment Process

Although prior to 1991 SNBTS albumin products (of which SPPS is one) were released on the basis of Crown Immunity, the formal position was that all products would be manufactured against the requirements of relevant written guidance. In the UK, albumin products were manufactured against a monograph contained in the British Pharmacopoeia (BP) which provides essential standards for the manufacture and release of medicinal products. The SNBTS product (termed SPPS) was a particular form of albumin, either known as Plasma Protein Solution or Plasma Protein Fraction. Batch 1194 was issued in 1983 and the version of the BP in force at that time was published in 1980. The monograph from the 1980 version of the BP is appended as a pdf file. In addition, the introductory text is reproduced below

Plasma Protein Fraction

Human Albumin Fraction (Saline)

Plasma Protein Fraction is a solution of the proteins of liquid human plasma, containing albumin and globulins that retain their solubility on heating. It exerts a colloid osmotic pressure approximately equivalent to that of pooled liquid human plasma containing 5.2 per cent w/v of protein; it contains no fibrinogen or antibodies. It is prepared from pooled liquid plasma obtained from blood from human subjects to whom all the conditions (a) to (d) described under Albumin apply. The albumin fraction, prepared by a suitable fractionation technique, is dissolved in water and sufficient sodium caprylate or other suitable substances are added to stabilise it to heat, and Sodium Chloride is added to adjust the content of sodium ions to between 130 and 160 millimoles per litre. No bactericide or antibiotic is added at any stage during preparation. The solution is sterilised by filtration, distributed aseptically in sterile containers, and sealed so as to exclude micro-organisms. It is then heated to, and maintained for ten hours at, 59.5° to 60.5° so as to prevent the transmission of hepatitis. Finally, the containers are incubated for not less than fourteen days at 30° to 32° and examined visually for signs of microbial contamination.

Plasma Protein Fraction contains not less than 4.3 per cent w/v of total protein, not more than 15 millimoles of citrate ions per litre, and not more than 2 millimoles of potassium ions per litre.

It will be noted that the approved heat treatment conditions were to heat in the final containers at 59.5° to 60.5° "...***so as to prevent the transmission of hepatitis"***. In manufacturing batch 1194, the SNBTS used manufacturing and test procedures which complied fully with this requirement.

4. Details of Heat Treatment Process

This albumin product was dispensed as a 4.5% protein solution, stabilised with sodium caprylate. The product was dispensed in 400mL volumes into 500mL bottles. Each bottle was placed into a spray chamber which sprayed

water heated at 60°C over each bottle. Temperature sensors were placed in six bottles distributed throughout the chamber to measure temperature. The data from these sensors were recorded on a chart recorder. Each chart recording was reviewed to confirm that the heat treatment process was controlled between 59.5° to 60.5°C for a minimum period of 10 hours.

It should be noted that although SNBTS operated under Crown Immunity, this operation was inspected by the UK Medicines Inspectorate and was found to be suitable and was eventually licensed when Crown Immunity was withdrawn in 1991.

5. Details of Batch Manufacture

The full original batch record is available in microfiche format and a copy is appended as a pdf file. Key details from this batch record are as follows:-

Date of Dispensing: 10 March 1983
Date of Pasteurisation: 10 March 1983
Start of Run: 3.15 pm: 10 March 1983
End of Run: 1.15 am: 11 March 1983

Examination of the manufacturing and quality control records for this batch (which were supplied to Professor Allain and Dr Soutar) indicates that all control parameters were normal and within established acceptable limits. Importantly this includes the pasteurisation step (60°C/10 hours) which the records confirm had been carried out correctly, appropriately monitored and checked by the appropriate supervisor and manager.

The batch was released by the Quality Control Inspector (Dr RJ Perry) on 10 August 1983 after a final check of the batch manufacturing records. For ease of understanding, a flow sheet has been prepared which shows the key stages in the process covered by this batch record. This flow chart is appended as appendix 1.

6. Basis for the Misinterpretation by Professor Allain

The batch record supplied to Professor Allain consists of 39 pages of records, including both Quality Control records and Manufacturing records. The pasteurisation record is provided on page 39 (final) of the batch record with additional information relating to pasteurisation on page 26.

In the Quality Control section, there are a series of 5 sheets, entitled "Biological Indicators" (pages 21 to 25). These refer to tests which were carried out to demonstrate that the equipment used to receive the albumin (bottles, stoppers) had been sterilised correctly. These tests are widely used in the pharmaceutical industry to confirm the satisfactory performance of sterilisers. This sterilisation step is at 121°C for 15 minutes. In each sterilisation run, a number of biological indicators are used to demonstrate that the sterilisation step has been carried out correctly. These indicators contain spores of heat-resistant bacteria (Bacillus stearothermophilus) which will not be fully inactivated if the correct sterilisation conditions are not achieved. Once the sterilisation run had been completed, the biological indicators were transferred to the bacteriology laboratory where they were incubated at 56°C to promote the growth of any bacterial spores which had not been inactivated. In addition to indicators taken from each sterilisation run, negative controls were included of spore strips which had not been heated in the autoclave.

For each of the 5 sterilisation runs, there is a record sheet which shows that the spore strips that had been included in the sterilisation run were negative for bacterial growth after incubation in the bacteriology laboratory for 48 hours at 56°C, whereas the control strips that had not been subjected to a sterilisation run were positive for bacterial growth after incubation for 24 hours. In reviewing the batch record for batch 1194, Professor Allain has mistakenly interpreted these records of the routine autoclave/steriliser validation test as being those for the pasteurisation process. As should be clear from the above

description, this routine quality control test (identified in the batch documentation as 'Biological Indicators') is entirely unrelated to the pasteurisation process which was routinely monitored and validated using temperature sensors located throughout the batch during the pasteurisation process.

7. Safety of Pasteurised Albumin Products

As described above, the BP monograph stated in 1980 that this product is "*...then heated to, and maintained for ten hours at, 59.5° to 60.5° so as to prevent the transmission of hepatitis.*" It is very rare for a regulatory document to make such a positive statement on the safety of a particular product type. This statement is based on widespread safety of pasteurised albumin products, heated in the final container, as was this batch of SNBTS product. The well known and established safety (with respect to virus transmission) of this type of plasma product is the result of a pasteurisation step in the manufacturing process in which the product in its final container is subjected to heat treatment at 60°C for 10 hours. The control of this manufacturing step is vitally important for the safety of the product. There are no known instances worldwide in which albumin products subjected to this treatment have transmitted virus infections to recipients.

8. Comments On Security Of SNBTS Processing

Since writing the original report in November 2010, comments have been received from Thompsons Solicitors, enquiring about the possibility of error during the processing of this batch of SPPS. A number of possible scenarios have been proposed, and these are discussed as follows under 2 headings as suggested by the Solicitor for the Public Inquiry.

8.1 Is it possible that batch 1194 could have left the PFC without heat treatment having been carried out?

During the manufacture and testing of albumin products by PFC, there were a number of checks which were designed to ensure that each bottle of each batch was subjected to full and effective pasteurisation, without

risk of mix up between unpasteurised and pasteurised bottles. Prior to pasteurisation of a batch being initiated, two non-pasteurised bottles were transferred directly from the filling area to a separate Quality Control Laboratory, which was removed from the Production area where the pasteurisation facility was located. The rest of the batch proceeded to pasteurisation. Each pasteurisation chamber (referred to as a bath in the batch record, so this term is used in the following text for clarity) held exactly 600 bottles in crates of 10 bottles. Six 'dummy' bottles held temperature probes, which allowed 594 bottles of SPPS to be pasteurised. The dispensed bottles were placed directly into crates which were transferred immediately and directly from the filling area to the pasteurisation baths. Unpasteurised SPPS was not stored in manufacturing areas therefore eliminating the possibility of any mix up between pasteurised and unpasteurised product. Records are present in the batch record to show that 60 crates were loaded into the bath. After unloading the bath, the requisite number of samples (12 bottles) were submitted for quality control testing. The crates holding all of the remaining bottles were then placed in a unique, labelled cage and incubated and stored pending release to labelling and packaging. No bottles will have been transferred for storage until the pasteurisation step had been completed. Each packaging event was carried out on discrete batches of product. The total number of bottles inspected and packaged is recorded in the batch record, with accurate number reconciliation being demonstrated. Although it is virtually inconceivable that non-pasteurised SPPS could have been included in a batch intended for clinical use, a further safeguard, which would have prevented the inclusion of one or more non-pasteurised bottles resulted from the inspection of each individual bottle prior to labelling and packaging. Each bottle was individually inspected for the presence of abnormal characteristics, such as foreign bodies, bacterial contamination and damage to bottles, or overseals. Detection of unpasteurised bottles during this inspection would have been very easy, based on the different physical appearance of pasteurised and unpasteurised material. Prior to pasteurisation, albumin is a transparent, light brown solution, whereas

following pasteurisation, it is an opalescent, greenish brown colour. Any unpasteurised bottles would have been easily detected at this inspection stage.

The batch record includes a number of items of information which demonstrates that the procedures described above were carried out correctly. This information is summarised as follows.

Firstly, the reconciliation sheet (page 38 of the batch record) demonstrates that all of the 594 bottles can be accounted for, either as samples, as rejects following inspection, or as labelled for release.

Secondly, the pasteurisation run sheet (page 26) shows that 60 crates were loaded into the pasteurisation bath and that the position of the temperature probes was recorded correctly. In addition, this sheet shows the results of an independent check using a separate monitoring system in order to confirm that the temperature of 60°C had been attained. This is in addition to the primary temperature recording presented on page 39. This information is augmented by the filling sheet on page 9 which shows that 594 bottles were passed for pasteurisation. Taken together, these documents demonstrate that the correct number of bottles was heated at the correct temperature for the correct length of time .

Thirdly, only two bottles of albumin remained unpasteurised. As described above, these were taken from each batch and transferred to a separate Quality Control Laboratory for testing. These unpasteurised bottles were labelled as A Bottles in the batch record and the 12 sample bottles of pasteurised material were labelled as B bottles. It will be noted in the batch record that these 2 bottles were delivered to the separate Quality Control Laboratory on 10 May by a member of the sterile filling team (ref page 16 of batch record), whereas the bottles that were taken for quality control testing following completion of pasteurisation were taken from the batch and delivered to the Quality Control Laboratory on 11 May 1983 (ref page 15). The unpasteurised bottles were incubated, unopened, in the Quality Control Laboratory for 14 days and were then opened in the Quality Control Laboratory and used for chemical analysis.

There is therefore no possibility that any of these non-pasteurised bottles could have been included in or returned to the batch held in Production pending release.

Fourthly, the quality control data in the batch record also provides unequivocal evidence that the batch was subjected to pasteurisation. This comes from the fact that the material from the unpasteurised bottles was tested in parallel with samples taken from bottles which had been subjected to pasteurisation . A number of changes are typically observed following pasteurisation , and these are all present in this batch in the analysis test sheet (on page 6), as follows

- Elimination of the enzyme Alkaline phosphatase from 44IU/l before pasteurisation to 0 IU/L after pasteurisation.
- Increase of high molecular weight material (D peak) in gel filtration testing (increased from 2.5% before pasteurisation to 11.2% after pasteurisation).
- Detection of albumin polymer in polyacrylamide gel electrophoresis testing of a pasteurised sample whereas none was detected in the unpasteurised sample,

The above evidence indicates that there was neither opportunity for the SPPS batch 1194 to have included one nor more non-pasteurised bottles nor failure to carry out the correct manufacturing procedures.

8.2 *Is it possible that the batch could have become contaminated in some way after treatment which could have caused it to transmit HCV?*

This was not possible for a number of reasons, as follows

- SPPS was pasteurised in the sealed, final bottles. After the product had been dispensed into the glass bottles, each bottle was sealed with a secure rubber stopper and oversealed with a

crimped aluminium overseal. The contents were therefore entirely secure and could not be contaminated.

- No manipulations such as pH measurements are made on the finished bottles which remained sealed with tamper evident overseals until required for patient treatment. The quality of these overseals was checked during the Inspection of each bottle carried out prior to release. If the tamper evident overseal was not seen to be secure on any bottle during inspection, it would have been rejected.

- There are several reasons why albumin could not have been cross-contaminated from the virology studies carried out to demonstrate the efficacy of the heat treatment process.

    - HCV was never used in any "virucidal efficiency trials", so could not have contaminated any bottle from any batch of SPPS. At the time that SPPS batch 1194 was prepared, the viruses being used for such studies by the SNBTS were Vaccinia, Mumps and Semliki Forest Virus, all of which were chosen to demonstrate the efficacy of heat treatment processes.

    - All such virus validation studies were carefully controlled to prevent cross contamination from the laboratory studies into manufacturing processes. In particular all manipulations of solutions, addition (spiking) of model viruses and testing of samples before and after heating were carried out in a separate, purpose built microbiological containment facility which was removed from any manufacturing areas.

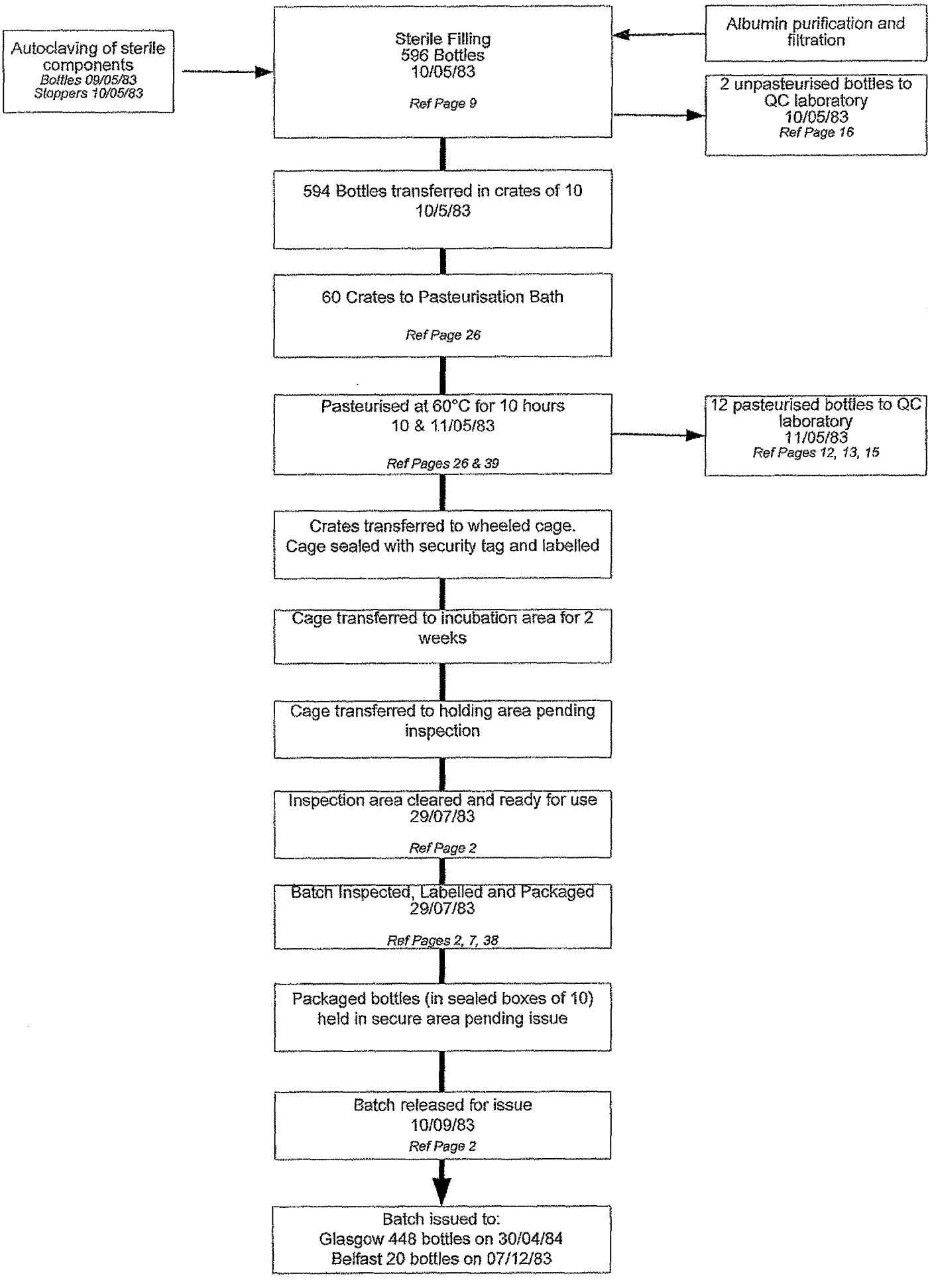
9. Summary

The SPPS product prepared by SNBTS at that time was typical of those available worldwide and complied with industry standards and pharmacopoeia monographs current at the time.

In conclusion, the manufacturing and quality control records for this batch of SPPS provide unequivocal evidence of its satisfactory manufacture and in particular its pasteurisation at 60°C for 10 hours in line with recognised industry and pharmacopoeia standards. Safeguards were in place to prevent the issue of any unpasteurised bottles.

It should also be pointed out that no case of virus transmission by PFC Albumin products, including SPPS, has ever been reported to SNBTS (see appended statement).

FLOWCHART OF SPPS MANUFACTURING PROCESS



Formal Review of Adverse event reports for SNBTS Albumin Products

A formal review of the Scottish National Blood Transfusion Service Pharmacovigilance files has been performed.

SNBTS have received 42 reports of Albumin product (Human Albumin 4.5%, Human Albumin 20% and SPPS) associated adverse reactions, spanning the years 1975 to 2003. None of these adverse events were related to any infectious episodes and to confirm SNBTS have received no reports of a transmission of any infectious disease associated with the use of Albumin or SPPS.

Jacqueline Barry
11/02/2011

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed.....

Dated.....4.....MARCH.....2011.....