Witness Name: Dr RV McIntosh
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The Penrose Inquiry
Witness statement of Ronald Vance McIntosh
Topic C3: Hepatitis C – Viral Inactivation 1985 to 1987

The implementation of heat treatment sufficient to inactivate Hepatitis C in blood products by the Protein Fractionation Centre in Scotland in 1987, and the technological background to such implementation, including the achievement of this objective by the National Blood Transfusion Service in England and Wales in 1985.

1) *When and how did the SNBTS/PFC first become aware of BPL/PFL's research and development work on 8Y, including severe heating of the product? When and how did the SNBTS/PFC first become aware that BPL/PFL were able to dry heat FVIII and IX concentrates at 80°C for 72 hours?*

Response

The events which lead to staff at the PFC becoming aware of the development of the 8Y process and that freeze fried FVIII and FIX products could withstand heating at 80°C for 72 hours are described in briefing papers prepared by the SNBTS and submitted previously to the Inquiry. These are "Events concerning the safety of blood and blood products with specific reference to the treatment of haemophilia" (October 2009) and "The development of heat treatment of coagulation factors" (November 2010). I would agree with these descriptions.

One comment I would add is that we were aware of some of the major features of the 8Y process, such as using high concentrations of heparin as a precipitating agent and using size exclusion chromatography for solvent exchange (formulation of the product), prior to receiving a more detailed description of the method of manufacture in a copy of the patent application, received after its publication in March 1985.

2) *When did it seem likely, from evidence of its clinical use, that the heating regime for 8Y (80°C for 72 hours) resulted in a product which did not transmit NANBH?*

Response

The development of evidence that the heat treatment of 8Y at 80°C for 72 hours could prevent the transmission of NANBH, from the initial report to the UK Haemophilia Directors to the later published findings, is described also in the briefing papers referred to above.

I would first have learned of these clinical results from Peter Foster, ahead of them being reported or published, as Jim Smith at the PFL kept the PFC up to date on these matters through Dr Foster.

3) *In October 1985 PFC discovered that their existing intermediate NY FVIII product withstood heating at 80°C:*

(a) Why was such heating of the existing intermediate NY FVIII product not introduced immediately?

Response

The "discovery" to which the question refers did not, in fact, demonstrate that the "existing intermediate NY FVIII product" withstood heating at 80°C but rather that small samples of NY FVIII material could withstand 80°C heat treatment when freeze dried in a particular way.

This observation was made, initially, during the experiments being carried out to design a new freeze drying cycle for the high purity, high potency FVIII product that would have resulted from the NYU project. (Freeze drying of the high purity material had completely failed using a model cycle based on the standard production cycle of that time). The experimental samples were in small volumes (e.g.2-3 mL), dispensed into relatively small (e.g.10 mL) vials because this was the dose form in which we anticipated a high purity, high potency product would be presented; the control samples of intermediate purity FVIII were prepared in the same way.

The observation that the control samples withstood heating at 80°C was important in suggesting that intermediate purity FVIII material could be successfully heated at that temperature when freeze dried in a particular way.

However, even if these new freeze drying conditions could have been applied to the normal NY dose form, 35-40 mL in a 65mL, vial the time taken to complete the new cycle with this amount of material in each vial of a batch would have vastly exceeded the available production capacity.

What was required, therefore, was a more concentrated FVIII solution so that the height of the filled product in the vial was much lower than NY to give better freezing conditions and an acceptable cycle time. To prepare a more concentrated FVIII solution, some additional purification was needed and this could be achieved using the cryo-precipitate processing conditions employed in the NYU project which had been derived from the ZHT process. This was the basis of the Z8 project i.e. to prepare a FVIII solution of sufficient purity, such that it could be concentrated into a formulation that would allow the FVIII solution to be freeze dried in a manner that would enable the product to be heated at 80°C.

(b) *Why did it take until May 1987 before intermediate FVIII manufactured by PFC and dry heated at 80°C for 72 hours was available for clinical use?*

Response

The decision to develop an intermediate purity FVIII concentrate that could be heat treated at 80°C was made in late December 1985 and the product (Z8) was available for clinical evaluation in early December the following year.

Albeit that part of the strategy was to retain as much of the existing manufacturing methodology as possible, this development required new purification, concentration, formulation, freeze drying and heat treatment procedures to be introduced and adapted to Production scale operation under conditions suitable for the preparation of clinical grade material.

Standard operating procedures for Production and Quality Control needed to be prepared and approved for use together with Batch Record documentation.

Finished product would have to complete the necessary Quality Control testing and Batch Release procedures before being made available for clinical use.

To take this project from R&D laboratory scale work to Production scale clinical grade product inside a year would normally be considered a rapid rate of development.

(c) *What changes in the manufacturing processes were made, and when, to enable PFC to produce Z8 (dry heated at 80°C for 72 hours)?*

Response

The process changes from the NY method to the method used for Z8 are described in the witness statement made by Peter Foster "Heat Treatment to 1985 – the Development of Heat Treatment of Coagulation Factors". This witness statement has been submitted previously to the inquiry.

All of these changes were made (at Pilot and Production scale) in the production facility at the PFC between June 1986 and December 1986.

Some adjustments were made to the new processes following the experience gained during routine full scale manufacture.

Thereafter, further changes were made as part of on going continuous improvement.

(d) *What was the original timescale for the production and introduction of Z8? If that timetable was not met, when and why did it slip?*

Response

The time table for the introduction of Z8 was to complete the development as quickly as possible.

In mid 1986 the production of NY for heat treatment at 68°C/72 hr was stopped so that Production facilities and the Quality Control and Engineering resources associated with Production could be dedicated to the development and production of Z8. The time available to complete the introduction of Z8 became, therefore, the length of time for which the stocks of NY (68°C/72hr) would last before production of that product would have to be resumed. In the event we were able to establish Z8 production in that time frame and no further NY (68°C/24hr) was manufactured after mid 1986.

4) *Did PFC's work on the development of a high purity FVIII concentrate (NYU), in collaboration with Professor Johnson, result in any delay in the introduction of Z8?*

Response

I have no recollection of being concerned that the NYU project delayed the introduction of Z8.

In fact, the experience and expertise gained during the development of a number of the processing steps in the NYU project (e.g. cryo-precipitate processing, formulation, freeze drying) were directly transferable to the Z8 process.

I would also comment that, in general, having an active R&D programme in FVIII concentrate development, directed towards new improved safer products was, in itself, an important feature of being able to respond rapidly to developments in the field, such as the significant increases in the time and temperature of dry heat treatment made at the PFL. The PFC was the first Plasma Fractionation plant in the world to respond successfully to that break through at PFL by developing an 80°C/72 hr dry heat treated FVIII product.

5) *Did any difficulties in commencing clinical trials of Z8, because of concerns over compensation/indemnity, result in any delay in the introduction of Z8?*

Response

I was not involved in the planning of the clinical trials for Z8 or in the discussions concerning compensation for patients taking part in the trials and indemnity for clinicians administering the product in the trials.

I am not in a position, therefore, to comment on whether the discussions over compensation/indemnity took unduly long or not.

6) *Did any wider management, organisational or other issues result in any delay in the introduction of Z8 e.g. by R&D staff not being sufficiently involved in the manufacture and production of products and processes that had been developed by them?*[1]

[1] See, for example, Dr Perry's memo of 22.12.88 to Dr Foster and others (SNB.006.7120) and Dr Foster's letter of 21.11.90 to Dr Prowse (SNB.007.7576)

Response

The PFC Management Team stopped the production of NY 68°C/24hr in mid 1986 to allow R&D full access, for the Z8 development, to the Production, Engineering and Quality Control facilities that would normally be used for FVIII manufacture. All of the staff involved from the different departments in the Centre were fully committed to the project.

The memo from Bob Perry (footnote 1) referred to in the question was not addressed to me and I do not recall what the exact issue might have been. However, I would comment that the memo is from 1988 and in general seems more related to the role of R&D in on-going Production support rather than regarding the introduction of Z8.

The letter from Peter Foster to Chris Prowse, also referred to in footnote 1, was not copied to me and I had not had sight of the draft report. I assume that in the context of the question, the first paragraph of page 4 of the letter is the relevant passage. Again this related more to the level of on-going support from R&D to Production rather than access to production for the development and implementation of Z8, which I would say was open and fully committed. The function of providing a greater level of support to Production and other operational areas of the Centre became part of the changes in the role of R&D as the product range at the PFC increased in number and complexity.

7) *There was informal contact and exchange of information between PFC and BPL/PFL, in particular, between Dr Foster and Dr JK Smith. There appear to have been difficulties with more formal contact, in particular, at a senior, or managerial, level.*[2] *Did any difficulties at a more senior level inhibit in any way the exchange of information between BPL/PFL and PFC in respect of the development of 8Y, including severe heating of the product? Did any such difficulties contribute to any delay in the development and introduction of Z8?*

Response

I do not recall having any sense that communications with R&D staff or Operational staff at PFL or BPL were in any way inhibited by difficulties at a

[2] see, for example, Dr Cash's letter of 17.12.82 to Dr Lane (SNB.004.3163) and Dr Cash's Background Notes dated 1.1.84 (SNB.011.1308)

more senior level. Consequently I would not consider that any such difficulties contributed to any delay in the development and introduction of Z8.

8) *The Central Blood Laboratories Authority (CBLA) Central Committee on Research and Development in Blood Transfusion first met on 21 June 1983.*[3] *It, presumably, provided a more formal forum for the exchange of information between the respective national blood transfusion services in respect of the research and development of coagulation concentrates. Dr Lane, the Director of BPL, was a member of the committee. While Dr Brian McClelland, Edinburgh BTS, was a member of the committee, there was no member from PFC.*

(a) Was the committee truly a UK committee or was its' role restricted to research and development in England and Wales?[4]

Response

I had no knowledge of the CBLA Central Committee on R&D in Blood Transfusion and so I am not in a position to comment on the extent of its role.

(b) *Why was there no PFC representative on the committee? Ought there to have been such representation? If there had been such representation, is that likely to have led to the earlier and/or fuller exchange of information between BPL/PFL and PFC in respect of the development, manufacture and clinical use of 8Y, including severe heating of the product? If there had been PFC representation on the committee is that likely to have led* to Z8 having been introduced earlier?

Response

As I commented earlier, I had no knowledge of the CBLA Central Committee on R&D or its workings. I am unable, therefore, to take a view on its membership or on how the make up of its membership would have affected the flow of information between PFL/BPL and PFC and how that would have influenced the development of Z8.

(c) There appear to have been concerns in Scotland as to whether that committee was an appropriate forum for the exchange of information

[3] PEN.016.1156. The committee subsequently met on 7.11.83 (PEN.016.1130), 28.2.84 (PEN.016.1158), 9.11.84 (PEN.016.1148), 2.4.85 (PEN.016.1125), 9.7.85 (PEN.016.1142) and 19.12.85 (PEN.016.1152). The Inquiry does not have minutes for meetings of the committee in 1986 and 1987.

[4] See, in that regard the views of Mr Smart, Chairman of CBLA, as noted in SNB.006.5100 c.f. the views of Dr Cash, as expressed in SNB.011.1308

between BPL/PFL and PFC, based, at least partly, on the perceived "commercial brief" of the CBLA.[5] Did any such concerns about this committee inhibit in any way the exchange of information between BPL/PFL and PFC in respect of the development of 8Y? Did any such concerns contribute to any delay in the development and introduction of Z8?

Response

Having no knowledge of the CBLA Central Committee on R&D, I am not able to comment.

9) *Were more formal links between PFC and BPL/PFL desirable?[6] Were more formal links eventually established and, if so, when and how?*

Response

In my experience at PFC, the nature of communications with PFL/BPL took the form that as the occasion required; a phone call, letter/e mail, a site visit to view a particular aspect of processing or a more structured project. For example, in the early 1990s BPL and PFC engaged in a joint project, which had as a key objective the agreement with the MCA on the critical features of the validation of dry heat treatment. The project group was made up of staff from BPL and PFC and meetings were held alternately at BPL and PFC and chaired alternately by myself and Lowell Winkleman. Minutes and actions were kept and approved at each subsequent meeting. A joint paper was prepared and a successful meeting with representatives from BPL and PFC held with the MCA.

The underlying feature of these and other examples of BPL/PFL and PFC working together was, in my view, that the lines of communication remained open between the relevant groups in the two organisations. I am not sure that "formal links" would have been able to improve upon the trust and openness that existed at a professional level in several areas of both organisations.

I do not think that "formal links" (if by this the question means, for example, regular, structured meetings with an agreed membership, terms of reference

[5] see, for example, letter dated 11.12.86 from Dr Gunson to Dr Cash (SNB.002.4347); Dr Cash's reply of 9.4.87 (SNB.013.7021); minute dated 10.6.87 from Dr Smithies, DOH, (SGH.001.8487) with enclosure (SGH.001.8488); minute dated 26.8.88 from J Hamill, SHHD, (SGH.002.4677) and minute dated 30.8.88 from Dr Forrester, SHHD (SGH.002.4672)

[6] See, for example, the discussion at the meeting at the NIBSC on the virological aspects on the safety of blood products on 7.2.86 (SNB.005.1495)

and reporting arrangements) between BPL and PFC were ever eventually established.

10) *Why was PFC able to make available for clinical use FIX concentrate that had been dry heat treated at 80°C for 72 hours in October 1985 but FVIII concentrate that had been subjected to a similar heat treatment regime (i.e. dry heated at 80°C for 72 hours) was not available for clinical use until May 1987?*

Response

This question is answered in part in the witness statement from Dr Peter Foster "Heat Treatment to 1985 – the Development of Heat Treatment of Coagulation Factors". In his statement Dr Foster explains that the existing SNBTS FIX concentrate (DEFIX) was physically able to withstand heat treatment at 80°C and only a relatively simple step in processing terms (the addition of Anti Thrombin III to the product formulation) was needed to ensure that the 80°C heat treated product (HT DEFIX) met the required finished product specification.

The existing FVIII concentrate (NY), on the other hand, could not withstand heating at 80°C and several relatively complex process changes (also described in the same witness statement) were needed to the NY process to prepare a FVIII product (Z8) suitable for heating at 80°C.

I would add that although NY and DEFIX shared the same dose form (i.e. freeze dried products for reconstitution in water for injections before use) they were very different products. The protein contents and the structure and type of the proteins contained in each of the products were very different, as were the chemical formulations in which the products were prepared. The fill volumes (10mL for DEFIX and 35-40mL for NY) were also significantly different as were the vial sizes; 30mL and 65mL respectively. It would not necessarily be the case, therefore, that because one freeze dried product could be heat treated at 80°C that another (with very different characteristics) could also be heat treated in the same way.

It should also be noted that unlike FVIII production, there were no yield constraints on the production of FIX concentrate. Only a relatively small proportion of the plasma fractionated at the PFC was needed to produce enough FIX concentrate to meet the demands of the NHS in Scotland. As Peter Foster's

statement describes, in FIX concentrate production, stored intermediate product can be selected for further processing. In this way high potency material could be selected (and less potent material discarded) to ensure that the final heated product had the required level of activities.

There was no such room for manoeuvre in the development of heat treated FVIII products at PFC where achieving an acceptable process yield was critical to meeting the demands for FVIII concentrate.

Statement of Truth

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

Signed: Ronald VanFinton

Dated: 05 | SEPT | 2011