Witness Name: Dr Diana Walford CBE
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INFECTED BLOOD INQUIRY

SECOND WRITTEN STATEMENT OF DIANA WALFORD

Contents

Section 1: Introduction

I, Diana Walford, will say as follows: -

1.1. My full name is Diana Marion Walford. My date of birth and address are known to the Inquiry.

1.2. I am providing this statement in response to the Inquiry's Rule 9 request dated 13 December 2022. This is my second written statement to the Inquiry. I provided my first written statement on 5 July 2021.

Section 2: My role in the application for variation of product licence 0215/0003

2.1 Product licence number 0215/0003 related to a coagulation factor concentrate called Kryobulin and manufactured by Immuno Ltd. By an application dated 11 November 1976, Immuno Ltd sought to vary the product licence to produce a concentrate derived from American plasma in addition to its existing Kryobulin product which was derived from plasma collected from Austrian and German plasmapheresis centres **[MHRA0033321_085]**. The existing licence had been granted on 22 March 1973 **[SHPL0000376_005]**. In addition, details of how the new and existing products would be distinguished and samples of the proposed packaging were set out in a letter to Dr Fletcher dated 29 November 1976 **[SHPL0000271_069]**.

2.2. At that time, the application for the variation was being assessed by my predecessor, Dr Fletcher. He wrote to Mr Norman Berry of Immuno Ltd on 26 January 1977 informing him that before the variation could be granted, he required additional information concerning the proposed source of the plasma **[SHPL0000271_077]**. It appears from the file that Mr Berry replied on 27 January 1977 **[MHRA0033321_078]**.

2.3. I understand that the processing of the application thereafter was delayed because the Medicines Division erroneously believed it had not received a response to Dr Fletcher's letter. Further detail is set out at paragraphs 6 to 11 of the Note by Counsel to the Inquiry **[INQY0000415]**.

2.4. I succeeded Dr Fletcher as the Medical Assessor for biological products in around November 1977. At some point thereafter, I was assigned by the Head of the Biologicals Section, Dr John Holgate (or by someone acting on his behalf), to take over dealing with the assessment of the application to vary the Kryobulin licence.

2.5. Although I cannot recall when I became involved with the application, I have been shown a handwritten internal note dated 8 February 1978 that I sent to Mr Kemp in which I commented [**MHRA0033321_009**] that:

> *"As far as I can see the Company have not supplied the further information requested to support the proposed variation. The S44 letter requesting information is dated 26 Jan. 1977(!) and the Company reply promising further information is dated 27 Jan 77(!!)"*

2.6. On 14 February 1978, Mr Berry was notified that the Medicines Division were yet to receive a response to Dr Fletcher's letter dated 26 January 1977 which sought further information **[SHPL0000271_059]**. On 16 February 1978, Mr Berry responded that *"…we answered Dr Fletcher's letter on 1st February 1977, and a photocopy of our reply is attached"* **[SHPL0000271_058]**.

2.7. I have been shown a copy of the earlier letter from Immuno Ltd dated 1 February 1977 **[MHRA0033321_066]**, which I presumably saw after Mr Berry had resent it. I see from my initials *"DW"* on this document that I underlined the passage which said, "*We are at present obtaining material from plasmapheresis stations in New York, Baltimore, Birmingham (Alabama), Philadelphia and Knoxville*". Although I cannot now recall why I put a question and exclamation mark against the underlined words, I assume that my underlining was made when I first saw the letter in February 1978, one year after it had been written. My underlining might have been to emphasise to myself that *"at present"* actually referred to one year previously.

2.8. Mr Berry's covering letter dated 16 February 1978 conceded that his 1 February 1977 response to Dr Fletcher was still deficient, as he had not answered Dr Fletcher's question about whether Immuno still intended to use plasmapheresis centres in Austria and Germany **[SHPL0000271_058]**. He confirmed that Immuno Ltd wished to retain the use of five plasmapheresis stations in Austria

and two in Germany. As regards the proposed variation, he said, *"What we do wish, is the ability to use American plasma in the same way that our competitors do".*

2.9. I have been shown a handwritten minute dated 20 February 1978 and addressed to me that said, *"the attached correspondence refers to an application that you are assessing. It contains S44 information you will wish to see."* **[MHRA0033321_064]**. *"S44"* would have been a reference to section 44 of the Medicines Act 1968. I can see from the document that underneath I had handwritten the comment, *"Please obtain gold file PL 0215/0003"*. That was a reference to the product licence file.

2.10. I do not know what correspondence was attached to this minute. I note that when I drafted my 8 February 1978 minute, I had seen Immuno Ltd's letter of 27 January 1977, but not their letter of 1 February 1977. It seems probable that Immuno Ltd's letter of 1 February 1977 was sent to me under cover of the minute of 20 February 1978.

2.11. After Dr Andrews, the Pharmacist Assessor for this application, initialled his approval, I then approved Immuno Ltd's variation application on 7 March 1978 **[MHRA0033321_084]**. Immuno Ltd were informed of the approval by a letter dated 28 March 1978 signed by Mr Kemp **[MHRA0033321_062]**.

2.12. I should add that I have been provided with a copy of a handwritten note written by me dated 5 April 1978, which stated:

> *"Mr Kemp*
>
> *Please see my minute dated 6.3.78. The variation was to be granted on condition that… It looks as if it has been granted unconditionally and I think we had better let the matter stand at the moment. Has there been some confusion somewhere*?" **[WITN4461159]**.

2.13. It appears from this that I must have written a memorandum on 6 March 1978, imposing a condition when I approved the licence variation. Unfortunately, I am told that despite searches, no copy of this memorandum has been found, so details of the proposed condition have not been found.

2.14. Looking at it now, I suspect that I had advised that a condition should be applied that the US product was to be supplied only to hospitals and Haemophilia

Treatment Centres. If so, it would not have been necessary to take further action as I would have expected that the original licence would have already been subject to this condition **[SHPL0000376_005]**.

Section 3: Individuals involved with the variation application

3.1. I have been asked about the roles in the process of various people:

a) Dr Gordon. From the information provided, I believe that he was one of the Pharmacist Assessors, who was replaced by Dr Andrews as Pharmacist Assessor for this application.

b) Dr Fletcher. As I explained, he was my predecessor as Medical Assessor who began the process of assessing the application.

c) Mr Kemp. I believe he was a Medicines Division administrator, who dealt with the administrative details pertaining to each licence.

3.2. I have been asked if there was anyone else within the Medicines Division or wider Department of Health and Social Security (DHSS) who might be relevant to this application. It is possible that I may have consulted my line manager, Dr Holgate, on the handling of this delayed application – we were in adjacent rooms and I spoke with him frequently – but I do not think that, apart from secretaries and administrators in Mr Kemp's team, anyone else would have been involved. I would expect that the files would show the input of anyone else who had been involved in any part of the process – even if only by initialling to show they had seen or were content.

Section 4: Involvement of the Committee on Safety of Medicines and the Sub-Committee on Biologicals

4.1. The Committee on Safety of Medicines (CSM) was a statutory committee established under Section 4 of the Medicines Act 1968 that advised the Licensing Authority on the safety, quality and efficacy of new medicines for human use. The Sub-Committee on Biologicals (CSM(B)) was the CSM sub-committee that dealt with blood products.

4.2. I have not seen any documents to suggest that the CSM(B) was consulted on this application. That would have been standard practice for what appeared to be a straightforward variation to a product licence if the opinion of the Pharmacist and Medical Assessors was that the application should be approved.

4.3. If CSM(B) were not consulted, it follows that the CSM would not be. However, if it were decided that the variation to the licence should not be approved, then that recommendation was required to go to the CSM(B) and its decision would, thereafter, be endorsed by the CSM.

Section 5: Other persons or bodies consulted

5.1. I cannot now recall whether anyone else or any other body was consulted during this application. The only other potentially relevant parties that I can think of that might have been consulted, were the Blood Products Division of the National Institute of Biological Standards and Control (NIBSC) or, if there had been an issue regarding the manufacturing, then the Medicines Inspectorate would have also been consulted.

Section 6: Additional reports or written analyses regarding the application

6.1. I have been asked if further reports or other written analyses were produced by or at the request of the Medicines Division in respect of the application.

6.2. It was not the role of the Medicines Division to try to remedy any deficiencies that were perceived in an application. If there were a need for additional reports or analyses, the company would have been asked to prepare them. However, there are no records suggesting that additional reports or written analyses regarding this particular Kryobulin application were requested by the Medicines Division (other than, of course, the information initially requested by Dr Fletcher).

Section 7: Further documentation

7.1. In regard to whether I expect there would have been further documentation produced regarding this application to vary the licence for Kryobulin, in addition to that set out in Counsel to the Inquiry's Note **[INQY0000415]**, I have the following observations.

7.2. It is apparent that the full file has not been retrieved (or, at least, shown to me for the purpose of this Statement). Of course, the original documentation for the product licence granted in March 1973 would have been voluminous and I cannot say now how much I would have reviewed, for the variation application. The copy of the handwritten note written by me dated 5 April 1978, to which I have referred at paragraph 2.12 above shows that the documents are not complete - I must have written a memorandum on 6 March 1978, when I approved the licence variation, which has not been found.

7.3. There could have easily been some 'to-ing and fro-ing' about the application on the file between any of us involved in the handling of the application internally, including the Pharmacist Assessor, the person dealing with the administrative aspects of the licence (or someone from their team) and myself. However, if any such documents had raised issues suggesting problems with approving the

variation (other than the apparent non-response of the company to Dr Fletcher's queries), the application would likely have been referred to the CSM(B) for refusal.

Section 8: Consideration of the application

8.1. The Inquiry refers me to a German language note of a meeting between Dr Schwarz, Dr Elsinger, Mr Lendvay and Mrs Diernhofer, on 24 November 1976, shortly after Immuno Ltd applied to vary the product licence **[SHPL0000071_083]**. The Inquiry has provided me with an English language translation of the meeting note **[SHPL0001094]**. The Inquiry notes that those attending appear to be Immuno A.G. employees. The topic was *"Kryobulin England"*. The English language translation of the meeting records:

> *"In the future, two types of KRYOBULIN concentrate will be sold - KRYOBULIN 1 and KRYOBULIN 2.*
>
> *KRYOBULIN 1 = Made from European plasma (with a lower hepatitis risk - publication by [illegible]*
>
> *KRYOBULIN 2 = Made from US Licenced Source Plasma (proven to have a significantly higher hepatitis risk - publication by [illegible]*
>
> *KRYOBULIN 2 will be significantly cheaper than KRYOBULIN 1 because the British market will accept a higher risk of hepatitis for a lower-priced product. In the long term, KRYOBULIN 1 will disappear from the British market."*

8.2. Reference to the German original shows that the word translated as *"illegible"* seems to be *"KRASK"* but with a handwritten name that is difficult to decipher written over the top; although one possibility is the name *"Magrath"*, see below.

8.3. I have been asked if I was made aware of the view of either Immuno A.G. or Immuno Ltd, on whether Kryobulin manufactured from American plasma would carry a higher hepatitis risk than Kryobulin manufactured from European plasma.

8.4. Until shown this documentation for the purpose of this Statement, I had no knowledge whatsoever of the reported meeting between Dr Schwarz et al on 24 November 1976. Likewise, I had not been shown any correspondence from

Mr Berry of Immuno Ltd to suggest that they believed the product made from American plasma would carry a higher risk of hepatitis (and, for completeness, it is contrary to the statement that he apparently made to Professor Ingram in August 1979, see paragraph 13.4.b) below).

8.5. The Inquiry asks me whether, at that time, I had any view on which of the two versions of Kryobulin carried a higher hepatitis risk. I cannot be sure now, more than 40 years later, what I thought at the time. The document in German gives rise to the question of what publication(s) there might have been at the date of the discussion (November 1976) to show the relative risks of American versus Austrian/German plasma, and I have addressed this question in some detail at Q15 below.

Section 9: Obligation to disclose certain information

9.1. The Inquiry asks if Immuno A.G. or Immuno Ltd considered that the American Kryobulin would carry a higher hepatitis risk, whether they were under an obligation to state that as part of their application to vary the product licence. Given the passage of time, I cannot now recall what I would have known of the precise legal requirements at the time, and I would think that this issue would be better analysed by a lawyer now. However, if the company knew that its final, fractionated, product was likely to be more risky than other commercial Factor VIII concentrates on the market (including its own European plasma version) then it might be said that it had an ethical obligation to disclose that information as part of the application; although I suppose the ethical obligation would also depend on the extent of Immuno's knowledge.

9.2. At the time the focus will have been on hepatitis B, rather than non-A non-B hepatitis, about which I have commented below. If the company could reasonably argue that it was using state-of-the-art testing for hepatitis B (Radioimmunoassay, or RIA) for HBsAg in its donors, its donations and during manufacture, then its final product should have been as hepatitis B-free (or otherwise) as any of the competitor products on the market that were all based

on the use of US plasma from FDA licensed premises. Furthermore, each batch would have to undergo testing by NIBSC and that included testing for hepatitis B by RIA. The infectious nature of non-A, non-B hepatitis was first established in 1978 by experimental transmission to chimpanzees, see Leveton, Sox and Stoto. eds. 1995, *HIV and the Blood Supply: an analysis of critical decisionmaking*. Washington DC: National Academy Press, at pages 84 to 86 (pages 98 to 100 of the Inquiry's copy) **[JREE0000019]**, and could not reasonably, I believe, have been a focus for regulators at the time of the decision on the variation application. I have already explained the development of my own understanding of the potentially serious consequences of non-A, non-B hepatitis in my first witness statement. No one, of course, was able to test for non-A, non-B hepatitis for at least another decade.

Section 10: Factors considered when assessing the application

10.1. The Inquiry asks what factors were considered when assessing the application for the licence variation. The Medicines Act 1968 required the Licensing Authority to give particular consideration to safety, efficacy and quality when assessing applications for a grant of a licence. The Act also required consideration to be given to *"methods, standards and conditions of manufacture"* if the licence related to an imported product. I believe these considerations would also have applied to a variation application. The Inquiry asks, in particular, what consideration was given to:

a) <u>The relative hepatitis risks of the two products.</u> As I explained above, I cannot now recall what I knew of this at the time. But having reviewed the documents for the purpose of this statement, it seems to me there is some doubt about the correctness of any assumption or belief than the original Austrian/German plasma product was, indeed, safer: please see Q15 below.

b) <u>Any other matters relating to the relative safety of the product.</u> With the passage of time, I cannot recall any other matters.

c) The argument made by Immuno Ltd that they wished *"to… use American plasma in the same way that our competitors do"* **[SHPL0000271_058]**. All I can say now, is that the argument made by Immuno Ltd does not seem to be an unreasonable one. The context was, of course, that other products, such as Hemofil, Profilate and Factorate, that used US plasma sources, had already been licensed for use in England and Wales at the time. My assessment of the variation was made against that background.

d) The prospect of cheaper Kryobulin being available on the UK market. This would not have been a proper consideration for the Licensing Authority. The price of products was explicitly excluded (under the Medicines Act) from consideration by the Licensing Authority.

e) Any risk there may have been to Immuno A.G. withdrawing or limiting the supply of its existing Kryobulin product in the UK market were the application to be refused. The papers suggest that assurances were given by Immuno that it would continue to supply its existing product, even if it obtained a licence to supply the US-plasma derived product; see the form completed by Mr Berry dated 11 November 1976 **[MHRA0033321_085]**. However, I do not see that would have been a relevant consideration to the assessment of whether to grant the variation. Companies could not be compelled to keep a product on the market. The proposed variation to the PL could only be considered in terms of the safety, quality and efficacy of that particular product and not any potential effect that the granting of the licence might have on either other products made by the same manufacturer, or any competitor products.

Section 11: The final decision

11.1. The inquiry asks who made the final decision. As I said above, the documents that I have been provided with indicate that after Dr Andrews initialled his approval, I was the person who signed-off on the variation application

[MHRA0033321_084]. However, approval would only be given after all those involved in the consideration of the application were satisfied it should be approved. If there were doubts, the case would be referred to the CSM(B) committee.

Section 12: The grant of variation

12.1. The Inquiry asks why the application was granted. The application was granted because, as far as I was aware, there was no reason, under the Medicines Act 1968, to not grant it. I referred above to the fact that other US-manufactured products had already been licensed for use in the UK, in decisions made by my predecessors (before I joined the DHSS). Without any reason to rethink those decisions, or any information to suggest that the US Kryobulin product would differ from the other US products already available, there was no reason to reject it.

Section 13: Labelling and the geographical source of plasma

13.1. The Inquiry asks whether it is right that the variation to the product licence did not require the packaging of the variants of Kryobulin to carry any express reference to the geographical source of the plasma used to produce the concentrate. To the best of my knowledge, based on the documents I have seen, that analysis is correct.

13.2. I have been asked why the application was granted without such a requirement. The Inquiry has referred me to the following documents:

a) Example of Kryobulin red European packaging distributed by Serological Products Limited **[SHPL0000071_130]**.

b) Example of Kryobulin blue American packaging distributed by Immuno Ltd **[MHRA0033321_022]**.

c) Fax dated 9 November 1978 from Mr Berry to Mrs Diernhofer at Immuno A.G. which stated that,

"1. We confirm that the factor viii concentrate prepared from american plasma can be called kryobulin.

2. Immuno blue will be the most suitable colour for the pack.

3. There is no mention of plasma source on red kryobulin so there is no need to mention it on the blue packs." **[SHPL0000071_066]**.

d) Fax sent on behalf of Dr Schwarz of Immuno A.G. which indicated that *"kryobulin… is manufactured from european plasma. in the future the origin of source plasma will be indicated on the accompanying test protocol of samples for batch release*" **[SHPL0000071_061]**.

e) Immuno Ltd price list dated January 1980 which referenced "*Kryobulin (red pack – plasma source – Europe)*" and "*Kryobulin (blue pack – plasma source – America)*" both under the same licence number **[DHSC0046258_098]**.

13.3. It is clear from these documents and others referring to the intended differential in pricing that Immuno would be selling the two products in differently coloured packaging and at different prices, so it was clearly intended that the products made from the two different sources of plasma would be clearly distinguishable.

13.4. I do not think that there was a requirement that the competitor US products must state the source of their plasma on labels etc, either (although it could be inferred from the place of manufacture, perhaps). The product was a prescription-only medicine, to be supplied to hospitals and Haemophilia Treatment Centres only. The Inquiry has referred me to:

a) The Immuno price list, which described the existence of two types of product and stated the plasma sources clearly;

b) Minutes of the eighth meeting of the Haemophilia Reference Centre Directors, held on 6 April 1979 **[HCDO0000403]**. Paragraph 5 discussed the two preparations of Kryobulin,

> *"It was pointed out that the company was now selling Kryobulin factor VIII at two prices, the cheaper preparation being made from American plasma. The implication is that the cheaper product carries the higher risk of plasma viral hepatitis. This has worried some of the Directors. Professor Ingram has been in contact with Mr Berry of Immuno who had said that their action was aimed at making available to clinicians material which may carry less risk of transmitting hepatitis…".*

This was followed up by correspondence suggesting that Mr Berry had said that the *"Company regarded both products as equally safe",* see the letter of 8 August 1979 from Professor Ingram at **[LOTH0000012_136]**.

c) In addition, I see that these events were then followed by further discussion in the ninth meeting of Haemophilia Centre Directors on 15 October 1979 **[PRSE0000539]**. This records the amendment of the previous minutes to reflect Professor Ingram's letter. Further:

> *"There was some discussion regarding the two types of Immuno material on the market a "Blue" material and a "Red" material. Dr. Craske suggested that the Directors should perhaps look at the different types of Immuno products to find out how much "Red" and "Blue" material was used and to assess the difference, if any, between these two types of material. It was agreed that the question of "Red" versus "Blue" Immuno material should be referred to the Hepatitis Working Party. The question of the source of plasma used by Immuno for Factor VIII production was raised and there was a feeling that the plasma came from places other than Europe and USA. There was some suspicion that African plasma was being imported to Austria."*

13.5. Overall, it seems that the different sources of plasma in the two types of Kryobulin will have been well known to the Haemophilia Centre Directors who, at that time had the freedom to purchase whichever brand of commercial product they favoured, whether on clinical or cost grounds.

Section 14: Reflections

14.1. Looking back and considering whether I now have any concerns about the decision to grant the variation to the licence, I do not think it was the wrong decision provided the only substantive change requested was to use US-

derived plasma as the source plasma, which was the same source of plasma as used by all Immuno's licensed commercial competitors.

14.2. In relation to information that I did not have, I have referred to the (translated) note of the discussion held on 24 November 1976, and to the possible ethical obligation of Immuno to disclose information about a higher hepatitis risk, if established by the company **[SHPL0001094]**. However, as I explain in Q15 below, I do not know what evidence this discussion was based on, or that, in fact, the US product was, actually, more risky.

14.3. Whether the geographical origin of the plasma needed to be explicitly stated on the packaging might depend on whether that was a stipulation required of other US-plasma based competitor products and, possibly, whether Immuno had previously stated the geographical origin of the plasma when marketing its Austrian plasma-derived product. It is clear that Immuno was required to provide this information to NIBSC for the purpose of batch-release **[SHPL0000071_061]**.

14.4. In regard to whether I have any concerns by which the decision(s) on the application were taken, the process for handling this variation to the licence seems to me perfectly proper except in so far as the process seems to have been in limbo for about a year, because some correspondence was deemed to be missing. Potentially, this delay might have been reduced if the missing correspondence had been chased sooner. Perhaps this was overlooked because Dr Fletcher had left Medicines Division. There was also an administrative error in that, as mentioned above, the condition to be attached to the licence was omitted.

Section 15: Other issues

15.1. In the light, in particular, of the translation of the Note of the German discussion held on 24 November 1976 **[SHPL0001094]**, I have considered what the apparent reference to a "publication" showing that the US product had a significantly higher hepatitis risk might have been, and the broader issue about such a risk.

15.2. The Note does not disclose what form of hepatitis was under discussion. I would have expected it to be hepatitis B, however (for the reasons given below but also because hepatitis B was the virus which could be tested for, enabling statements on risk to be made).

15.3. While I am not able to search German publications, two possible interpretations of the German document are that it referred to a publication by either Dr John Craske (misspelt in the document as "KRASK") or to Dr Magrath (whose name bears some resemblance to the word handwritten over the top of the top of KRASK, especially if misspelt as Macgrath/MacGrath). Dr Magrath was a scientist employed at NIBSC at the time.

15.4. Dr Craske published a paper in the Lancet in August 1975, which described an outbreak of hepatitis associated with a particular brand of US commercial FVIII concentrate. Whilst there was some discussion in the paper contrasting the risks of commercial versus NHS concentrates, there was no mention of Immuno nor of where European-derived concentrates might fall on the risk spectrum. **[CBLA0000297]**.

15.5. Dr Craske (jointly with Dr Peter Kirk of Treloar's College and others) also submitted a paper to a journal in September 1977 with the results of a retrospective study of the risk of contracting hepatitis after infusion with the Factor VIII concentrate Hemofil in the period January 1974 to December 1975 **[CBLA0000648]**.

15.6. That paper was published in J.Hyg.Camb (1978) 80,327-336 **[WITN4469160]**. It is worth noting that, in its conclusions, the paper is extremely useful in describing the state of knowledge of non-B hepatitis at the time:

> *"(5) We do not yet know the nature of the non-B hepatitis we have described. The epidemiology of the disease, the definite incubation periods observed, the association with commercial plasma derivatives and the absence of illness when a convalescent patient is transfused with batches producing hepatitis in other patients - suggesting the acquisition of specific immunity – are all consistent with the view that an infective agent is involved, and elicits specific immunity."*

15.7. I have not identified or been shown any relevant publications attributed to Dr Magrath. However, I understand, from the papers provided to me, that Dr Magrath was to be involved in a prospective study in England, to be undertaken by Dr Kirk and others on whether Factor VIII concentrates increased the incidence of hepatitis in haemophiliacs on regular replacement therapy. The protocol for this proposed study, dated September 1975, is at **[CBLA0000312]**. Dr Magrath, who worked at NIBSC, was to be responsible for testing the concentrate by RIA. I have been unable to locate any publication resulting from this proposed research but some relevant correspondence between Dr Kirk and Dr Magrath is at 1.56.b).

15.8. These two possible interpretations of the illegible author's name therefore do not give any help in answering the question about what publication was referred to in the German Immuno document.

15.9. My limited investigations do, however, cast some doubt on an assumption that the European Immuno product would necessarily be of lower risk than the US product. I note that this assumption is reflected, for example, in the transcript of the Presentation by Counsel to the Inquiry on the Pharmaceutical Companies on 23 September 2021 at pages 87 and 101 **[INQY1000146]** and the continuation of the same presentation on 24 September 2021 at page 35 **[INQY1000147]**. That assumption is presumably based both on the concern that the prevalence of hepatitis B (and thus, possibly, non-B, although its presence could not be detected) was likely to have been greater in American than European plasmapheresis donors and on what was said about the relative risks of the European product versus the American product in the note of the meeting between Immuno A.G employees of 24 November 1976.

15.10. It may be helpful if I draw the Inquiry's attention to material which casts doubt on that thesis:-

a) First, the Austrian/German product was produced from donors who were paid a relatively generous 'honorarium' for their time. I have been shown a record of an informal visit to the Immuno factory in Vienna by the UK's Dr Duncan Thomas, which included notes of the visit to a plasmapheresis station. There was a panel of about 1,000 donors who

attend x1/week who were paid approximately £5 per session (this would have been worth just under £70 in 2022 or just over £77 in 2023, according to https://www.in2013dollars.com/uk/inflation/1973?endYear=2022&amount=5). Dr Thomas wrote: *"Although I did not see any of the donors, I was assured that they were not "down and outs". It is of interest that the Austrians pay their donors two and a half times the amount paid in the United States. I asked Dr. Schwarz how the Austrian Red Cross felt about his firm paying donors for plasma…"* **[DHSC0103054_011]**. The report was signed by Dr Thomas and dated 3 July 1973.

b) Second, the UK research being performed at the time did not suggest differences between the European Immuno and US products. Thus on the subject of Dr Kirk's hepatitis survey, on 1 April 1977, Dr Kirk wrote to Dr Magrath at NIBSC **[CBLA0000590]**. He said that almost all the cases of hepatitis were confined to patients restricted to commercial concentrate. But he continued: *"There were no significant differences between the cases restricted to Hemofil and Kryobulin"*. In his reply of 20 April 1977, Dr Magrath agreed he had seen no differences between the commercial concentrates in their positivity for hepatitis B. (He also confirmed that at that stage Kryobulin was prepared solely from Austrian or German donors whereas Hemofil was a US-only product, in response to Dr Kirk's statement that both were US products) **[HHFT0000925_002]**.

c) Further doubt arises from the correspondence of July 1975 between Dr Dane (virologist at The Middlesex Hospital) and Mr Berry in July 1975, which was referred to at pages 4 to 12 of the transcript of the Presentation by Counsel to the Inquiry on the Pharmaceutical Companies on 24 September 2021 **[INQY1000147]**. The point that was being made by Dr Dane was that the screening tests for donors and their donations apparently then in use by Immuno in 1975 (countercurrent electrophoresis, CEP), was relatively insensitive, compared to the RIA tests being used by Dr Dane in his hospital. *"I should make it clear to you that if Immuno uses CEP screening on original donations then they are certain to miss a proportion of HBsAg carriers amongst their donors*

and that we may then be able to detect HBsAg in the final product by RIA."

d) By contrast, the American plasma-derived competitor products on the market were, in all likelihood, being tested by the more sensitive PHA or RIA tests from at least July 1975 onwards. On this, see the publication *HIV and the Blood Supply*, cited above, at page 85 (page 99 in the Inquiry's copy), which states, of the US: *"In July 1975, the use of a third-generation test for HBsAg with a greater degree of sensitivity, utilizing radioimmunoassay or reversed passive hemagglutination, was required by the FDA*" **[JREE0000019]**. The date at which the use of third-generation testing was mandated by the Bureau of Biologics of the FDA was March 1976, according to a publication from Alpha Therapeutics, a US manufacturer of commercial FVIII concentrates, to which the Inquiry has drawn my attention [**BAYP0000021_003**]. The paper also states that the most sensitive current RIA test had been used routinely since February 1975. In addition, I have been shown an appendix to the draft statement produced by Dr Richard Lane for the HIV litigation which indicates that RIA testing was in use in American plasmapheresis centres from 1972 **[BPLL0004833]** at least raising the possibility that the RIA tests were in use before they were mandated by the FDA. But the central point is that, until Immuno swapped its European testing from CEP to RIA (which I note from page 79 of the transcript of the Presentation by Counsel to the Inquiry on the Pharmaceutical Companies on 23 September 2021 **[INQY1000146]** was in October 1975), an argument can be made that products then being made from European plasma were actually less safe (in terms of hepatitis B), than the US ones.

e) To take the position at BPL by way of further comparison with the US products, BPL began screening plasma with RIA from January 1976, according to paragraph 452 of Dr Lane's draft proof of evidence **[CBLA0000005_002]**. Dr Richard Lane's statement appended the 1976 Report to the Advisory Sub-Committee on Blood Products and Blood Group Reference confirmed that RIA testing was carried out not on single

donations but on the 5-litre donor pools sent to BPL from Regional Transfusion Centres (RTCs) which meant that a positive result in one pool unnecessarily implicated some 25 to 30 other donations **[CBLA0000664]**. In addition, the dilution effect of 5 litres on a single donation might invalidate even the more sensitive RIA test (this was one reason behind Dr Lane's advocacy of a swap to single packs, **[CBLA0000801]**, pages 2 and 7). The other reason was that some RTCs were using a less sensitive HBsAg test to screen their donors, which might give false- negative results if there were a low viral load and, with the added effect of 5-litre pooling, could go undetected even when tested by RIA at BPL.

f) Finally, in relation to non-A, non-B hepatitis, I draw attention to a paper published in 2007 by Ferenci and others (*Morbidity and mortality in paid Austrian plasma donors infected with hepatitis C at plasma donations in the 1970s*). This retrospective survey described several epidemic outbreaks of hepatitis non-A, non-B in plasma donors in Austrian plasmapheresis centres between the 1970s and the mid- 80s **[WITN4461161]**.

g) Given there is no direct person-to-person spread of hepatitis C, the only explanation for such outbreaks is cross-contamination in these plasmapheresis centres. Large numbers of donors were infected. This must, inevitably, have compromised the safety of the products manufactured from plasma from the implicated centres. However, this will not have been known to the Licensing Authority at the time.

15.11. Whilst I appreciate the limitations of the research that I have personally been able to conduct, it seems to me that there remains an open question to be answered as to the relative safety of the Austrian and US products at the time which, even with the information that is available now, may not be susceptible of resolution.

Statement of Truth

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

Signed: ..... GRO-C .....

Dated: 31 January 2023