Witness Name: ANNE RYAN
Statement No.: WITN7183001
Exhibits: WITN7183002-WITN7183011
Dated: 19/08/2022

INFECTED BLOOD INQUIRY

FIRST WRITTEN STATEMENT OF ANNE RYAN

I, Anne Ryan, will say as follows:

1. Section 1: Introduction

1.1. I am Anne Ryan and my address and date of birth are known to the Inquiry.

1.2. I am providing this written statement in response to the Inquiry's Rule 9 request dated 29 June 2022 (the '**Rule 9 request**'), on behalf of the Medicines and Healthcare products Regulatory Agency ('**MHRA**').

1.3. I am employed by the MHRA as Policy Lead in the Regulatory Reform team in the MHRA's Partnerships Division.

1.4. The MHRA has been asked by the Inquiry to respond to the Rule 9 request, which principally concerns events and records dating from the 1970s and 1980s. I therefore have no personal recollection of those events or the processes I describe in this witness statement from that period, since I had no involvement with them.

1.5. I have co-ordinated the MHRA's responses to the Rule 9 request. In doing so I liaised with a number of MHRA colleagues with relevant knowledge and experience across the MHRA in order to collate information. Their contributions have been used to respond to the questions in the statement which follows. I do not have any personal expertise in these areas and my statement relies on those contributions.

1.6. In making this statement, I am reliant on document archive searches conducted by colleagues and the documents provided to me by the Inquiry. My statement is entirely reliant on a review of the contemporaneous written material. I do not personally hold any documents relating to the Inquiry's Terms of Reference.

1.7. My statement should be read subject to the caveats above. If further material is made available to me, I would be happy to add to or clarify this statement to take it into account. I have done my best to assist the Inquiry wherever I can on behalf of the MHRA.

2. Section 2: Historical Dissemination of Information

2.1. The Inquiry has shown me a paper produced by the Medicines Division of the then Department of Health and Social Security in July 1977 [**MHRA0004773**] which lists the Department's methods for disseminating information, including 'Adverse Reactions' leaflets, 'Dear Doctor' letters and 'Current Problems' leaflets. In particular, I am asked when the 'Adverse Reaction' leaflet system ceased and whether any 'Adverse Reaction' leaflets, 'Dear Doctor' letters or 'Current Problem' leaflets were issued concerning the risks of Factor concentrates between 1970 and 2000.

2.2. The MHRA records indicate that the 'Adverse Reactions' series ran from 1964 to 1985. My source for this is a journal article in *Drug Safety*: '*25 Years of the Committee on Safety of Medicines*' dated May 1990 (Bem, J.L., Wood, S.M., West, L. et al. 25 Years of the Committee on Safety of Medicines. Drug-Safety 5, 161–167 (1990)) [**WITN7183002**]. The article considers the system for spontaneous reporting of suspected adverse drug reactions, "the Yellow Card Scheme" in the UK, which was one of the first countries to set up a monitoring scheme under the responsibility of the Committee on the Safety of Medicines ('**CSM**'). The article records that the 'Adverse Reactions' leaflets series ran from February 1964 until 1985, with the last title on record being issued in January 1985.

2.3. In our efforts to assist the Inquiry, the MHRA has conducted a search of its archives and digital files for the period between 1970 and 2000. No communications in respect of the risks of Factor concentrates were located. I am aware, however, that our archives do not contain complete sets of records;

so copies of some communications may not have been retained by the MHRA. I am therefore unable to verify the position in respect of some records (such as the full copies of the 'Adverse Reaction' leaflets series and 'Dear Doctor' letters issued between 1995 and 2000). Since the MHRA's records on this point are incomplete I cannot say whether or not there were any communications in respect of the risks of Factor concentrates issued by the MHRA or any other UK Government department or agency between 1970 and 2000.

2.4. For completeness, I set out below the document archive searches which have been undertaken by the MHRA in response to the Rule 9 request and the gaps in our records which we have identified:

(1) My MHRA colleagues have searched the National Archive for copies of the 'Adverse Reaction' series, 'Current Problems' and 'Current Problems in Pharmacovigilance' as well as 'Dear Doctor' letters. In addition, MHRA's own online archives in its 'Documentum' database have been searched manually, focusing on the document folders entitled 'Communications' and 'Vigilance and Risk Management of Medicines' (**'VRMM'**) as these folders were most likely to include relevant documents as VRMM, and its departmental predecessors, were responsible for monitoring safety and issuing communications.

(2) We have not been able to locate the full set of 'Dear Doctor' letters for the period between 1970 and 2000. In 1995, in response to a Parliamentary Question, the MHRA prepared an index of 'Dear Doctor' letters for the period 1964 to 1995 [**WITN7183003**]. Given the passage of time it is not now possible for the MHRA to verify that the index produced in 1995 is complete. The MHRA does not hold a central index of 'Dear Doctor' letters issued between 1995 and 2000.

(3) Notwithstanding that there is no central index of 'Dear Doctor' letters for the period between 1995 and 2000, individual 'Dear Doctor' letters may be stored within online or paper archives held in respect of each authorised medicinal product. The historical archive available online, either as part of the National Archive or the MHRA's own archive may not be complete and comprises scanned versions of the original paper

files. The electronic files cannot be digitally searched and requires a manual review of each page. It is possible that some original paper files have been destroyed or stored in the MHRA's paper archive. Any search of these would be conducted by active substance or require the marketing authorisation or product licence numbers for each medicinal product.

(4) The MHRA is willing to assist the Inquiry in relation to any further archive document searches it deems are necessary and would be helpful.

Section 3: Adverse Drug Reaction Reports

3.1. I have been referred to a table ('**Table 1'**) of all UK spontaneous suspected Adverse Drug Reaction ('**ADR**') reports between 1 January 1970 and 31 December 1995 [**WITN6406025**], which purportedly shows several reports of HIV/AIDs in the years before HIV and AIDS were first identified. My MHRA colleagues have conducted some more detailed analysis of the data underlying this table (and explored how it was originally put together) and would like to take this opportunity to apologise on behalf of the MHRA that the original table was unclear and misleading and that the position was not fully explained in the information provided to Sir Michael Rawlins or to the Inquiry. I hope that this full explanation assists the Inquiry.

3.2. The MHRA operates, jointly with the Commission on Human Medicines, the Yellow Card scheme, which collects and monitors information on suspected safety concerns involving healthcare products, for example a side effect of a medicine or an adverse medical device incident. The scheme relies on voluntary reporting of a problem suspected to be associated with a healthcare product by the public (including patients, parents and care givers) as well as by healthcare professionals. Pharmaceutical companies also have a legal obligation to report any adverse incidents which have been notified to them to the MHRA.

3.3. During the period that Table 1 covers (1970 to 1995), the Yellow Card scheme was run by the MHRA's predecessor organisations jointly with the Committee on Safety of Medicines. Reporting of suspected adverse drug reactions was

limited to medical practitioners. It was also possible for doctors to submit suspected adverse reaction reports in other ways, such as by writing letters to the Committee on Safety of Medicines.

3.4. The MHRA holds the data recorded on historical Yellow Cards. The Inquiry may find it useful if I first provide some information on the dictionary that the MHRA uses when classifying ADR reports: the Medical Dictionary for Regulatory Activities ('**MedDRA**'). This is a clinically validated dictionary of international medical terminology. It is organised by System Organ Class ('**SOC**'), divided into High-Level Group Terms ('**HLGT**'), High-Level Terms ('**HLT**'), Preferred Terms ('**PT**') and finally into Lowest Level Terms ('**LLT**'). The MHRA uses these terms to code ADR reports within its database.

3.5. My MHRA colleagues have conducted searches for relevant ADR data by searching the MHRA's ADR database, which is known as Sentinel. Sentinel holds all ADR reports received via the Yellow Card scheme, as well as those reports received from pharmaceutical companies. All the MHRA's ADR data is held electronically on this database and therefore no search of paper records has been conducted in relation to ADRs.

3.6. The search was conducted for all UK spontaneous ADR reports received between 1 January 1970 and 31 December 1995 associated with a blood product and a suspected ADR in one of the following MedDRA SOCs: Blood and lymphatic system disorders, hepatobiliary disorders, infections and infestations and investigations.

3.7. The final column of Table 1 was entitled '*Total Number of ADR reports of blood products relating to HIV/AIDs*'. Had HIV/AIDS been reported, it would have fallen within the category of *'blood, hepatobiliary disorders, infection and investigation SOC*' and it was these overall category figures that were searched for and provided in the original Table 1. The SOCs used for this search included all relevant terms and while they would have included any results for HIV/AIDS if there were any, they also included reactions other than HIV/AIDS. This is why, unfortunately, the table purported to show reports of HIV/AIDS in the years before HIV/AIDS had been identified.

3.8. Having examined the underlying data closely, this column would better be described as the total number of ADR reports of blood products relating to reactions within the i) blood and lymphatic system disorders, ii) hepatobiliary disorders, iii) infections and infestations and iv) investigation SOCs. The title of the final column of Table 1 should therefore more accurately read: '*Total number of ADR reports of blood products relating to reactions within the blood, hepatic, infection and investigation System Organ Classes*'. The MHRA has prepared a new version of Table 1 accordingly [**WITN7183004**].

3.9. Having now examined those figures, the MHRA has found that, in fact, none of the reports related to HIV/AIDS. There were therefore no UK spontaneous suspected adverse reaction reports of HIV or AIDS reported in any blood products in the time period covered by Table 1, that is from 1970 to 1995.

3.10. By way of further information, the MHRA has produced a breakdown of the ADR reports by year in respect of each listed category between 1970 and 1995 ('**Table 2'**) [**WITN7183005**]. Table 2 illustrates all UK spontaneous suspected ADR reports received by the MHRA between 1970 and 1995 concerning a blood product and one of the four SOCs of interest, broken down by year reported and the preferred term which caused the report to fall within the scope of the request. As can be seen from the data, the majority of reported reactions related to reactions in the hepatobiliary disorders SOC, including 35 reports of hepatitis, 16 reports of abnormal hepatic function and 20 reports of jaundice. In addition, there were 2 reports of Hepatitis A and 2 reports of Hepatitis B.

3.11. As an example, Table 2 shows that in 1979 there were 6 ADRs in relation to blood products categorised under 'Hepatitis'. In the same year, there were no ADRs in relation to blood products categorised under 'Hepatitis A' and only 1 under 'Hepatitis B'. There was 1 ADR categorised as 'Hepatitis infectious mononucleosis' and 1 ADR categorised as 'Hepatitis non-A non-B'. As this gave rise to the question why there were reactions marked at 'Hepatitis' but neither hepatitis A nor B, we have looked at the underlying Yellow Card reports.

3.12. My MHRA colleagues have retrieved and anonymised 8 ADRs in relation to blood products relating to 'Hepatitis', 'Hepatitis B' and 'Hepatitis non-A non-B' dating from 1979 [**WITN7183006**]. These are summarised in Table 3

[**WITN7183007**], which provides details of the 8 ADRs received by the MHRA in 1979 concerning blood products and the preferred terms 'Hepatitis', 'Hepatitis B' or 'Hepatitis non-A non-B'.

3.13. Seven of these results come from Yellow Card reports and one is from a Report of Case for Post-Transfusion Hepatitis, which is recorded and analysed using the same processes as Yellow Card reports. The 1979 Yellow Cards allowed the reporting clinician to report the drug and brand name, the route and dose, the dates on which the product was administered and any indications. The indications show that seven of the eight patients were clearly identified as people with haemophilia with the final patient suffering haemarthrosis (which may also suggest they too suffered from haemophilia).

3.14. The reports ask for reactions to be listed. Reactions reported on these cards were:

b. Jaundice

c. Anorexia

d. Nausea

e. Vomiting

f. Discoloured urine

g. Raised liver function tests ('**LFTs**')

h. Hepatitis (including one case from which the patient is said to have recovered)

i. A suspected case of Non A Non B hepatitis in a transfusion patient.

3.15. The information coded within the Yellow Card database is a direct transcription of the information provided by the original reporter. The data is not interpreted or reclassified by the MHRA within the Yellow Card database. This can result in different terms being used to report effectively the same medical condition, such as the general term "Hepatitis" compared to a more specific term, for example "Non A Non B Hepatitis". This can be observed in Table 3 [**WITN7183007**], which provides details of the 8 ADRs received by the MHRA in 1979 where the test results provided in the narrative text may verify a specific

form of Hepatitis which is not necessarily reflected in the classified Reaction LLT. One additional point to note is that for Case 3 in Table 3 the Drug Name as classified lists Factor VIII twice because this patient received generic Factor VIII as well as the Profilate brand of Factor VIII. Profilate is no longer marketed and is not available within the MHRA's drug dictionary used to classify reports. Therefore, the substance rather than the brand is listed.

3.16. Finally, to assist the Inquiry, I have exhibited two blank Yellow Card reports used today: [**WITN7183008**] and [**WITN7183009**]. The version for members of the public also contains a guidance leaflet about the system and reporting. As well as hard copies available for download such as these, there in an online Yellow Card report "smart form" which asks a series of questions and which can be found here: https://yellowcard.mhra.gov.uk/, a freephone Yellow Card reporting line on freephone 0800 731 6789 (10am to 2pm Monday-Friday only) and an app called 'Yellow Card'.

Section 4: Investigations into potential adverse reaction incidents

4.1. Finally, the Inquiry has referred me to the witness statement of Professor William Asscher dated 27 January 1989 [**WITN64060254**]. Professor Asscher was, at that time, the Chair of the CSM. Professor Asscher's witness statement described the process of assessment, analysis and investigation undertaken once a possible adverse reaction problem with a particular drug had been identified. This required a number of steps which were variously described at paragraphs 23 to 28 of the statement, which I have read and considered.

4.2. My colleagues have reviewed the CSM minutes from 1970 to 1989. From the records we located, it is not possible to confirm whether or not the full process Professor Asscher describes (i.e. adverse reaction reports being received by the CSM and leading to an investigation) took place in relation to blood products, although it should be noted that my colleagues' interpretation of the 'process' described by Professor Asscher is that he was describing a theoretical model which was often varied in its practical implementation in specific cases at the time.

4.3. What the CSM minutes show is that the CSM considered issues relating to infections associated with blood products on a number of occasions, as follows:

j. At the CSM meeting on 22 November 1984, the CSM considered cases of AIDS in haemophiliacs [**DHSC0003947_015**]. The minutes record (on page 6) that Dr Joseph Smith '*informed the Committee that heat treatment of Factor VIII, which is used in the treatment of haemophiliacs, abolished detectable infectivity of AIDS virus… companies should be encouraged to apply for variations of licences to permit widespread use of heat-treated Factor VIII, so that the incidence of AIDS in haemophiliacs might be reduced.'* The CSM therefore '*requested that the Licensing Authority propose to the companies concerned that they make early applications for variations to use a dry heat treating process in the manufacture of their Factor VIII products*.'

k. At the CSM meeting on 26 July 1985, the CSM considered the safety of intravenous immunoglobulins [**WITN5281063**] (page 6 of the minutes). The paper which they considered is at [**DHSC0000368**] (page 13 onwards). The minutes record that there had been reports of transmission of hepatitis C associated with intravenous immunoglobulins and recorded that the matter had already been considered by the Biologicals Subcommittee ('**CSM(B)**') whose recommendations were endorsed. The CSM(B) had considered the issue at their meeting on 3 July 1985 [**WITN5281062**] at which they had discussed a paper and made recommendations. The paper appears to be the same one that the CSM considered according to the annotations: [**DHSC0000368**] (page 13). It seems that further work then took place as can be seen in the undated report of Dr Mary Duncan [**DHSC0000368**], which must have been written after November 1985.

l. At the CSM meeting on 27 May 1987 [**WITN7183010**], the CSM noted (at page 6 of the minutes) '*the need for validation of in vitro screening tests for viral contamination of blood donations used in the manufacture of blood products*'. In doing so, the CSM considered and endorsed the recommendation of the CSM(B) of 13 May 1987 [**WITN7183011**], page 2 of the minutes of which record the CSM(B)'s endorsement of a tabled paper, whose recommendations are summarised as follows:

> *'All manufacturers applying for new licences for blood products should supply full information on the screening procedures currently carried out for HIV…*
>
> *Ongoing monitoring for current licence holders and for all new licences should be by submission of quality assurance and performance evaluation data with the protocols supplied for the batch release process.*
>
> *The Licensing Authority should write to individual manufacturers and ask them to provide this quality assurance information from data to be agreed.'*

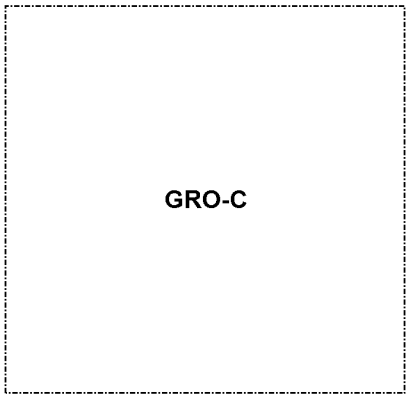
4.4. In addition to the CSM (and CSM(B)) minutes described above, my colleagues have also retrieved and reviewed the minutes of the Safety, Efficacy and Adverse Reactions Subcommittee ('**SEAR**') for the period we hold, 1982 to 1989, which is the extent that has been retained by the MHRA. Beyond the points described above, there were no references to ADRs involving Hepatitis, HIV/AIDS or any licenced Factor concentrates in those minutes.

Section 5: Final Remarks

5.1 Finally, on behalf of my MHRA colleagues, I would like to express my deepest sympathies to those who have been infected via blood products and to the affected families. The MHRA will continue to do everything possible to assist the Inquiry in its work.

Statement of Truth

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



Signed

Anne Ryan

Dated: 19 August 2022