Submission to the Penrose Inquiry Dr Mark Winter

1.1 The core of my submission to the Penrose Inquiry is the written and oral testimony that I gave to the Archer Inquiry (document 7 attached).

1.2 Having restudied this submission, from my perspective it still articulates what I believe to be the core issues surrounding the outbreak of viral infections in patients with haemophilia. There is nothing of significance which I feel that I need to add to this submission but I have been asked to respond to the following supplementary questions:

1.3 It is a small point, but our research appears to demonstrate that "Birch" was Carroll LaFleur Birch, MD at the Research and EducationalHospital of the University of Illinois in Chicago. Was her study on life expectancy therefore an American one?

1.3 I would agree that the Birch report – which is very relevant as it sets out the natural history of untreated haemophilia – was an American publication. There is obviously no reason to believe that the likely survival of untreated British patients with Haemophilia should be any different to that of American patients.

1.4 Our Preliminary Report in paragraph 3.12 sets out a current explanation of the gradations of haemophilia from mild to severe. As we recorded, Dr Winter would prefer that mild be seen as 5 to 50% - perhaps that could be included.

1.4 The various grades of Haemophilia severity have been agreed by the World Federation of Haemophilia, as follows:

<1iu/dl: Severe

1-5iu/dl: Moderate

5-50iu/dl: Mild

1.5 We have a DVD of the World in Action investigation in 1975 into self sufficiency in the UK and the manufacture of blood products in the USA. This is referred to in paragraph 6.48 of the Preliminary Report. We would like you to view the programme, and have sent a copy in order to enable you to do so. We would be interested in any further comments once you have seen the programme.

1.5 I have reviewed, as requested, the World in Action documentary and have the following comments:

- The opening scenes, with various British teenage haemophiliacs and their families, are especially important since they underscore the very great improvement in quality of life afforded by the new concentrates, as compared with the use of cryoprecipitate, which was clumsy, time consuming, associated with side effects and in particular had to be administered in hospital. These comments are supported later in the programme by the Haemophilia Society. It is thus clear why patients, their families, and their treaters were so reluctant to consider a switch back to cryoprecipitate treatment once concerns about concentrate safety had been raised.

- The programme sets out visually what was already clear at the time – that blood products derived from commercial donations were significantly more likely to be associated with viral infections than those from voluntary donors, because of the socio-economic backgrounds of the donor populations.

- The practice of blood collection from developing countries such as Africa was always denied by the commercial manufacturers but there was subsequent evidence from the study of Hepatitis C genotypes that suggested that blood of African origin may have found its way into pools of commercial concentrate

- One notes that most of the medical comments made by Professor Zuckerman, and by Baxter representatives, relate to Hepatitis B, whereas we now know that probably all haemophiliac patients treated with concentrates in the 1970's acquired Hepatitis C (not identified till 1989) whilst only a minority of patients acquired Hepatitis B. Comments about screening for Hepatitis are in hindsight not especially critical since this would only have been for Hepatitis B and not for the more common non-A, non-B Hepatitis (Hepatitis C).

1.6 What is your response to Dr Cash's letter also referred to in that paragraph of the Report? (A copy is enclosed- document 1).

1.6 In retrospect, the implication in Dr Cash's letter to the Lancet of January 1976 that the magnitude of the problem was being exaggerated by World in

Action appears inappropriate, given the subsequent mortality. His comments in the final paragraph, that self-sufficiency was not likely to happen before 1977, even following the additional funding of £500,000, proved to be correct.

1.7 We have carried out some research into the outbreaks of hepatitis B associated with concentrates in the mid 1970s, and enclose some articles dealing with this (document 2). This may enable you to firm up the part of your written submission at page 2, first full paragraph.

1.7 The provided articles concerning the report of both Hepatitis B and "non-B Hepatitis" (i:e Hepatitis C) in Bournemouth, and the finding of abnormal Hepatitis-like liver function tests in most patients who had received concentrate, doubtless formed the basis of the view held by UKHCDO by the mid 1970's that one or more forms of Hepatitis were likely to be transmitted by commercial concentrates. Similar findings had been identified by Professor Mannucci and his colleagues in Milan, including liver biopsy evidence suggestive of Hepatitis. It would have been around this time that UKHCDO were in dialogue with DOH about the possibility of attaining self sufficiency.

1.8 There is a narrative of the preparation of cryoprecipitate in the Preliminary Report at paragraph 3.27. There has also been subsequent correspondence about this passage with a transfusion expert. Do you have any comment on it? We were also interested in the remarks about the patients getting "chills and shakes" and would be grateful if those could be expanded.

1.8 Cryoprecipitate, though an effective treatment for haemophilia, had a number of practical disadvantages. It had to be deep frozen and was not thus not suitable for home therapy. It was of large volume – which could be a problem in children – and this also made it difficult to inject intravenously. Its preparation was particularly laborious , taking two people up to an hour to prepare one injection. The amount of factor VIII in each bag was unknown and this made scientific calculation of treatment dosage impossible. Finally, the use of cryoprecipitate was often associated with chills and shaking, thought to be due to pre-existing antibodies to plasma proteins, and these could be thoroughly unpleasant.

1.9 Again, as discussed, we have become aware of some reluctance to use Scottish NHS Factor VIII rather than commercial material prior to the AIDS problem becoming known. What were the general reasons why clinicians preferred commercial product?

1.9 As set out in the World in Action documentary, there was a strong and understandable preference amongst patients and their families for concentrate of British origin; these sentiments were shared by mostclinicians in the 1970's, as outlined above. Once heat treated factor VIII and IX had been universally adopted (c1985) clinicians believed that both commercial and voluntary donor derived concentrate were likely to be free of known viruses.

1.10We discussed the issue of pharmaceutical company funding over the telephone. We understand that, at least in England, certain centres received funding for research, staffing and other patient-care related expenses from drug companies.

1.10 At that time there was a certain dynamic in that the commercial companies had a very professional mode of operation, which clinicians and nurses liked, including the prompt provision of scientific data, satisfactory arrangements for delivery to hospital and home and good communication networks to discuss and react to any centre or patient based issues. For whatever reason, these services were not so well provided by BPL (I cannot speak of Scotland) and this lead some clinicians to prefer commercial product. It is possible that cost might also have been an issue.

Some centres were also in receipt of modest levels of financial support from commercial companies, usually related to areas such as the publication of patient based materials or support for clinicians, nurses and patient representatives to attend scientific meetings.

1.11 Since writing the Preliminary Report we have become aware of further documents. For example, the PHLS bulletin for week ending 6 May 1983, a copy of which we enclose (document 3), refers to AIDS in a 20 year old man from Cardiff with haemophilia. That was the time when the letter quoted in the Preliminary Report at paragraph 8.25 was sent. Do you have any comments on the letter?

1.11 The first reported case of AIDS in a British haemophiliac involved a patient from the Cardiff centre, published in the CDR of 6th May 1983. This was published two days after Professor Bloom's letter to the Haemophilia Society. His rather conservative tone - which in retrospect appears inappropriate - may have been related to a view held amongst some UK clinicians that not enough clinical information was available at that time about the small number of reported cases in American haemophiliacs. UK clinicians were also aware of the lack of any such cases in Germany, despite their very high use of concentrates.

1.12 We enclose a copy of Council of Europe Recommendation R(83)8 on AIDS (DHF.002.2149 – document 4). How does this compare with the various recommendations in the UK around this time? How does it reflect practice in the UK? We were particularly interested in your comments about possible underuse of DDAVP.

1.12 I am not aware that the recommendations of the Council of Europe were ever circulated through UKHCDO. Their general recommendations are broadly in keeping with those of UKHCDO at around the same time.

Not mentioned in the Council of Europe document is the use of DDAVP (Desmopressin). One of the more poignant aspects of the viral epidemic in patients with Haemophilia was the infection with HIV and/or Hepatitis in patients who were not regular users of concentrate. This subgroup would include patients with mild Haemophilia, patients with mild von Willebrand's disease and females who were Haemophilia carriers. These patients would have been given concentrate to cover surgery, dental treatment or episodes of trauma.

In 1977, Professor Mannucci, then at St Thomas's Hospital in London but subsequently Professor in Milan, demonstrated that the injection of DDAVP to the above subgroups of patients resulted in a significant increase in factor VIIIwhich lasted for a few days. DDAVP was thus used as a very valuable tool for mildly affected patients as it avoided the use of concentrate, with all its attendant risks. DDAVP was not effective in more severely affected patients. This work had been widely published. DDAVP was widely available.

The use of DDAVP was included in the recommendations contained in Professor Bloom's letter of 24th June 1983. This is the letter erroneously referred to in my Archer testimony as being from July 1983.

1.13 We would like to deal with Dr Galbraith's letter and the outcome of his raising of the issue of banning imports of concentrates in July 1983. In particular, might the analysis of the problem have been different in Scotland, where there were greater quantities of NHS product available?

1.13 By July 1983, there had been only one reported case of AIDS in the British Haemophilia population; there was more than 10 years of scientific evidence documenting the likely transmission of Hepatitis from concentrates, particularly of commercial origin. However, the majority of patients, despite

having these biochemical changes, remained fit and well and were indeed thriving as a result of the apparent improvement in quality of life afforded by concentrates.

Against this background it might thus have appeared premature at this time to consider withdrawal of commercial concentrates, particularly given the only alternative option – that of moving patients back to cryoprecipitate, since in England (with its significant reliance on commercial concentrate) there was in any case clearly inadequate supplies of cryoprecipitate for this decision to be made, even if it was considered appropriate. Such a move would presumably have been more feasible in Scotland, where a lesser proportion of commercial concentrate was being used, but one notes that concerns about potential supply problems were raised by the COSM sub-committee.

1.14 You referred to Kenneth Clarke's statement in November 1983 – he appears in fact to have said that there was no "conclusive" evidence that AIDS was transmitted by blood products. (paragraph 8.63) What is your view of this line, which was often repeated in government messages about AIDS and blood products at this time? Could you refer in your statement to Koch's postulates?

1.14 In medical practice, a series of criteria known as Koch's postulates are used to determine whether an organism might be directly responsible for a certain disease. By mid 1983, the virus now known as HIV had been identified but no blood test was available. To be certain that a patient with Haemophilia had developed AIDS from contaminated blood one would need to demonstrate:

- thata blood donor who had contributed to a batch of concentrate received by a patient had either developed AIDS or had been shown to be HIV positive

- that HIV had been identified in the suspected batch of concentrate

- that the Haemophilia patient had developed AIDS or had been shown to have HIV

By November 1983, it would not have been possible in my view to have satisfied all of these criteria and thus the statements of Kenneth Clarke at this time cannot strictly be criticised

1.15 As seen from page 73 of the transcript, you referred to the meeting in December 1983 (which we think was actually October 1983 – see paragraph 8.61 of the Preliminary Report). We have not been able to trace any record of a meeting in December, and the material quoted is in the October minutes. Do you agree?

1.15 The UKHCDO AGM of 1983 must have been held in October rather than December 1983

1.16 You referred to the absence of a standard body to advise on matters virological, and to the establishment of the EAGA in 1985. Could it be said that the body really required was the Advisory Committee on the Virological Safety of Blood, which was established in 1989? If so, should that body have been set up earlier?

1.16 I have tried to make the point in my previous submissions that one of the major problems facing Haemophilia clinicians in the early years of AIDS was the lack of substantial viral advice, particularly on a formal national basis. As soon as it had become apparent that patients with Haemophilia were being infected with HIV from contaminated concentrates (this information was available in the autumn of 1984) there was a clearly defined need for urgent viral advice of this type. Until such bodies were eventually established, UKHCDO had to rely on the invaluable assistance of Dr John Craske.

1.17 Would advice from virologists have made a difference? What comes across is that haemophilia clinicians made their decisions on a balance of risk to benefit, not against a background of feeling inadequately informed about the virology. This is reflected in the transcript at page 76. We have the impression that Professor Bloom was a key figure in the formulation of advice. Is this so?

1.17 We now know that most patients with Haemophilia were infected with HIV between 1981 and 1984. There were however a small number of patients infected during the latter part of 1984 at a time when some centres had made a decision to switch to heat treated commercial concentrate, available on a named patient basis, whilst other centres persisted with unheated concentrate of voluntary blood donor origin. This was a time when more substantial viral advice would have been invaluable.

1.18 The reference to a letter of January 1982 at page 105 line 5 appears to be to a letter of 11 January 1982, LOT.003.5278, a copy of which we enclose (document 5). Is this correct?

1.18 It was on 11th January 1982 that Professor Bloom wrote to Haemophilia directors concerning the potential use of heat treated concentrates.

1.19 In evidence to the Archer Inquiry you mentioned a hypothetical situation where he would discuss with a haemophilia patient the relative merits of heat treated concentrates as opposed to non-heated treated concentrates and offer them a choice. Was this his practice with his patients? If so can he advise from when he started to follow this practice? Is it possible to say whether this was the prevailing practice amongst Haemophilia doctors at that time? Did he continue offering his patients this choice after heat treated products had been given a licence and it was not necessary to proceed on a "named patient" basis?

1.19 Heat treated concentrate, commercial in nature, was first used in my centre in May 1984. This was an especially critical and difficult time, as set out in my Archer submission, because in particular patients were being asked to switch from concentrate of UK origin to concentrate of US origin, which they had always distrusted. Considerable time had to be spent with each patient, and their family, to explain the basis of this recommendation. Because a switch was not formal UKHCDO policy at this time, this process would have been performed on an ad hoc and individual basis by those centres that were recommending a switch at that time.

Initially, to my knowledge, only the centres in Sheffield, UCH, St Thomas's and Canterbury made a decision to switch to heat treated commercial concentrate in May 1984, on a named patient basis. This decision was criticised at UKHCDO meetings by other directors who thought that viral transmission through the use of concentrate derived from voluntary UK donors was very unlikely (subsequently shown to be untrue). The commercial concentrate was also 50% more expensive and it proved difficult to persuade hospitals to provide the additional funding, particularly as there was no national recommendation behind the change of treatment.

1.20 We are also interested in the arrangement referred to at page 82 onwards, whereby Dr Tedder received samples from haemophilia clinicians for testing. Can this be expanded?

1.20 By October 1984, an antibody test against HTLV-3 (now known as HIV) had been developed by Dr Richard Tedder at University College Hospital in London. UKHCDO came to an arrangement with Dr Tedder so that all Haemophilia centres in the UK could forward patient samples to him for analysis. It was assumed that clinicians would send samples from all patients who had been treated with concentrate. The patients had to be specifically bled for the purpose, so would have been informed as to the purpose of the

test. The results were returned by post, in individual envelopes, the process taking about six to eight weeks. By say December 1984 therefore, UK clinicians knew the HIV status of their regularly treated patients.

1.21 In his evidence to the Archer Inquiry you mentioned not knowing in December 1984 what the implications of the HIV test results were. Are you able to say at what stage you became aware of the medical implications of a positive antibody test?

1.21 As the test measured antibody against HIV, and not the presence of the virus itself, there was initial uncertainty as to the meaning of a positive antibody test, as set out in more detail in my Archer submission. An understanding that a positive antibody test indicated almost always the presence of the HIV virus was not established definitely until testing for HIV antigen had been developed at least a year later.

1.22 We enclose a copy of document LOT.003.4331 (document 6), which appears to be a standard letter with Dr Ludlam's address typed on in different font. Is this the letter referred to at page 81, line 13?

1.22 A further reflection in the incomplete knowledge about HIV and AIDS at the time are the comments, subsequently shown to be untrue, contained in Dr Craske's letter of November 30th 1984.

1.23 The advice referred to on page 88 also appears to have been in this letter. It appears to differ from the resolution of the UK Reference Centre Directors at their meeting on 10 December (paragraph 8.116 of the Preliminary Report). We are interested in this difference.

1.23 There was a diversity of opinion at the UKHCDO meeting of December 1984 as to whether patients should be informed or not, and these uncertainties are echoed in Dr Craske's letter of 30th November 1984 in which he stops short of recommending unequivocally that all patients should be told the results of their tests.

1.24 In terms of the information that was provided to patients about their medical condition at what point, in your recollection, did the balance shift from the paternalistic approach to the modern patient centred informed consent approach? Prior to 1988 were doctors already dealing with HIV positive patients in the way that was suggested in the 1988 GMC Guidance ("HIV Infection & AIDS: the ethical considerations" (1988)? If so can you say how widespread the approach was and from what date it would have started?

1.24 As set out in my Archer submission, the onset of the AIDS epidemic changed for ever the nature of medical practice in this country. Never before had there been a situation in clinical medicine in which the performance of a blood test – **even if the result of that test was negative** – could have profound lifestyle consequences for the patient, particularly in obtaining mortgages or life insurance. This led to the development of pre-test counselling. This concept had never existed previously.

Furthermore, AIDS was very likely to be fatal, the treatment choices complex and most of the original patients were articulate and intelligent homosexual patients who, quite rightly, demanded a full partnership with their doctors in the treatment process. By 1988, there were AIDS patients sitting on ethical committees monitoring AIDS drug trials; this would have been unthinkable only a few years previously and medical practice would never be the same again.

1.25I would like to ask you about the criticism that you received for prescribing UK heat treated concentrates as opposed to domestic untreated concentrates in about 1984. Where did this criticism come from? How did it manifest itself? Do you have any written evidence of it – i.e papers, letters, memos?

1.25 ..

My comments on this matter are addressed in section 1.19

Dr Mark Winter

29th February 2011