Comments from RP 30/4/03

**Minutes of the Microbiological Safety of Blood and Tissues for Transplantation vCJD Subgroup**

**Meeting 2: Tuesday 8 April 2003**
**Room 136B, Skipton House, SE1 6LH**

**Present:**

**Chair**
Professor Don Jeffries (St Bartholomew's Hospital)

**Members**
Dr Trevor Barrowcliffe (NIBSC)
Dr Moira Carter (SNBTS)
Dr Jonathan Clewley (PHLS/HPA) attended for Dr Philip Mortimer
Dr Roger Eglin (NBS)
Mr Peter Garwood (NBS)
Dr Kieran Morris (NIBTS)
Dr Neil Raven (CAMR/HPA)
Mr Graham Rowe (WBS)
Dr John Saunders (DH/MRC Advisory Group)
Dr Marc Turner (SNBTS)

**Officials**
Dr Peter Bennett (EOR/DH)
Mrs Jill Dhell (MDA/MHRA)
Mr Stephen Dobra (EOR/DH)
Dr Pip Edwards (CJD/DH)
Mrs Mary Holt (CJD/DH)
Dr John Stephenson (RD/DH)

**Secretariat**
Ms Sara Johnston (DH)
Dr Linda Lazarus (DH)
Mr Charles Lister (DH)

**Agenda item 1 Welcome and Chairman's introduction**

1. The Chair opened the meeting and welcomed those who had been unable to attend the first meeting. Members were informed that Professor James Ironside from the National CJD Surveillance Unit had been invited to join the subgroup and would attend the next meeting. Two organisational changes affecting subgroup members' affiliations had come into effect from 1 April 2003. The Medical Devices Agency and Medicines Control Agency had merged to form the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Public Health Laboratory Service and Centre for Applied Microbiology and Research had both become part of the new Health Protection Agency (HPA).

2. The following papers were tabled:

   - Selected presentations from the Canadian Consensus Conference on vCJD Screening of Blood Donors (annex to paper 8/04/03 – 8).
   - A Working Standard for vCJD assays (as an annex to paper 8/04/03 – 5)

**Agenda item 2 Apologies for absence**

3. Apologies were received from Dr Rowena Jecock (DH), Dr Vicki King (DH) and Dr Philip Mortimer (HPA).

**Agenda item 3 Minutes of the last meeting**

4. Comments were invited on the accuracy of the minutes. The minutes were accepted as an accurate record of the meeting subject to the following changes:
   - Page 2, paragraph 8, first sentence changed to 'assays for detecting transmissible spongiform encephalopathy agents (TSEs)...'
   - Page 3, paragraph 10, abbreviation corrected to erythrocyte differentiation related factor (EDRF).'
   - Page 7, paragraph 31, second sentence updated to 'When it was first undertaken in October 2001...
   - Page 7, paragraph 32, third sentence changed to 'Assurances need to be offered to minimise...'

**Agenda item 4 Matters arising**

5. Actions from the previous meeting were reviewed and updates provided for those not listed as separate agenda items.

   - Action 1: Declaration of interest forms: The majority of members had now completed and returned their declaration of interest forms to the Secretariat. Outstanding forms would be requested.

   - Actions 9 & 10: Research and development issues: It was reported that advice on collecting a nationally representative cohort of blood samples for long-term studies would be sought from the SEAC Epidemiology Subcommittee on May 12 and the Research Advisory Group on July 1. The issue of securing pre-clinical blood samples from animals experimentally infected with BSE or scrapie was on the agenda of the forthcoming Joint Funders meeting on May 15.

**Agenda item 4.1 Update on DH 'Seminar on the Ethical and Social Issues Surrounding a Diagnostic Test for vCJD'**

6. A final decision on whether the seminar would go ahead had not yet been made, but officials were currently working towards holding the event at the end of June. Many useful lessons had been learnt from the Montreal conference (see agenda item 11).

   **Action 1(1):** Members to be advised of the date of the seminar as soon as it has been confirmed and an update provided on progress at the next meeting.

**Agenda item 4.2 Legal position on disclosure by MHRA (MDA) to DH of IVD registration of a vCJD blood test**

7. The MHRA are still seeking legal advice on whether they can disclose information to DH if they became aware of a CE-marked product being placed on the market. Only UK manufacturers need register their product with the MHRA when placing it on the market. A European-wide database, yet to be established, will track registration information for all IVD devices. As registration and placing a product

on the market can occur simultaneously, this was unlikely to generate lead time. However, where a notified body is involved (i.e. for Annex II List A devices), MHRA may [DN: will?] have advanced notice [why?]. It seemed plausible that the blood services would become aware of a potential kit before the Competent Authority as the manufacturers might approach them to obtain suitable samples for pre-launch evaluation.

**Action 2(2):** MHRA (MDA) to confirm the legal position on disclosure. [action carried forward from first meeting]

**Agenda item 4.3 Role of the Kit Evaluation Group [8/04/03 – 1]**

8. The Kit Evaluation Group (KEG) undertakes laboratory evaluations of test kits against the standards required by the NBS. Kits that evaluate well are added to the list of kits suitable for use within the NBS. The final choice of kit is determined by operational considerations. The evaluation work is split between the HPA (within the new Evaluations and Standards Laboratory) who perform sensitivity work and NBS who perform specificity work. Independently of KEG, additional checks for confirming the performance of kits are conducted with newly released lots/deliveries. No formal links exist between the NBS KEG and the equivalent group that evaluates kits for SNBTS and NIBTS.

**Agenda item 4.4 Risk assessment: rationale for full containment Level 3 facilities**

9. NBS reported that they were consulting with the Health and Safety Executive (HSE) on the need for full containment level 3 facilities for donation screening and confirmatory testing for CJD (and test kit evaluation). Initial indications were that such stringent containment would not be required for this work unless amplification or concentration of the TSE was necessary. HSE wish to encourage the use of rational risk assessment, backed up with appropriate safety measures, in preference to creating sub-categories of containment levels as has previously been the practice.

10. The need to run positive control samples routinely was acknowledged. Work with concentrated material (e.g. to make dilutions for a working standard – see paragraph 31) could best be undertaken in collaboration with HPA/NIBSC who have the appropriate facilities. Positive controls are usually attenuated in some way to reduce the handling risk to workers. Use of recombinant prion protein, for example, might be considered although there are currently doubts about its stability other than at low (non-physiological) pH.

11. The HSE have recently **[DN: when?]** issued a biologicals bulletin on handling TSEs **[Sara: please track down and include among papers for next meeting. Pip should have a copy]** and guidance from the joint ACDP/SEAC Working Group on handling biological specimens is to be issued shortly.

(Biological Agents Bulletin No. 5, Dec. 2002, www.hse.gov.uk/hsehsc/noframes/hdjnls.htm #biol.

**Action 3(2):** NBS to feedback HSE's views.

**Agenda item 5 Blood screening for vCJD: implications of test results [8/4/03 – 2]**

12. Paper [8/4/03-2] models the number of false positives and false negatives that would be expected to result from different values of test specificity, sensitivity and disease prevalence. For a rare disease, a much higher number of false positives

than true positives will result unless the test has very high specificity. [For example, at a prevalence of 1 in 100,000 and sensitivity and specificity of 99%, from 2.5 million donations you would expect 25 true positives but around 25,000 false positives.] False positives are of particular concern both in terms of replacing discarded donations and recruiting new donors, as well as informing and counselling donors who have been deferred. A high proportion of those volunteering as donors (around 30% in Scotland) are already deferred.

13. Assuming a steady-state demand for blood, those deferred will have to be replaced and new donors introduce a higher risk for other infections. MSBT will need to discuss the broader implications associated with the introduction of a screening test for vCJD (e.g. donor acceptability and perceptions, infrastructure for counselling/lookbacks, insurance issues). NBS/EOR work to evaluate the impact of exclusion of previously transfused donors on the blood supply/safety could be a useful starting point.

14. It may be some time before we have a reliable estimate of vCJD prevalence in the UK population. The prospective tonsil screening programme will take some years to complete. However, an approximate prevalence for near-overt disease may be available later in 2003 from current retrospective studies to detect abnormal prion in tonsil and appendix tissue. **[DN: John Stephenson to modify as necessary]**

proposed/

15. It was agreed that it would be unacceptable to introduce a screening test in the absence of a confirmatory test. The latter, ideally, should have a different format (e.g. capture mechanism) from the former allowing greater confidence in a concordant result with the two tests. As this might be too stringent a requirement in the early stages of test development, using an alternative configuration of the screening test (e.g. same format but different antibody/target), might be acceptable as a confirmatory test.

16. Any equivocal results should still result in deferral (and follow-up) as a precaution against an early-stage infection. Using tonsil biopsy as a confirmatory test was unlikely to be acceptable to donors because it is a painful procedure. Quarantining donations or deferring donors allows for lengthier assays to be used in the confirmatory algorithm.

17. It was noted that when HIV screening was introduced, the US blood services employed an ELISA for screening and a Western blot for confirmation whereas the UK used more than one ELISA in their screening/confirmation algorithm. A drop in donations also occurred which was attributed to false perception of donors that they could acquire the infection through donating.

I am still uncertain as to the exact proposal for testing - can you clarify with NBS.

18. The NBS indicated that it could manage the donor losses that would result from a 0.2% repeat reactive rate but would examine in more detail the financial implications with respect to two tests.

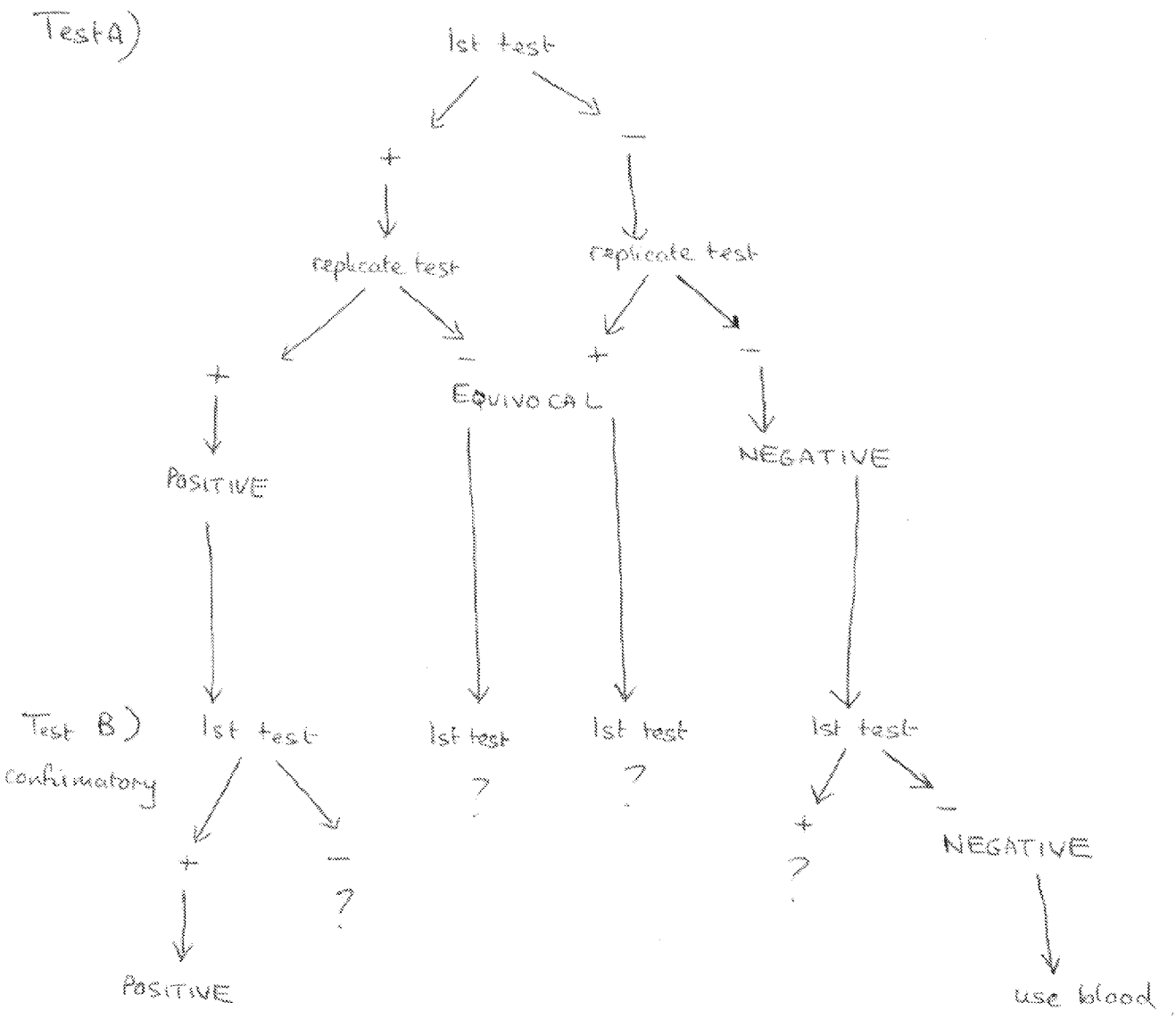
**Action 4(2): NBS** to calculate the implications for the blood supply of different repeat reactive rates based on two tests.

**Agenda item 6 Mechanism for amendment to Annex II List A of the IVD Directive [8/4/03 – 3]**

I have drafted a scheme with gaps for completion.

19. The implications of the IVD Directive for commercial development of vCJD test kits were summarised again. Members were asked to note, in particular, that an

# Testing Schedule



in-house assay developed in a clinical/research setting but subsequently used in a commercial testing service would require CE marking. For example, the NBS carries out testing of patient samples for some hospital trusts. If they were to use an in-house assay for confirmatory purposes, that assay would need to be CE marked.

20. At the last meeting the subgroup agreed that vCJD should be included in Annex II List A of the IVD Directive but did not address the specific requirements for amending List A as described in Article 14. Referring to the relevant extract of the directive (see annex C of paper 17/2/03 – 5 for the complete directive), the subgroup discussed the four criteria in turn, all of which need to be met.

21. Consideration of *"**Any relevant information available from the vigilance procedures and from external quality assessment schemes as referred to in Article 11**"*: This first criterion is not applicable because it relates to requirements placed on manufacturers to report (to the Competent Authority) any deaths or serious injuries resulting from the use of the device. This is a post-marketing requirement.

22. *"**whether total reliance has to be placed on the result obtained with a given device, this result having a direct impact on subsequent medical action**"*: This is interpreted as meaning that no other form of clinical investigation, such as an x-ray or medical history, would be used in conjunction with the screening test result to determine whether a donor would be deferred. Since deferral requires informing the donor that they are potentially carrying a disease, this may lead to medical action (e.g. follow-up investigations). This criterion is met.

23. *"**whether action taken on the basis of an incorrect result obtained using a given device could prove to be hazardous to the patient, to a third party or to the public, in particular as a consequence of false positive or false negative results**"*: This was the easiest criterion to satisfy. False positive results clearly impact on donors who are deferred and may have substantial social, psychological and medical implications for those informed they may be incubating an incurable disease. False negative results could lead to recipients being infected through transfusion of contaminated blood components. Both have the potential to cause widespread public anxiety with detrimental impacts on the blood supply (donors unwilling to donate) and the acceptability of transfusion as a therapeutic option.

24. *"**whether the involvement of a notified body would be conducive to establishing the conformity of the device**"*: The subgroup were not asked to address whether a Notified Body with the relevant expertise would exist, only whether its involvement in the CE-marking process would be beneficial. It was agreed that the virological markers in List A set a precedent – if involvement of a Notified Body in assessment of devices used for other blood screening tests is desirable, by extrapolation the same standard would be required for a CJD device to be used in blood screening.

25. In conclusion, the subgroup agreed that all the criteria had been met and their recommendation to MSBT was that the UK should seek, via the MHRA and with UK-wide ministerial agreement, to have Annex II List A amended to include detection etc of markers for CJD.

**Action 5(2): Secretariat** to seek MSBT's endorsement to recommend addition of CJD to Annex II List A and through MSBT engage the devolved administrations.

**Agenda item 7** **Draft case for amending Annex II List A of the IVD Directive: risks and barriers [8/4/03 – 4]**

26. Some of the risks/barriers to amending Annex II List A were summarised. Without inclusion on List A, the UK blood services would need to create their own conformity requirements for any CE-marked device to provide independent scrutiny. The lack of listing need not matter in the short-term as the user (blood services) ultimately decide which test kits they will use. List A also allows a Common Technical Specification to be drawn up at European level.

27. A possible concern was raised about what safeguards would be in place if one of the UK blood services elected to import a fresh blood component from Europe. MHRA (MCA) would have oversight of licensed therapeutics derived from pooled products and would need to be aware of any differences in screening strategies employed in other countries versus the UK. **[DN: Charles – can you clarify what the issue was here?]**

28. Members were reminded that Annex II A listing was likely to involve protracted negotiations at the European level in which the UK would be expected to take the lead. Furthermore, the UK would be seeking to amend the directive before it has even been implemented. Nonetheless, by initiating the process, the UK would be demonstrating its commitment to future blood safety.

**Action 6(2): DH (RD) and MHRA** to clarify outside the meeting the boundaries for DH involvement in the evaluation work to ensure DH does not engage in activities that constitute a technical barrier to trade (i.e. in breach of the IVD Directive).

meeting John Stephenson Rp, Jill Bell 9 May

**Agenda item 8** **Contract for the supply of test kits and associated equipment for the detection of vCJD: Draft Technical Specification [8/4/03 – 5]**

29. NBS were commended for providing a useful draft technical specification based on others prepared for tender (e.g. virology and genome tests) and the requirements were mostly standard, some being covered by the IVD Directive. Others relate to operational considerations such as preferring a microtitre plate format because this is already widely used and can be automated. The time taken to complete the assay also needs to be compatible with other screening to enable timely release of products.

30. The arguments for and against making the target reactive rate less stringent than for other blood screening markers (i.e. 0.2% initial reactive and 0.1% repeat reactive) were considered. It was decided that the specification could reflect the ideal, whilst recognising that first-generation tests were likely to be less accurate than desirable and these may be in use for some time.

31. Working standard (document tabled as annex to paper 8/4/04 – 5): The NBS will require a Working Standard of positive prion material to go into every CJD test run to comply with Good Manufacturing Practice (GMP). By analogy with the virology assays, a considerable quantity of the working standard is likely to be needed (approx. 6000 vials/year). While there is no shortage of viral material (an

infected donation can be used), a plentiful supply of infected material for a CJD standard will need to be identified.

32. Infected brain has been established as the international reference standard (unit to be defined) but this would not be a suitable substrate – something more akin to white cells would be better. Spleen is currently the most promising alternative. If recombinant prion proves to be unsuitable (see paragraph 10), then it may be necessary to use spleens from experimentally infected animals. Sheep may be the animal of choice as transmission of endogenous infection by transfusion has been demonstrated. Using human brain material to infect sheep could present ethical problems, but using BSE-infected brain has the drawback of requiring any screening test to be cross-reactive for CJD and BSE. The manufacturers of kits will have to evaluate their products against available reference materials and standards (for abnormal prion protein and surrogates) will certainly be needed during the validation phase.

**Action 7(2): NBS/NIBSC** to discuss taking forward work on a standard, possibly involving the Veterinary Laboratories Agency.

**Agenda item 9** **Matching specimens/sources with likely/promising assay platforms [8/4/03 – 6]**

33. The need for a standardised Test Assessment Panel and how to collect and store it was discussed. The ideal would be to have sufficient replicates in the panel to perform comparative testing on new assays as they are developed. If the sample preparation requirements differ between assays, however, a new panel would need to be collected and the old assay and new assay compared in parallel rather than sequentially using appropriate samples for both assays from the same donor. The alternative would be to collect a panel comprising many different blood components/preparations to allow for a broad range of test scenarios.

34. NBS provided a summary of potential sources of specimens and their suitability. The key features of the sample(s) were that they should be: available from all donors; collectable without disruption to the donor session; amenable to standard handling/processing (including process control) and scale up; capable of irreversible anonymisation (for the panel only). Samples such as saliva and urine were considered impractical to collect at donor sessions.

35. There was no consensus regarding the timing of collection of the panel. It was argued that it would be better to wait until a test becomes available to ensure that samples are processed according to the manufacturer's specification. On the other hand, this would increase the lead time to implementation (time needed to collect and process a nationally representative panel in addition to a panel from non-exposed donors) at a time when there might be considerable pressure to introduce blood screening rapidly. Any decision to introduce a test will need to consider the public interest in its broadest sense, including the far-reaching implications for blood donors and recipients.

36. The test kit manufacturer will have to state the type and volume of sample required. Serum and plasma are probably not significantly different as a substrate for a CJD assay. The NBS considered a PPT tube, that separates the plasma from the cellular material and which can be frozen following a centrifugation step thus retaining the white cells (considered a likely reservoir of infectivity), to be a front-runner. However, citrated samples may be preferable to the standard EDTA

anti-coagulant as calcium chelation may change the infectivity or conformation of prion protein. Concerns were also expressed about the suitability of –20°C for long-term storage as freezing may be incomplete at this temperature and –40°C was suggested as an alternative.

**Action 8(2): SNBTS** to check what temperature they have used for the Scottish archive panel.

37. It is imperative that blood samples from CJD patients stored at NCJDSU should be processed and stored in the identical fashion to panel samples as these will be positive controls. SNBTS had agreed a handling protocol for small-scale (20-30ml) blood samples with NCJDSU (in connection with the Delfia assay) and this could be a useful starting point.

**Action 9(2): SNBTS/NCJDSU** to forward agreed protocol for handling blood samples to the Secretariat for inclusion in papers for the next meeting.

38. It was noted that CJD patients and their carers may be reluctant to consent to use of their samples for commercial purposes. In addition, specific consent from blood donors will be needed if their donation is to be put to commercial use (ethical sample collection in accordance with the European Convention on Human Rights and Biomedicine). Less stringent consent requirements are imposed for quality assurance uses of samples such as in comparing the effectiveness/performance of tests used by laboratories for clinical tests.

**Action 10(2): Secretariat** to seek view from NCJDSU about whether clinical specimens are likely to be forthcoming for non-commercial test evaluation.

39. Taken together, there appear to be substantial barriers to obtaining clinical samples to evaluate a CJD blood screening kit (unless assay cross-reacts with BSE and serial bleeds from animals can be used to create commercial panels) and commercial developers may seek the collaboration of blood services to access such samples.

**Agenda item 10 Scenarios for evaluation of a vCJD blood 'screening' test [8/4/03 – 7]**

40. Annex II A listing allows for a Common Technical Specification (CTS) to be drawn up at European level. This takes some of the onus for evaluating kits off the individual users by clearly defining the number and types of sample that the manufacturer needs to include in performance evaluation. It was suggested that the UK (blood services with NIBSC) could take the lead in drawing up a draft CTS for consideration by EU states once the first test becomes available. Members cautioned against setting too high a standard for the CTS; as for the virological markers, the NBS could still require a higher specification than the CTS.

41. The suitability of US blood donors for creating a panel of 'unexposed' samples was questioned. NBS reported that tentative arrangements had been made to source samples from non-remunerated Californian donors. Concerns about higher risks in paid donors had therefore been addressed and localised issues such as chronic wasting disease could be circumvented.

**Agenda item 11** **Feedback from Canadian consensus conference on vCJD screening of blood donors** **[8/4/03 – 8]**

42. The consensus conference on vCJD screening of blood donors had taken place in Quebec, Canada on 27 and 28 March and selected presentations from the conference were tabled. The presentation by Stephen Vamvakas was commended as providing step-by-step calculations for test scenarios with different parameters of prevalence, sensitivity and specificity. An interesting conclusion of the consensus panel regarding whether to implement the first test to become available was to wait and monitor the UK experience.

**Agenda item 12** **Next steps**

43. A draft workplan based on the information gathered so far would be required for the third and final meeting. This would then be presented to MSBT with a recommendation for the way forward.

> **Action 11(2): Secretariat** to prepare a draft workplan for presentation at the next meeting, based on the information gathered to date.

**Agenda item 13** **Any other business**

44. None was raised.

**Agenda item 14** **Date of next meeting**

45. The next meeting will be held on 16 May 2003, 10.30am-1.30pm in room 125A Skipton House.

**Action Points**

**Action 1(2):** Members to be advised of the date of the seminar as soon as it has been confirmed and an update provided on progress at the next meeting.

**Action 2(2):** MHRA (MDA) to confirm the legal position on disclosure. [action carried forward from first meeting]

**Action 3(2):** NBS to feedback HSE's views.

**Action 4(2):** NBS to calculate the implications for the blood supply of different repeat reactive rates based on two tests.

**Action 5(2): Secretariat** to seek MSBT's endorsement to recommend addition of CJD to Annex II List A and through MSBT engage the devolved administrations.

**Action 6(2): DH (RD) and MHRA** to clarify outside the meeting the boundaries for DH involvement in the evaluation work to ensure DH does not engage in activities that constitute a technical barrier to trade (i.e. in breach of the IVD Directive).

**Action 7(2):** NBS/NIBSC to discuss taking forward work on a standard, possibly involving the Veterinary Laboratories Agency.

**Action 8(2): SNBTS** to check what temperature they have used for the Scottish archive panel.

**Action 9(2): SNBTS/NCJDSU** to forward agreed protocol for handling blood samples to the Secretariat for inclusion in papers for the next meeting.

**Action 10(2): Secretariat** to seek view from NCJDSU about whether clinical specimens are likely to be forthcoming for non-commercial test evaluation. Rowena has spoken.

**Action 11(2): Action 11(2): Secretariat** to prepare a draft workplan for presentation at the next meeting, based on the information gathered to date.