



## **POSITION STATEMENT EVALUATION CRITERIA FOR ANTE MORTEM DIAGNOSTIC TESTS FOR SUBCLINICAL vCJD**

### **Issue**

1. The Department of Health and the UK blood services requested SEAC's advice on the scientific criteria by which ante mortem diagnostic tests for subclinical vCJD could be evaluated and validated<sup>1</sup>.

### **Background**

2. The development of an accurate and sensitive ante mortem blood test to identify asymptomatic individuals infected with vCJD could substantially reduce the potential for transmission of vCJD via blood transfusion and other medical interventions. It could also be valuable in confirming the diagnosis of clinical cases and monitoring the effect of potential therapies. In addition, such a test could provide an important tool to ascertain better the prevalence of vCJD infections.
3. The safety, quality and performance requirements for diagnostic tests for many infectious diseases are laid down in the In Vitro Diagnostic Medical Devices (IVD) Directive 98/79/EC. Tests included in Annex II List A of the Directive must comply with performance requirements set out in a Common Technical Specification (CTS) to receive a CE mark<sup>2</sup>. Currently, diagnostic tests for subclinical vCJD are not included in Annex IIA of the Directive and so a CTS with clear performance requirements for such tests has not yet been defined.

### **Performance**

4. The Committee on Microbiological Safety of Blood Tissue and Organs (MSBTO) considers that, ideally, tests for subclinical vCJD

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<sup>1</sup> The papers considered by SEAC are given at:  
<http://www.seac.gov.uk/agenda/agen210906.htm>

<sup>2</sup> CE (Conformité Européenne) mark is a declaration by the manufacturer that a product meets all the necessary requirements of the relevant EU legislation.

should be highly sensitive and highly specific. Unless tests have extremely high specificity, they will generate a large number of false positive results with unacceptable cost and ethical consequences. Therefore, a reliable secondary test, to confirm reactive results in any initial screening test, would be required. Calculations to ascertain acceptable values for sensitivity and specificity of both the screening and confirmatory tests should be taken into account<sup>3</sup>.

### **Regulatory position**

5. Until diagnostic tests for subclinical vCJD are included in Annex IIA of the IVD Directive 98/79/EC, the CE mark must not be relied upon to indicate that a test is fit for purpose. Therefore, it is strongly recommended that ante mortem tests for subclinical vCJD are independently evaluated and validated using a clearly defined protocol prior to implementation.

### **Prototype Tests**

6. A number of prototype ante mortem blood tests for subclinical vCJD have been developed. Due to commercial sensitivities, availability of data for these tests is limited and the methodologies on which they are based are often incompletely specified. The available information suggests that many, if not all, of these tests are based on the detection of abnormal prion protein (PrP<sup>Sc</sup>).
7. The relationship between the presence of PrP<sup>Sc</sup> and vCJD infectivity is not well understood. It is important to emphasise that the presence of PrP<sup>Sc</sup> is not always correlated with vCJD infectivity. However, as a better biomarker has not yet been identified, PrP<sup>Sc</sup> is currently the most appropriate marker against which any assay should be targeted. Furthermore, it is possible that tests based on the detection of PrP<sup>Sc</sup> will not identify all infected individuals and might falsely identify individuals as infective. As previously stated, calculations to ascertain what proportion of false positives and false negatives might be acceptable, are critical to defining test criteria.

### **Evaluation and validation**

8. Preliminary evaluation of the specificity and sensitivity of tests could be achieved by using human blood spiked with brain or

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<sup>3</sup> Eglin R and Bennett P (2003). Blood Screening for vCJD: Implications of test results (see SEAC papers at <http://www.seac.gov.uk/agenda/agen210906.htm>)

spleen homogenate from vCJD cases. However, spiked samples may not be representative of the form of infectivity naturally present in blood. Blood of animals infected with transmissible spongiform encephalopathy strains which, like vCJD are derived from the BSE strain may also provide a source of material to conduct preliminary evaluations. However, it is critical to note that the response of tests when applied to blood from animal models or spiked human blood, may not accurately reflect the response from tests when applied to the detection of vCJD infectivity in human blood. Therefore, the final evaluation of screening and confirmatory tests must include testing against blood from human vCJD cases.

9. Blood from clinical cases of vCJD may not provide an indication of the sensitivity of a test to correctly identify subclinically infected individuals. This is due to uncertainty in the levels of vCJD infectivity (and PrP<sup>Sc</sup>) in blood during the incubation period of the disease. Individuals defined as 'at risk of vCJD for public health purposes' could provide a source of blood from potentially infected individuals at the preclinical stage of vCJD. Even so, such an evaluation would not inform on the ability of a test to detect infection from the point in the incubation period when blood becomes infectious. Such evaluation would require testing of blood collected from animal models at a number of time points through the incubation period, and extrapolation to humans.
10. As relevant human material is extremely difficult to obtain, it is essential that the quantity of materials required to validate tests is accurately determined prior to investigations starting. It is also important that an effective system to collect, manage and distribute these valuable materials is instituted and to ensure that the performance criteria that prototype tests must meet are clearly defined before such valuable materials are provided to evaluate and validate tests.

## **Ethical Considerations**

11. There are complex ethical issues associated with ante mortem testing for subclinical vCJD that have yet to be resolved<sup>4</sup>. These issues also relate to how many false positives and false negatives

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<sup>4</sup> The Chief Medical Officer (CMO) asked the Health Protection Agency (HPA) to host a seminar on the ethical and social aspects of testing for vCJD. This seminar produced a report with recommendations. At the request of the CMO, the HPA is currently undertaking a consultation exercise to determine the views of experts, health professionals and members of the public on the possible impact and implications of a test for vCJD.  
[http://www.hpa.org.uk/infections/topics\\_az/cjd/consultation.htm](http://www.hpa.org.uk/infections/topics_az/cjd/consultation.htm)

are acceptable and, hence, the test validation criteria. However, detailed consideration of these issues is not in SEAC's remit.

## **Conclusions**

12. Until diagnostic tests for subclinical vCJD are included in Annex IIA of the IVD Directive 98/79/EC, the CE mark cannot be relied upon to indicate that a test has been properly and fully evaluated and validated. Therefore, tests should be independently and rigorously validated using a clearly defined protocol that includes testing of blood from vCJD cases.

*SEAC*  
*November 2006*