

Batch Testing Protocol for Batch Release of TSE rapid test kits

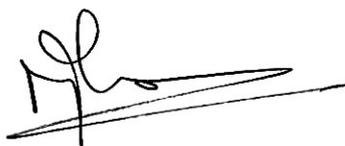
**To be used by all participating EU TSE National
Reference Laboratories**

Produced by the TSE EURL at VLA Weybridge UK

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This document replaces **EURLPDB01 v1.0** – which you should destroy or archive.



Signed

MJ Flowers.

Signed on **13/10/2010**

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1.0 PURPOSE:

To provide reassurance that TSE rapid tests kits are fit for the purpose of testing bovine samples by:

- a) Assessment of batch release data provided by the manufacturer, and if required
- b) Production of additional QC data within an NRL for an individual batch of a BSE rapid test kit.

Initially, all kit batches **have been** tested in the responsible NRL, but a risk-based approach is now adopted and, if evidence shows that [] paper based kit approval is sufficient, this **is** considered by the European Union Reference Laboratory (EURL) **to be acceptable, as agreed by participating Member State NRLs at the CRL Conference in June 2010**. In these circumstances, the right to test **any or all** kit batches will be retained **by the responsible NRL**. []. **Manufacturers should continue to supply representative kits from each new batch at least until a further review of effectiveness of the revised protocol.**

This batch release assessment will be available to all NRLs within the EU and can replace any formal batch release testing conducted by individual member states (MS).

This protocol deals with TSE rapid test kits, approving batches for use with bovine materials only. It had been agreed at the EU CRL Conferences (2009 & 2010) that a parallel system is unnecessary for scrapie testing of kits. This is still under consideration, as EFSA have expressed a wish for such testing to take place [EFSA Journal 2009; 7(12):1436 - summary, last point], but is not planned at present.

2.0 BACKGROUND-THE CURRENT POSITION

Each TSE rapid test kit that enters the market must be authorised for statutory use within the European Union and listed in the TSE Regulation 999/2001. The approval is linked to the particular test protocol used for the evaluation study. Any modifications to the protocol are approved by the EURL on the basis of evidence submitted by the manufacturer.

Additionally, varying amounts of batch release testing and /or approval had previously been carried out by different MSs. This varied from full release of all batches to acceptance of the manufacturer's release procedure.

3.0 AIM-UNIFICATION OF BATCH RELEASE THROUGHOUT THE EU

The aim of this protocol is to provide a single batch release testing procedure which is acceptable to all NRLs. This revision describes the current system in place.

4.0 APPROACH

Appropriate NRLs (as agreed) are responsible for the batch release of a particular BSE rapid test kit. The responsible person at the NRL (plus deputy) must have received training and be certified by the kit manufacturer as competent to perform the test specified. All NRLs involved must hold ISO17025 accreditation for the test for which they are responsible, to confirm their competency to perform the testing. NRLs may not control and approve tests manufactured in their own country.

5.0 MANUFACTURER'S BATCH RELEASE DATA

When a kit batch is ready and the manufacturer is satisfied that the batch is suitable for release, the manufacturer shall provide to the appropriate NRL:

1. An analytical batch release report. This shall contain analytical data, sensitivity, specificity and intra and inter-plate control.
The batch release protocol for each manufacturer is defined in their own Quality System standard operating procedures (SOPs) . These have been approved by the EURL as part of quality system approval- manufacturers shall confirm that these are current on an annual basis.
2. Additionally, the manufacturers shall provide evidence of consistent plate coating by testing at least 3 plates, taken from the beginning, middle and end of each batch using appropriate kit controls throughout the plate. In the case of strips/ gels/ other layouts, appropriate variation in sampling locations should be taken. In the case of uncoated plates, evidence that the plates are homogeneous.

Reports should be uploaded to the manufacturer's folder on the TSE-LAB-NET "Downloads" area. The NRL should be notified that this has been done, so they may access the reports during batch testing. If this cannot be done, the NRL should receive the report by email and pass it on to the EURL.

If the responsible NRL requires specific equipment to undertake the QC testing this shall be provided, at no extra cost, by the manufacturer.

6.0 NRL QC TESTING

Under the terms of this current revision, an NRL may choose to restrict their approval process to a review of the batch release QC data provided by the manufacturer as above. Additionally, a small amount of analytical testing may be undertaken by the NRL as before, using 2 sets of BSE positive materials

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and BSE negative materials, one set of which shall be provided by the EURL and one by the manufacturer- their current batch release panel. Each set shall consist of not more than 3 positives and at least 1 negative homogenate.

In exceptional circumstances, the kit manufacturer may elect not to use the sample panel prepared by the EURL. If the manufacturer makes this choice, they are responsible for:

- i) Providing the EURL with a full explanation of why the EURL panel is unsuitable for the use as a batch testing panel for a particular test, including precise details of how a suitable sample panel should be prepared and stored.
- ii) Providing an alternative sample set which is acceptable to the EURL (this is in addition to the current batch release panel). The manufacturer must provide the EURL with proper documentation attesting that the samples comply with the conditions in (i) above and detailing their origin and history
- iii) The manufacturer must prepare a suitable panel according to the above criteria, under EURL supervision and provide it to the EURL in sufficient quantity to be used as a stock for EC batch testing over a period of time. The EURL will use an alternative test method on aliquots from all panel samples to quantify and accept them as appropriate.
- iv) The sample set will be held by the EURL, provided to the responsible NRL for use and described as the "EURL approved panel"

6.1 BSE rapid test kits

These shall be provided by the manufacturers free of charge.

A representative selection of plates from the batch, shall be provided to the nominated NRL by the manufacturer.

As: a single kit (as long as it contains at least 5 plates/gels/combs, etc.)

or as: 5 plates from batch plus reagents,

or as: sufficient strips and reagents to provide the equivalent of 5 plates for testing purposes.

6.2 EURL Reference control sample set

These have been produced by the EURL, pre-tested for level of activity and initially provided to all manufacturers for pre-assessment testing to ensure that the range of reactions is detectable and relevant to the test kits.

6.2.1 EURL Reference negative control sample

One large pool of certified negative bovine brain material has been produced and sufficient supplied to all the relevant NRLs to undertake the required batch release analyses. This was also used as the negative material to dilute the BSE positive pool.

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6.2.2 EURL Reference positive control samples

This was in the form of pooled certified BSE positive bovine brain material, tested and supplied to the NRLs by the EURL (free of charge). This material is supplied as three discreet pools, providing samples of three levels of positivity in terms of signal produced ; high, medium and low (these have already have been diluted with the negative control pool and are ready to use).

6.2.3 Initial levels agreement

The reference samples are to be used by the NRL in consultation with the manufacturer to determine the acceptable range for this material in the kit they are responsible for, by testing plates from representative batches using the standard control material in 4 replicate wells on each kit batch. The assays should be repeated on 3 successive days to allow for variation of the assays. The acceptable range for each of the 4 reference samples should be calculated from the mean and within an upper and lower limit (e.g. +/- 3SD) of these values and must be negotiated between the NRL and manufacturer, before being agreed with the EURL, prior to undertaking the actual batch release analyses.

7.0 QC BATCH TESTING PROTOCOL

7.1 Review Process only

If an NRL chooses to approve by data review alone, a report should be produced which states this, as described in 7.6.

7.2 Sample Handling

All test samples will be treated, as far as possible within the instructions for each particular kit, as if they were real samples and assayed accordingly. This means that the samples (although homogenised) shall go through routine homogenisation/grinding/maceration etc. as described within kit instructions, including temperature and storage conditions as required. They shall be treated as whole tissue, with no compensation for homogenate diluent in the original sample.

Each of the 4 reference samples shall be tested in duplicate on each of 3 separate test plates. A mean result will be determined for each reference sample, and checked against the range. If all mean values for the sample set are within range the kit is considered to have passed.

If the results are out of range the testing shall be repeated in duplicate on both the remaining 2 plates, strips, etc.

Kit reference samples are also to be used to confirm plate control reference results. Interpretation of this is up to the NRL but the EURL will review such results. The EURL may make the final decision over interpretation of results.

7.3 Reference samples from manufacturer

In order to ensure continuity during the initial stages of EU wide batch testing the NRL shall test the manufacturers batch release panel for at least the first 4 kit batches tested.

TSE European Union Reference Laboratory

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A manufacturer shall provide, for each of these batches, the reference samples used for sensitivity checks by the company, together with the acceptable range. These will be run on the same plates as the EURL reference samples and so should provide good cross-checks on test performance. There should be three positive samples of different reactivity and one negative sample. They shall be tested in duplicate as for the EURL reference samples. If any of these fail to meet acceptance ranges provided by the manufacturer, the exercise shall be repeated in duplicate on the remaining 2 plates, strips, etc.

7.4 Reference Batches

The manufacturer shall also provide 3 plates from their current reference batch to the NRL. These shall be tested in parallel with the new batch, using both manufacturer's and EURL panel samples. The value ranges previously achieved for the reference batch shall be quoted by the manufacturer and used to ensure the kit under evaluation performs as well as, or better than, the reference kit.

If the kit reference batch is replaced, the manufacturer is obliged to provide details to both the EURL and relevant NRL undertaking testing (with new materials), and the new batch tested in conjunction with the original batch to ensure that continued validity of measurement is maintained during testing.

7.5 Analytical Timescale

Wherever possible, the entire testing and reporting protocol shall be completed within 10 working days of receipt of kits. This allows the NRL at least 5 days to undertake the testing and report to the EURL, and the EURL 5 days to complete analysis and report to the manufacturer, all NRLs and the Commission. If a problem occurs, the appropriate NRL shall notify the EURL and the manufacturer promptly.

7.6 Production of analytical data report

The NRL shall prepare a report containing:

- an analysis of the batch release data produced by the NRL **if performed** and that provided by the manufacturer. **Any NRL** original data should be appended as an annex.
- Comment upon whether the manufacturers batch release criteria have been achieved
- an analysis of the analytical results produced by the NRL **if performed**.
- Recommendations for kit release onto the European market

This shall be provided to the EURL, in English, **as a short report completed on the forms provided** (Ref EURL001v1.0.xls). These should be uploaded to the TSE-LAB-NET website, in the appropriate manufacturer's folder. Email notification of uploading should be sent to the EURL. Alternatively, the files can be emailed to the EURL for uploading if an NRL staff member does not have access to the upload facility. Uploading from the lab is to be preferred.

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The EURL will review the report and confirm approval. It will then co-ordinate the release of the **approval statement** via the TSE-LAB-NET website, and send alert e-mails to all the NRLs and to the appropriate manufacturer.

7.6.1 Reports that recommend non-release

These shall only be sent by email to the manufacturer from the EURL. It is then the manufacturer's responsibility to halt release of the batch and provide an alternative or re-worked batch for assessment. No other NRLs shall be notified, as no units of that batch should ever reach testing laboratories. The testing NRL shall treat all such information as confidential. In such a situation, it is imperative that the NRL performs actual kit testing prior to reporting batch failure and not restrict their approval to just review of manufacturer's data.

7.7 Data Retention

The EURL will retain all the manufacturer's analytical data for the appropriate batch release on the TSE-LAB-NET website for a minimum of two years *after the batch expiry date* and then archive to EURL secure electronic storage for a minimum of five years.

This is also to be kept as a hard copy at the appropriate NRL and on EURL registered files.

8.0 OPTION FOR INSPECTION OF MANUFACTURER'S FACILITIES

The responsible NRL shall retain an option, (but not a requirement), to visit the manufacturing facility to perform an inspection and provide a report to the EURL. This could be an initial visit, periodic visit, or visits if a problem occurs. Alternatively, the EURL shall perform the inspection.

9.0 CONTINGENCIES

In the event of a test failure, an inability to test (illness, facilities, workload crisis, etc.) or other such problem associated with batch testing within the 10 working day deadline, the appropriate NRL shall contact the EURL via the general email address (tseeucl@vla.defra.gsi.gov.uk) and the EURL will arrange alternative testing provision.

APPENDIX 1 : ACTIONS FOR MANUFACTURERS

1. On production of a new batch of TSE kits intended for bovine use, an assessment of the batch release data for bovine performance must be provided to the NRL.
 2. If the current test protocol for production and release of the kits is changed, any changes should be notified to the EURL and agreement obtained prior to authorisation for release.
 3. Constituents (plates, reagents, buffers, etc.) sufficient for retesting at least 3 plates of each kit batch must be archived for reference purposes.
 4. Representative samples of the production batch with appropriate controls and batch QC sensitivity reference samples, are to be supplied to the responsible NRL free of charge.
 5. Any relevant equipment which may be required by the said NRL is to be provided **at no further** charge by the manufacturer.
 6. Each delegated analyst for the kit testing at the nominated NRL must be certified by the kit manufacturer to undertake the QC testing as required.
 7. An analytical batch release report must be supplied to the nominated NRL, to include sensitivity, specificity and intra and inter-plate controls.
 - 8 The QC panel used by the manufacturer for batch release must be supplied to the appropriate NRL for parallel testing for at least the first 4 batches to be released by this procedure.
Following this, options 1 to 4 will be considered by the EURL **(order changed)**:
 1. **Paper review only, if satisfied with manufacturer's data.**
 2. Occasional re-test with EURL panel, plus perhaps manuf. panel.
 3. **Continue testing with EURL panel only.**
 4. Keep testing with both panels (especially if issues have arisen).
- If the NRL decide to **approve without** bench testing, the manufacturer will be notified immediately, but the manufacturer shall continue to supply all batch and QC materials as appropriate, to facilitate testing of the batch should it be required following data review by the NRL.
9. At least three plates from the current reference batch must be supplied to the nominated NRL for testing to ensure validity of measurement is achieved, for each batch release set.

APPENDIX 2 : ACTIONS FOR THE NOMINATED NRLS

1. Ensure that all required equipment is in place prior to commencement of QC testing. If not, liaise with kit manufacturer to supply, (notifying the EURL).
2. Ensure that both the delegated analyst and the deputy entrusted to undertake the analysis are trained and certified as competent to undertake the task prior to commencement, within the ISO17025 accreditation system.
3. Check that all required kit constituents and reference control materials are in place for analysis.
4. Check that there is sufficient of each of the EURL certified control materials prior to each round of batch testing, **if it is to be performed**, and contact EURL for further supply if necessary.
5. Ensure that all relevant kit controls are utilised as specified to ensure kit validity is maintained, and check that the current IFU is employed for all batch testing **if performed**.
6. On completion of the QC testing programme, prepare the required short analytical report, in English, and supply to the EURL via upload to the TSE-LAB-NET manufacturer's folder using the spreadsheet provided. Additionally, supply the EURL with an electronic copy of the full manufacturer's release report including raw data if this has not been already uploaded by the manufacturer; archive a copy at the NRL. Comment on whether the batch release criteria have been met.
7. Make a recommendation to the EURL as to whether the kit should be released onto the European market, on the analytical data report. Notify the EURL by email that this report is available.
8. As the delegated representative of the EURL, the nominated NRL may retain an option, but not a requirement, to make an inspection visit to the manufacturer's facility and prepare a report for the EURL. **Alternatively, the EURL may take on this visit.**

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APPENDIX 3 : REPORTING SPREADSHEET PAGES

TSE EURL Report TSE Bovine Kit Batch Testing Results Form 19/08/2010

Batch Test Result Recording Form

Name of Testing NRL :

TSE Kit Name : Kit Manufacturer :

Test Kit Batch Number or ID : Reference Kit Batch Number :

Date Received at NRL :

Interpretation Options - Positive, Negative, Inconclusive or No Result

Kit Batch Results: * These are new plates sent as representation of a newly produced batch for acceptance of the entire batch

Reference Sample :	Test Plate/Strip 1 values 1 & 2	Interpretation	Test Plate/Strip 2 values 1 & 2	Interpretation	Test Plate/Strip 3 values 1 & 2	Interpretation
EURL Negative 1						
EURL Positive 1						
EURL Positive 2						
EURL Positive 3						
Manuf. Negative 1						
Manuf. Positive 1						
Manuf. Positive 2						
Manuf. Positive 3						

Reference batch results: * These are reference plates provided by the manufacturer for comparison testing with new batches

Reference Sample:	Ref. Plate/Strip 1 values 1 & 2	Interpretation	Ref. Plate/Strip 2 values 1 & 2	Interpretation
EURL Negative 1				
EURL Positive 1				
EURL Positive 2				
EURL Positive 3				
Manuf. Negative 1				
Manuf. Positive 1				
Manuf. Positive 2				
Manuf. Positive 3				

Date of Testing :

Comments :

Accept Batch (Y/N) :

Reported by (name) : Date of Report:

EURL001v1.0.xls Page 1 of 1 1) Test Results

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TSE EURL Report TSE Bovine Kit Batch Repeat Testing Results Form 19/08/201

Repeat Test Values (If Repeats Performed)			
Name of Testing NRL :			
TSE Kit Name :			Kit Manufacturer :
Test Kit Batch Number or ID :			Reference Kit Batch No :

Kit Batch Results: * These are new plates sent as representation of a newly produced batch for acceptance of the entire batch				
Reference Samples :	Test Plate/Strip 4 values 1 & 2	Interpretation	Test Plate/Strip 5 values 1 & 2	Interpretation
EURL Negative 1				
EURL Positive 1				
EURL Positive 2				
EURL Positive 3				
Manuf. Negative 1				
Manuf. Positive 1				
Manuf. Positive 2				
Manuf. Positive 3				

Reference batch results: * These are reference plates provided by the manufacturer for comparison testing with new batches		
Reference Samples :	Ref. Plate/Strip 3 values 1 & 2	Interpretation
EURL Negative 1		
EURL Positive 1		
EURL Positive 2		
EURL Positive 3		
Manuf. Negative 1		
Manuf. Positive 1		
Manuf. Positive 2		
Manuf. Positive 3		

Date of Testing :

Comments :

Reported by (name) :	Date of Report:	
	Accept Batch (Y/N)	

Batch Testing Protocol for Batch Release of TSE rapid test kits

TSE EURL Report	Manufacturer's Batch Release Report Review Form	19/08/2010
Batch Release Documentation Check Sheet		
TSE Kit Name :		Kit Manufacturer :
Test Kit Batch Number or ID :		Reference Kit Batch No :
Manufacturer's Batch Release Data		
Batch Report Received (Y/N) :		
Batch Report Accepted (Y/N) :		
Manufacturer's Plate-Coating Data (if Applicable)		
Coating Report Received (Y/N) :		
Coating Report Accepted (Y/N) :		
Further Manufacturer's Correspondence received?		
Documents Received (Y/N) :		
Details (brief description) :		
Batch Report Accepted (Y/N) :		
Comments :		
Name of Testing NRL :		Reported by (name) :
		Date of Report :
Proposal to Accept Batch (Y/N) :		