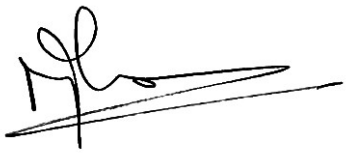
Batch Testing Protocol for Batch Release of TSE rapid test kits

To be used by all participating EU TSE National Reference Laboratories

Produced by the EU TSE CRL at VLA Weybridge UK

Reference : CRLPDB01 v1.0

Valid as from: 1st May 2006.



Signed

MJ Flowers.
6th April 2006

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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 shall be tested in the responsible NRL, but a risk-based approach will be adopted and, if evidence shows that a system of paper based kit approval may be adopted, this will be considered by the Community Reference Laboratory (CRL). In these circumstances, the right to test kit batches will be retained.

This batch release assessment will be available to all NRLs within the EU and will 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.

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 CRL on the basis of evidence submitted by the manufacturer.

Additionally, varying amounts of batch release testing and /or approval have previously been carried out by different MSs. This varies from full release of all batches, to accepting 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.

4.0 APPROACH

Appropriate NRLs (as agreed) will be 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. 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 CRL as part of quality system approval- manufacturers shall confirm that these are current.
2. Additionally, the manufacturers shall provide evidence of consistent plate coating by testing 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.

If the responsible NRL requires specific equipment to undertake the QC testing this shall be provided free, by the manufacturer.

6.0 NRL QC TESTING

A small amount of analytical testing shall be undertaken by the NRL using 2 sets of BSE positive materials and BSE negative materials, one set of which shall be provided by the CRL and one by the manufacturer. Each set shall consist of not more than 3 positives and at least 1 negative homogenate.

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 CRL Reference control sample set

These will be produced by the CRL, 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 CRL Reference negative control sample

One large pool of certified negative bovine brain material will be produced and sufficient supplied to all the relevant NRLs to undertake all the required batch release analyses for a full year in the first instance. This will also be used as the negative material to dilute the BSE positive pool.

6.2.2 CRL Reference positive control samples

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

6.2.3 Initial levels agreement

The reference samples will 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 CRL, prior to undertaking the actual batch release analyses

7.0 QC BATCH TESTING PROTOCOL

7.1 Sample Handling

All test samples will be treated as if 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 values are within range the kit is deemed 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.

7.2 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 the first 4 kit batches tested.

A manufacturer shall provide, for each of these 4 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 CRL 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 CRL 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.

7.3 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 CRL 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 CRL 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.

7.4 Analytical Timescale

Wherever possible, the entire testing and reporting protocol shall be completed within three weeks of receipt of kits. This allows the NRL one week to undertake the testing and report to the CRL, and the CRL one week to complete analysis and report to the manufacturer, all NRLs and the Commission. Another week has been included as a contingency if a problem occurs (If this happens, the appropriate NRL shall notify the CRL promptly).

7.5 Production of analytical data report

The NRL shall prepare a report containing:

- an analysis of the batch release data produced by the NRL and that provided by the manufacturer. The 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
- Recommendations for kit release onto the European market

This shall be provided to the CRL, in English, **as a short report completed on the forms provided** (Ref CRL001v1.2.xls).

The CRL will review the report and confirm approval. It will then co-ordinate the release of the data to all the remaining NRLs and to the appropriate manufacturer, both via the website and alert e-mails.

7.5.1 Reports that recommend non-release

These shall only be sent to the manufacturer by the CRL. 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.

7.6 Data Retention

It is imperative that the NRL retain all the manufacturer's analytical data for the appropriate batch release for five years *after the batch expiry date***.**
This is to be kept as a hard copy at the NRL.
In addition, a full electronic copy must be sent to the CRL for reference

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 CRL. This could be an initial visit, periodic visit, or visits if and when a problem occurs.

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 three week deadline, the appropriate NRL shall contact the CRL via the general email address (tseeucrl@vla.defra.gsi.gov.uk) and the CRL 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 CRL 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 free of 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 the first 4 batches to be released by this procedure.

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, liase with kit manufacturer to supply, (notifying the CRL).

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.

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 CRL certified control materials prior to each round of batch testing.

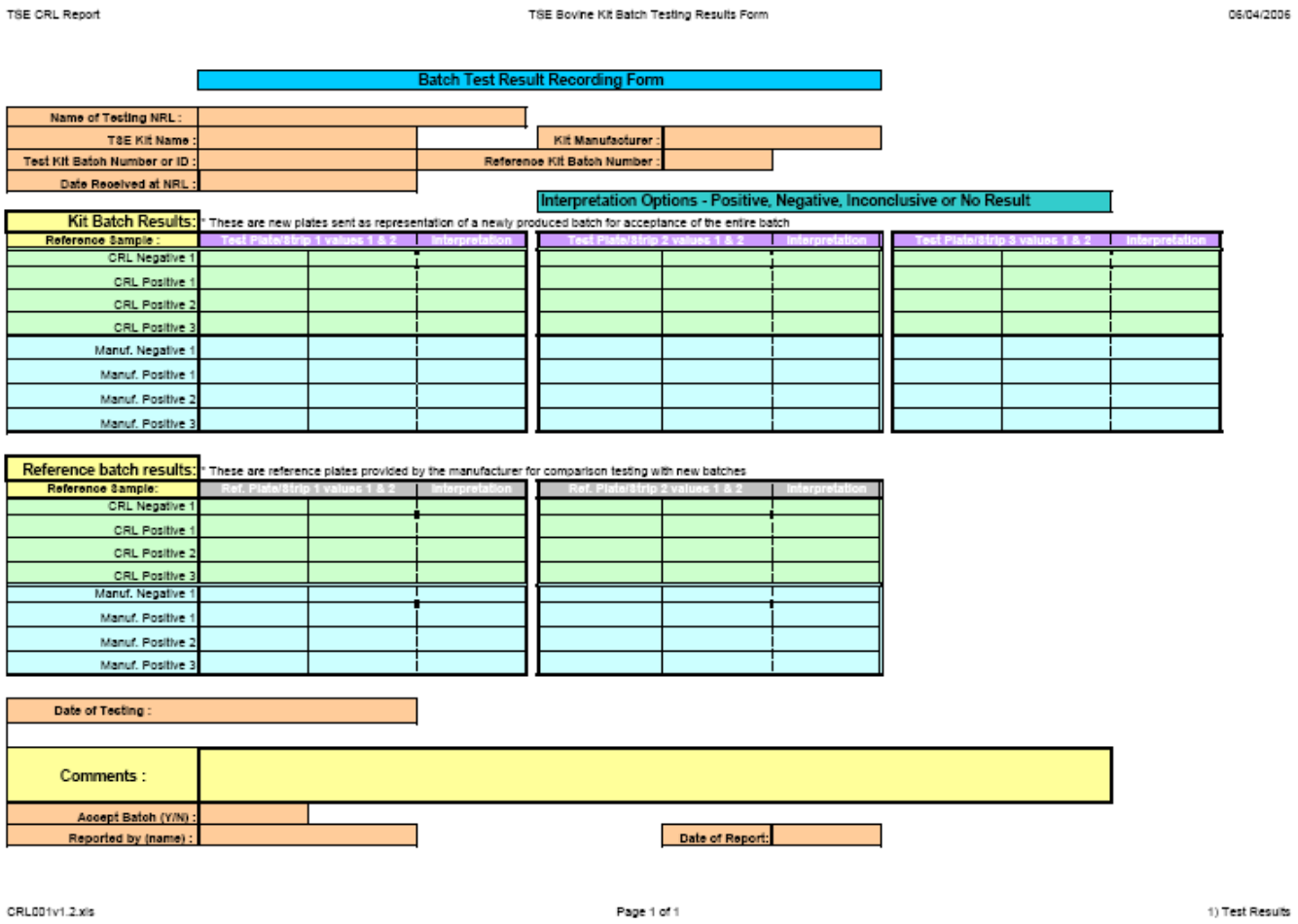
5. Ensure that all relevant kit controls are utilised as specified to ensure kit validity is maintained.

6. On completion of the QC testing programme, prepare the required short analytical report, in English, and supply to the CRL using the spreadsheet provided. Additionally, supply the CRL with an electronic copy of the full manufacturer's release report including raw data; archive a copy at the NRL. Comment on whether the batch release criteria have been met.

7. Make a recommendation to the CRL as to whether the kit should be released onto the European market, on the analytical data report.

8. As the delegated representative of the CRL, the nominated NRL may retain an option, but not a requirement, to make an inspection visit to the manufacturer's facility to prepare a report for the CRL.

APPENDIX 3 : REPORTING SPREADSHEET PAGES



TSE CRL Report | TSE Bovine Kit Batch Testing Results Form | 06/04/2006

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
CRL Negative 1									
CRL Positive 1									
CRL Positive 2									
CRL 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
CRL Negative 1						
CRL Positive 1						
CRL Positive 2						
CRL 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:	

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TSE CRL Report | TSE Bovine Kit Batch Repeat Testing Results Form | 06/04/2006

Repeat Test Values (If Repeats Performed)

Name of Testing NRL :	
TSE Kit Name :	
Test Kit Batch Number or ID :	
Kit Manufacturer :	
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
CRL Negative 1						
CRL Positive 1						
CRL Positive 2						
CRL 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
CRL Negative 1			
CRL Positive 1			
CRL Positive 2			
CRL 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)	

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CRL TSE Report | Manufacturer's Batch Release Report Review Form | 06/04/2006

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) :			

CRL001v1.2.xls | Page 1 of 1 | 3) Batch Release Report Review