

NATIONAL STANDARD METHOD

GUIDANCE NOTE

UNDER REVIEW

COMMERCIAL AND IN-HOUSE DIAGNOSTIC TESTS: EVALUATIONS AND VALIDATIONS

QSOP 23

Issued by Standards Unit, Department for Evaluations, Standards and Training
Centre for Infections

Association of Medical Microbiologists
Association of Medical Microbiologists
Association of Medical Microbiologists



COMMERCIAL AND IN-HOUSE DIAGNOSTIC TESTS: EVALUATIONS AND VALIDATION

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STATUS OF NATIONAL STANDARD METHODS

National Standard Methods, which include standard operating procedures (SOPs), algorithms and guidance notes, promote high quality practices and help to assure the comparability of diagnostic information obtained in different laboratories. This in turn facilitates standardisation of surveillance underpinned by research, development and audit and promotes public health and patient confidence in their healthcare services. The methods are well referenced and represent a good minimum standard for clinical and public health microbiology. However, in using National Standard Methods, laboratories should take account of local requirements and may need to undertake additional investigations. The methods also provide a reference point for method development.

National Standard Methods are developed, reviewed and updated through an open and wide consultation process where the views of all participants are considered and the resulting documents reflect the majority agreement of contributors.

Representatives of several professional organisations, including those whose logos appear on the front cover, are members of the working groups which develop National Standard Methods. Inclusion of an organisation's logo on the front cover implies support for the objectives and process of preparing standard methods. The representatives participate in the development of the National Standard Methods but their views are not necessarily those of the entire organisation of which they are a member. The current list of participating organisations can be obtained by emailing standards@hpa.org.uk.

The performance of standard methods depends on the quality of reagents, equipment, commercial and in-house test procedures. Laboratories should ensure that these have been validated and shown to be fit for purpose. Internal and external quality assurance procedures should also be in place.

Whereas every care has been taken in the preparation of this publication, the Health Protection Agency or any supporting organisation cannot be responsible for the accuracy of any statement or representation made or the consequences arising from the use of or alteration to any information contained in it. These procedures are intended solely as a general resource for practising professionals in the field, operating in the UK, and specialist advice should be obtained where necessary. If you make any changes to this publication, it must be made clear where changes have been made to the original document. The Health Protection Agency (HPA) should at all times be acknowledged.

The HPA is an independent organisation dedicated to protecting people's health. It brings together the expertise formerly in a number of official organisations. More information about the HPA can be found at www.hpa.org.uk.

The HPA aims to be a fully Caldicott compliant organisation. It seeks to take every possible precaution to prevent unauthorised disclosure of patient details and to ensure that patient-related records are kept under secure conditions¹.

More details can be found on the website at www.evaluations-standards.org.uk. Contributions to the development of the documents can be made by contacting standards@hpa.org.uk.

The reader is informed that all taxonomy in this document was correct at time of issue.

Please note the references are now formatted using Reference Manager software. If you alter or delete text without Reference Manager installed on your computer, the references will not be updated automatically.

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AMENDMENT PROCEDURE

Controlled document reference	QSOP 23
Controlled document title	Commercial and in-house diagnostic tests: Evaluations and Validations

Each National Standard Method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@hpa.org.uk.

On issue of revised or new pages each controlled document should be updated by the copyholder in the laboratory.

Amendment Number/ Date	Issue no. Discarded	Insert Issue no.	Page	Section(s) involved	Amendment
5/ 29.09.08	4	4.1	All	All	Department name changed
			2	Status page	Taxonomy sentence inserted.

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COMMERCIAL AND IN-HOUSE DIAGNOSTIC METHODS: EVALUATIONS AND VALIDATIONS

1 INTRODUCTION

Key roles of the laboratory are to decide what tests should be offered and to select the best method. Prior to procurement, a chosen method must be evaluated and following implementation of a new method it should be validated. Validations aim to show that the new method is at least as good as existing methods. Validation is an evidence-based assessment of how a test performs in the laboratory, and demonstrates suitability for intended purpose. Validation is a CPA, UKAS and ISO requirement² and requires that examination procedures shall be validated for their intended use prior to adoption, and the methods and the results obtained recorded.

This guidance note describes each stage in carrying out evaluations and validations of diagnostic methods. A method may be a new or modified commercial kit, an in-house method or reagent or a set of reagents bought separately and used to prepare an in-house method.

For more information on CE marking please refer to QSOP 33 - European Directive on in vitro diagnostic medical devices (98/79/EC) and for more information on quality assurance refer to QSOP 27 - Quality assurance in the diagnostic virology and serology laboratory.

2 DEFINITIONS

Evaluation – A generic term to describe the measurement of the performance capabilities of a system. This is a systematic and extensive process that compares different systems designed to perform the same or similar functions. Examples of evaluations within microbiology include comparison of different methods designed to detect the same marker/target, comparison of different culture media to isolate the same organism, or comparison of different equipment with the same function. Evaluation findings should be fed back to interested parties eg via publication of results. Where two kits have equivalent performance characteristics, the one which is easier to use, cheaper, faster or requires a more easily obtainable sample might be preferred.

Validation – Examines the whole process that is being used to check that results are correct. Each laboratory validates their ability to achieve acceptable results with the method or system in question. To document this ability each laboratory should produce a Validation File for each method or system. The file will include a range of information and will have a different emphasis depending on whether the laboratory is using a commercial system or has developed a system in-house. Typically the file will include sections such as evaluation data, tests on known samples, workbooks, relevant publications, ongoing quality control data, relevant standard operating procedures, error logs and customer complaints.

Accuracy – The closeness of agreement between the mean value obtained from a large series of test results and an accepted reference value.

Reproducibility – The ability to produce essentially the same diagnostic result irrespective of variations in operator, test batch, laboratory or validated ancillary equipment.

NB: The higher the number of variables the more robust a test must be in order to achieve this.

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Sensitivity³ – Is the ability of an assay under evaluation to identify correctly true positive (reference assays positive) samples. Therefore, sensitivity is the number of true positive samples correctly identified by the assay under evaluation (a) divided by the total number of true positive samples (eg those positive by the reference assays) (a+c), expressed as a percentage as indicated in the table below.

Specificity³ – Is the ability of an assay to identify correctly true negative (reference assays negative) samples. Therefore, specificity is the number of true negative samples correctly identified by the assay under evaluation (d), divided by the total number of true negative samples (eg those negative by the reference assays) (b+d), expressed as a percentage.

Calculation of sensitivity and specificity³:

Results of assay under evaluation	positive	True positive specimens	True negative specimens	Total
		a True-positives	b False-positives	a+b
	negative	c False-negatives	d True-negatives	c+d
		Total	a+c	b+d

Sensitivity = $a/(a+c)$ Positive predictive value (PPV) = $a/(a+b)$

Specificity = $d/(b+d)$ Negative predictive value (NPV) = $d/(c+d)$

Positive predictive value (PPV) is the probability that when the test is reactive, the specimen does contain antibody to the designated pathogen.

Negative predictive value (NPV) is the probability that when the test is negative a specimen does not have antibody to the designated pathogen.

NB: these parameters are highly population dependent and influenced by the prevalence of disease.

An online calculator for PPV and NPV can be found at:
http://www.hpa-midas.org.uk/online_apps/ppv_npv_calculator.asp

Reliability – Ability of a system or component to maintain performance with in the manufacturer’s stated specifications over time. The level of downtime considered acceptable is likely to vary between systems.

3 PURPOSE OF EVALUATIONS AND VALIDATIONS

Evaluation⁴

The objectives should be simple and within the capabilities of an evaluation site. Attempting to answer too many questions at the same time can result in practical difficulties, less accuracy in data recording/collection and a failure to achieve all the objectives set.

A check-list of points to consider for equipment and kit evaluations is summarised in Appendix 1.

Validation

The intention of validation is to provide documentary evidence that a diagnostic test or piece of equipment is performing within manufacturer's specifications. This may involve results of experiments to determine its accuracy, sensitivity, reliability and reproducibility. A validation may be extensive, for example to validate a newly developed in-house method, or narrow in scope, for example to validate a commercial method which is already in use and has had minor modifications.

For methods already in use for which no specific existing validation is in place, it is important to provide documentary evidence which supports reasons for their use. It is usually sufficient to prepare a file based on historical evidence, such as results from comparisons or other studies undertaken, copies of published papers, EQA, IQA and IQC results etc. Work book records can be cross referenced if appropriate in the validation report.

4 GENERAL CONSIDERATIONS WHEN CARRYING OUT EVALUATIONS AND VALIDATIONS

4.1 PERSONNEL

The responsibilities of all personnel involved should be defined in the protocol.

Project Manager – is the person with overall responsibility for the successful completion of the project. S/he has overall responsibility for the organisational aspects of the work including production of the protocol, data collection and analysis, writing the report and ensuring that there is peer group assessment of the protocol and report. The Project Manager should document any conclusions made based on the results analysis and s/he also needs to sign a formal declaration that the method is suitable for diagnostic use. The report should have the support of stakeholders identified in the protocol design.

Project Group – includes people with sufficient expertise to cover all aspects of the method involved. The size of the project group can range from as little as one person, ie the Project Manager, (if the individual performing the evaluation/validation has sufficient expertise in all aspects of the project area) to many and will depend on the complexity of the project. It may be necessary to include people from other laboratories to ensure sufficient expertise is available for a successful evaluation/validation to be conducted. Consideration should be given to the inclusion of a statistician (see Appendix 2).

NB: If multiple evaluation sites are involved, each site will also need a named local co-ordinator to manage the study.

4.2 COMPUTING REQUIREMENTS

Requirements should be assessed prior to starting the evaluation or validation including:

- Requirement for manual input, transfer or manipulation of data
- Whether equipment can be interfaced to the laboratory computer to download and/or upload data as appropriate
- Whether software can be tailored to individual laboratories by the user, versus that requiring intervention by the manufacturer (and any cost implications of this)
- Compatibility of systems between laboratories should also be considered

4.3 PROJECT DESIGN

The complexity of the project will depend on the circumstances. Projects involving new in-house methods and/or considerable changes to a method already in use will require a more thorough investigation than minor changes to existing methods. Likewise evaluations involving multiple sites will also require a more complex design. Whereas multi-centre evaluations will allow more samples or tests to be examined within a specified time-frame, care is needed to ensure data are rigorously derived and comparable.

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During preparation of the protocol, it is important to ensure that kits being evaluated are the same version as those currently marketed or about to be purchased. Kits changed at any time may render assessments invalid. Under the current licensing requirements, the dates of changes, or acknowledgement that they have occurred at all, may not be recorded other than by manufacturers.

The Project Manager must prepare a plan, considering the following as appropriate:

1. Define the purpose and objectives of the investigation. For example, is the assessment designed to define differences or similarities between kits?
2. Identify any training requirements where necessary to ensure everyone involved in the project has suitable levels of competency. Ensure training records are up to date for procedures being carried out. Where kits are involved the supplier should be given the opportunity to ensure that users are competent and the training provided by the supplier should be assessed.
3. Identify any risk assessments and COSHH assessments which need to be reviewed or written.
4. Identify standard or reference materials where available to allow the method to be standardised, to facilitate method comparison, and to permit test stability over time to be determined.
5. Identify a method to be used as a “gold standard” for comparison of the method undergoing testing. On occasion, there may be no true or widely recognised “gold standard” against which to compare a particular method, in which case pre-existing assessed methods, eg National Standard Methods, should be used, and justification for their use included in the project proposal. It is not appropriate to compare two non-validated processes.
6. Identify the types and numbers of samples to be tested (see Appendix 2). Consider the need to include known positives (low and high), known negatives and samples which are known or likely to be problematic or representative of a particular population whose values are known. Samples for analysis should be selected carefully to reflect the objectives of the study. These may include stored organisms with known characteristics and should ensure adequate representation of all known variants. Where applicable, material should be sourced from a wide geographic area including the area where use is intended. Test samples should be split wherever feasible so that the same material is used to compare different methods. Samples should be transported to the laboratory under defined conditions and examined within a stated period of time. Stored sera giving a predetermined range of results form the basis of most serology evaluations/validations.
7. Approval from the relevant ethics committee³ must be sought if samples used originate from patients. However ethics approval is not required for the use of residual sera in kit validation or evaluation. This should be done in accordance with “The Use of Human Organs and Tissue act”⁵.
8. As far as possible all methods used in a project should be subjected to full quality control procedures. Quality control samples should be processed during the study period, to assess the quality of the data collected and possible differences between sites.
9. Methods of data collection and analysis of results should be determined consulting a statistician where necessary.
10. Consider the need to hold reviews of project progress and who needs to attend those reviews. Reviews may be set to take place after a period of time or when a particular stage of the project has been reached.
11. Carry out the project as determined by protocol design and record results.

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4.4 INVOLVING COMMERCIAL COMPANIES

Confidentiality agreements may be sought by companies where prototypes are tested or where developmental work is undertaken.

Although commercial influences must not compromise scientific integrity, the manufacturer should be included in the study design where possible and must be given the opportunity to ensure that the protocol describes the correct use of the product and that equipment is used correctly.

The commercial company should be given the opportunity to comment on the report and any manuscripts to be submitted for publication.

4.5 AVOIDING BIAS

Great care should be taken to avoid bias at all stages. The possibility of bias might be introduced at almost every stage of an evaluation/validation and this may skew the results of the study in a particular direction. Potential problems should be considered and addressed before the study begins.

Areas where bias may be introduced include:

- Failure to standardise fully the procedures, eg sampling, method, media and reagents
- Failure to read results independently (results from one method may influence the interpretation of those from another)
- Inappropriate panel of specimens, for example selected on the basis of results from an assay involved in the evaluation/validation.
- Use of a panel that is over represented with specimens that have been pre-screened by a kit that is the same as that tested within the evaluation/validation
- Premature discussion or analysis of results (except by the statistician)
- Where multi-site evaluations are concerned, failure to perform the study simultaneously, thereby introducing potential differences due to seasonal differences in isolation or detection rates
- Failure to give full training in the techniques, protocol, use of kit or equipment involved in the study before commencement

4.6 COST-BENEFIT ANALYSIS

All aspects of costs need to be measured and compared with the specified “gold standard”.

Cost approaches to be considered include:

- Comparison with standard in terms of consumables, labour and overheads
- Equipment costs including capital/lease/reagent rental, maintenance, service costs, spare parts (availability), consumables, ancillary equipment required, staff costs and overheads for the instrument as used in a routine situation
- Comparison with specified manual method
- Cost of isolating specific organism
- Cost of isolating specific extra organism
- Costs of work done to prove a negative or confirm a positive result

A study of how the research will impact on the running of the laboratory should be considered as a way of objectively assessing all aspects of costs. The cost-benefit balance should be

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assessed in terms of the clinical value of the result and the effect on turn-around times. To this end, a health economists' involvement may also be appropriate.

4.7 TIME-SCALE

A suitable time-scale should be agreed in advance of the start of the project. This will depend on the statistical sample size, the rate of acquisition of suitable specimens, and the time needed for the test procedures to be approved. Studies should be carried out in centres where the samples or organisms to be tested are sufficiently common to achieve results in a reasonable time or in laboratories which hold a repository of characterised samples. Isolation and detection of organisms are subject to seasonal differences, eg respiratory pathogens: where feasible, the study should be conducted at times of high incidence to optimise the use of resources.

When preparing a study time-table any phasing of the trial should be taken into consideration. For example, with equipment the following three phases might be indicated:

- Familiarisation, ensuring that the equipment is ready for evaluation, and preliminary testing with reference material
- Extended testing with reference material and routine samples
- Routine use for all specimens in parallel with current routine method

5 DOCUMENTATION OF EVALUATIONS

5.1 DOCUMENTS REQUIRED FOR EVALUATIONS

The main body of the report should cover all details as outlined in the protocol design. The format and level of detail will vary with the study. Broadly, a report will include title, authors, location, summary, introduction, materials and methods, results, conclusions, discussion, bibliography, and appendices. If it is a report on behalf of the Centre for Evidence-based Purchasing (CEP) at NHS Purchasing and Supply Agency (PASA), it should follow their guidelines (available from CEP or from the Microbiological Diagnostics Assessment Service).

5.2 AVAILABILITY OF THE EVALUATION REPORT

The availability of the report will depend on the nature of the evaluation and any contractual agreement with manufacturers/suppliers.

A commissioned evaluation of equipment not yet marketed may be made available only to the commissioning supplier. If the supplier uses the evaluation to develop pre-production equipment further it would not be appropriate to publish the data widely. If the equipment is to be marketed as evaluated or if it is already being marketed it is unacceptable for the report to remain confidential. The supplier should be allowed to comment on the report before it is published.

Microbiological Diagnostics Assessment Service evaluation reports are available at <http://www.hpa-midas.org.uk/reports/>

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5.3 PUBLICATION OF EVALUATION

Results of any new, well performed evaluation may merit publication in a peer-reviewed journal. The work is thereby given further credibility by peer-review, duplication of effort is avoided and laboratories are given valuable information on which to assess best practice. Publication of results should be sought without delay.

6 DOCUMENTATION OF VALIDATIONS

6.1 DOCUMENTS REQUIRED FOR VALIDATIONS

A validation file should be produced for all existing, as well as new, methods and may include a summary of and reference to existing data which are likely to be recorded in workbooks, papers and reports. A validation file is also required for modifications to existing methods.

All documents relating to the validation must be filed in a retrievable and auditable manner. There should be a validation file where all related documents are either stored or cross-referenced.

Documentation includes review meeting minutes, workbooks, worksheets, methods used, published and unpublished papers and reports, manufacturers instructions, previous test results, and any other supporting information (see below).

This file may contain some or all of the following information, as appropriate:

- External Quality Assessment (EQA) data (several years, as available)
- Internal Quality Control (IQC) data
- Internal Quality Assessment (IQA) data
- For in-house methods, research and development carried out during the development of the procedures.
- Results of testing known positives, known negatives, low and high positives and samples which are known or likely to be problematic (possibly carried out before the introduction of the test to the department)
- Published and unpublished papers and reports
- Work books (especially applying to in-house testing)
- Work carried out with collaborating laboratories
- Comparisons with alternative methods
- Comparisons with previously used test methods
- Evaluation Reports eg from Microbiological Diagnostics Assessment Service. These reports cannot be used as the only evidence in a Validation File since evaluations establish kit performance only at a particular point in time and within a particular evaluation setting
- Manufacturer's instructions
- Manufacturer's product specification
- Health and safety information (data sheets, COSHH, Risk Assessments etc)

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- Relevant SOPs

Complete the validation summary report form and the accompanying checklist (Appendix 3 and 4). If key information is already documented, it is not necessary to transcribe it to the form, it is sufficient to cross-reference.

The Project Manager must review the data, complete the validation checklist, and sign the validation section to authorise release of a new or modified kit or reagent or to assure that sufficient information has been provided to confirm that a method already in use is performing within the manufacturer's specifications.

All SOPs relating to modified or new kits or reagents must be reviewed to verify that processes are in line with current procedures. It may be necessary to maintain new or revised SOPs as working drafts while their contents are being validated. SOPs should be authorised as fully controlled documents when the validation study has been completed.

7 ACKNOWLEDGEMENTS AND CONTACTS

This National Standard Method has been developed by Derek Brown, Jim Gray, Kathy Nye and Rod Warren, and reviewed and revised by the Standard Methods Working Group for Bacteriology (http://www.hpa-standardmethods.org.uk/wg_bacteriology.asp) and the National Working Group for Standards and Quality for Virology (http://www.hpa-standardmethods.org.uk/wg_virology.asp). The contributions of many individuals in clinical bacteriology laboratories and specialist organisations who have provided information and comment during the development of this document, and final editing by the Medical Editor are acknowledged.

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For further information please contact us at:

Standards Unit
Department for Evaluations, Standards and Training
Centre for Infections
Health Protection Agency
Colindale
London
NW9 5EQ
E-mail: standards@hpa.org.uk

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APPENDIX 1: ADDITIONAL INFORMATION FOR EQUIPMENT OR KIT EVALUATIONS

Due to the diversity of what can constitute an evaluation, it is impossible to be prescriptive about the information required. The following section gives some sample forms, plus more detailed suggestions of things to consider.

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EVALUATION PROCESS FORM

(1) Title of evaluation:

(2) Project team

Role	Name	Laboratory	Area of expertise*
Project Manager			
Evaluator			
Statistician			
Expert Advisor			
<i>etc</i>			

* e.g. statistician, molecular scientist, HIV serology

(3) Background and purpose of evaluation:

(4) Brief details of evaluation design, including “gold standard” method:

(5) Target completion

Evaluation phase	Target date
Preparation/Setup	
Technical	
Report	

(5) Summary of specimen panel composition:

Specimen category/type	Number

(6) Relevant SOPs

SOP number	Title

(7) Relevant COSHH and Risk assessments

Number	Title

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(8) Cross-reference all other related documents associated with this study

(list can be added to and deleted from as appropriate)

e.g.

- Evaluation checklist
- Correspondence with manufacturers/suppliers (e.g. agreed loan of equipment, modifications to 'Instructions For Use', comments on evaluation report)
- Agreement/contract with manufacturer/supplier
- Agreements with collaborating laboratories
- Published and unpublished papers and reports
- Protocol
- Specimen panel details
- Statistical advice/analyses
- Manufacturer's product 'Instructions For Use' (IFU)
- Invoices (where applicable)
- Equipment details, service and maintenance
- Workbooks (evaluation results and supplementary/confirmatory tests)
- Results
- Adverse incident forms (where applicable)
- Report edits/reviews/final version
- Review meeting minutes

(9) Diary (include dates of all important events, such as review meetings)

Event	Date
Project start	
Project end	

(10) Conclusions (include brief summary and lessons learnt)

Complete evaluation checklist before completing the authorisation section below

EVALUATION AUTHORISATION SECTION

The assessment/evaluation has fulfilled its aims as stated in section 3

Comments:

Signed (Project Manager)

Date _____

Post-evaluation: A change in practice is desirable which will be instigated following validation/ no further action required at this time*

*Delete as appropriate.

Comments:

Signed (Project Manager)

Date _____

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EVALUATION CHECKLIST

1) Evaluation planning and setup:

- a) Proposal prepared Yes No
- b) Key kit/system information obtained Yes No
- c) Specimen panel obtained Yes No ongoing
- d) Collaborators/stakeholders identified and recruited Yes No N/A
- e) Protocol written and approved Yes No
- f) Target dates defined Yes No
- g) Costings prepared and funding agreed Yes No N/A
- h) Risk and COSHH assessments completed Yes No
- i) Training date(s) arranged Yes No N/A
- j) Kits/reagents and equipment ordered/access arranged Yes No

2) Technical assessment:

- a) Acceptance testing¹ Yes No
- b) Performance testing² Yes No
- c) Retests/confirmatory testing Yes No N/A
- d) Report any Adverse incidents Yes No N/A
- e) Usability comments Yes No

3) Data analysis, report & archive

- a. Data checks Yes No
- b. Results analysis
 - o Sensitivity Yes No
 - o Specificity Yes No
 - o Reproducibility Yes No
- c. Write 1st draft report Yes No
- d. Vertical audit Yes No
- e. Review and revise as appropriate Yes No N/A
- f. Sign off by project leader/manager Yes No
- g. Manufacturer comments Yes No
- h. Final evaluation report (publish, distribute, web link) Yes No N/A
- i. Archive data, emails, report copies etc Yes No

1: Acceptance testing – does the kit/component/equipment perform as described in the manufacturer's literature in your laboratory? (a 'trial run')

2: Performance testing – testing specimens as described in the agreed protocol

Next step: validate any new or modified practices

Comments:

Signed:

Date: _____

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ADDITIONAL INFORMATION

Details of equipment

Equipment details including:

- Make, model, manufacturer (is this a trial model, or are any modifications planned?)
- Manufacturer and supplier name and address
- Purpose of equipment
- Principle of operation
- Technical operation of the system
- Physical specifications – dimensions, weight, electrical requirements, additional features
- Recognition by any official international regulatory body, eg FDA, CE mark
- Availability of COSSH and risk assessments available for the system, reagents and any aerosols produced by the system

Ownership and acquisition of equipment:

- Who owns the equipment
- How has the equipment been purchased or leased?
- Is there a contractual agreement for the purchase of consumables?
- Is there an arrangement to assess the machine?

Equipment maintenance / service continuity

- Is maintenance contract required?
- Cost of maintenance contract
- Level of user maintenance required
- Records of down time from a laboratory which has been using the system for at least 1 year? (where applicable)
- Annual service down time, and routine servicing and maintenance to be undertaken by trained laboratory staff
- Response times of the company service engineers
- Time to replace the system in the event of a catastrophic failure? Can the tests be run manually if necessary? Will another local laboratory be able to take on the testing for a short time?

Level of automation provided

- Throughput of the machine (eg expressed as specimens or tests/hour)
- Number of samples/plates run at any one time
- Range of incubation temperatures available
- Reusable or disposable parts (e.g. tips for reagent additions)
- Closed system or operator programmable
- Bar-code reading ability (eg for data entry or reagent batch details)
- Does the machine check that sufficient volumes of the reagents etc are available
- Method of data capture eg wavelength of spectrophotometric reader?

Computing information

- Operating system and software
- Can the software be interfaced with the laboratory diagnostic software to enable exchange of worksheets and results?
- Specimen entry by hand and/or bar-code
- Is there on-line help?
- Can the user modify the software?

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- Specify the walk-away time associated with a test run; will the machine run to conclusion from the start of the walk-away time?
- Can the equipment run safely overnight?
- Total method time
- Can the software analyse results?
- Does the system maintain a dated audit trail at any level?
- Is access to the system password controlled with tiered levels of access?

The method of equipment installation (by the supplier or the user) should be recorded. Any problems encountered during installation should be recorded.

Details of kit/reagent

Kit/reagent details including:

- Name, description and purpose
- Manufacturer/supplier name and address
- Format (eg number of tests per kit/per run, number of controls per kit)
- Lot/batch number; expiry date
- Principle of kit/reagent
- Technical details of the system
- Associated automated equipment requirements
- Additional requirements
- Incubation times and conditions
- Time to availability (eg currently available or under development)
- Suitability for automation

Kit/reagent presentation and packaging:

- Usefulness of product insert
- Adequate safety information provided
- Container and reagents clearly labelled
- Lot numbers, expiry dates and other important details easily located?
- Is the manual clear and unambiguous – can it be used as an SOP?
- Does it fulfil requirements for COSHH assessment?

Manufacturer/supplier support

- Has the level of company support been satisfactory?

Safety considerations

- Did any additional hazards arise throughout the course of the evaluation which were not identified during the initial risk assessment
- Has the manufacturer done everything possible to control the risks?

Documentation, training and support

These should be assessed in terms of:

- Quality of documentation provided - is it comprehensive, accurate, unambiguous and easy to follow?
- Ease of learning to use the equipment/kit
- Need to refer back to manuals or the supplier because it is unclear what should be done at any stage
- Ease of user modifications (if appropriate)
- Possibility of modifications by the manufacturer and likely costs to the user

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- Need for interpretation by the user
- Training provided by the manufacturer's representative
- Grades of staff required to operate the equipment. The staff involved in the evaluation should include those expected to perform the tests routinely, under the supervision of senior staff
- Other support required: was it adequate, timely and satisfactory?

Results and data analyses

Raw data should be appended to the report (if appropriate). The results should be presented in detail, and analysis of results presented.

The following points should be addressed:

- Identify the positive and negative features of the equipment/kit/media
- Has the equipment/kit/reagent performed satisfactorily?
- Any changes in performance compared to the previous/current equipment/kit/method used
- Improvements in consistency
- Improvements in turnaround times
- Evidence that the kit/equipment is inadequately sensitive or specific
- Reproducibility of results
- Stability of reagents
- Ease of result interpretation
- Would you recommend the use of this equipment/kit/reagent or method to other laboratories?

Problem log (equipment/kit)

- Detailed records should be made of any problems, faults or supplier interventions
- Observations on any aspect of the system should be recorded in a log book to be completed daily by anyone using the equipment

Faults may be recorded in terms of:

- Nature of fault
- Time/date observed
- Time/date reported to supplier
- Response time of supplier
- Outcome

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APPENDIX 2: STATISTICAL ISSUES

Statistical advice

Although statistical analysis is not usually required until the end of a study, it is essential to obtain advice at the outset of study design from a statistician on sample size and the data collection system and documentation. The main statistical methods to be used in analysis should be identified at the planning stage. This will help ensure that the study has sufficient power to meet all its objectives and that the data are collected in the most appropriate form for an efficient and timely analysis. It is advisable to identify a statistician to provide any necessary advice during the study.

Preliminary analysis of results should not be undertaken except by the project statistician. Any premature communication of results could lead to bias being introduced into the study, thus undermining the reliability of the conclusions.

Statistical sample size

For the study to have sufficient power to meet all its objectives, ie to detect the smallest important differences or estimate test characteristics sufficiently precisely, it must use an appropriate number of samples for microbiological testing. This is the study sample size in statistical terms.

The study sample size and the assumptions made to obtain it should be part of the evaluation protocol. The study sample size will identify the number of specimens or tests to examine and how it is calculated will depend on the magnitudes of the test characteristics to be estimated or compared ie sensitivity and on the precision required or the smallest important difference to be detected.

Whereas information on likely outcomes may exist, there may not be enough information at the planning stage on which to base a calculation of the size of study needed. In these cases a pilot study may be used or alternatively a deferred estimate by the project statistician could be made once the study is underway using the results from the early specimens. The statistician should advise on how many results are required for this estimate.

Where it becomes apparent that very large numbers would be required to show that a small but important difference is statistically significant (as may be the case when isolation rates are very low), the benefits of continuing the study need to be addressed carefully.

Data collection

The more complex data collection is, the less likely it is to be accurate. Data recorded at the bench should be entered to record sheets either manually or electronically.

Record sheets should be simple and, whenever possible, be reduced to a series of "tick-boxes" or simple key strokes. Some form of data entry audit is necessary.

Results should be read and recorded independently, without influence of one method on another (the identity of specimens should be anonymised at the time of reading so the reader is "blind").

Entry of data to the main study database should be the responsibility of the local study co-ordinator. Although spreadsheets are often simple to set up and use, a database should be designed which limits the options available for entry and thereby reduces the likelihood of incorrect or incomplete entries. The type of database used should be determined based on the size of the study involved.

Analysis of results

The main statistical analysis planned should be specified as part of the study protocol.

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Results should be assessed statistically against the criteria specified in the protocol which may include:

- All or specific aspects of the methods, kits or equipment
- Available product information
- Relative workload
- Sensitivity/specificity
- User acceptability
- Clinical relevance
- Cost-benefit analysis
- Health economics

The design of the study, the statistical analysis and the conclusions of evaluations should be peer reviewed.

Where two methods give similar isolation rates, one might have significant benefits over the other. Benefits include fewer false-positive/false-negative results, lower costs associated with the method or test, and less labour involved in performing the method or test.

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APPENDIX 3: VALIDATION REPORT SUMMARY FOR THE INTRODUCTION OF A NEW OR MODIFIED DIAGNOSTIC KIT OR REAGENT

1) Brief description of the method:

2) Project team

Role, e.g. statistician, lab. worker	Name	Laboratory	Area of expertise e.g., statistician, molecular scientist, HIV serology
Project Manager			

3) Purpose of method and background, including reason for introduction:

4) Brief details of method validation plan:

5) Relevant SOPs

Number	Title

6) Relevant COSHH and other risk assessments

Number	Title

7) Cross-reference all other related documents associated with this study

(list can be added to and deleted from as appropriate)

EQA data

IQC data

IQA data

In-house R&D records

Results of testing:

known positives

known negatives

low positives

high positives

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problem samples
 Published and unpublished papers and reports
 Work books (especially applying to in-house testing)
 Work carried out with collaborating laboratories
 Comparisons with alternative methods
 Comparisons with previously used test methods
 MiDAS reports
 Review meeting minutes
 Manufacturer's instructions
 Manufacturer's product specification

8) Diary (include dates of all important events, such as review meetings)	
Event	Date
Project start	

9) Conclusions (include brief summary)

Complete validation checklist before completing the authorisation section below

VALIDATION AUTHORISATION SECTION

This method is suitable for diagnostic use

Signed (Project Leader) _____ Date _____

Introduction of method authorised

Signed (Project Manager) _____ Date _____

APPENDIX 4: DIAGNOSTIC KIT OR REAGENT VALIDATION CHECKLIST

1) Validation of method:

- i. Has a comparison with existing methods (currently or previously in use) taken place? Yes No
- ii. Has the performance in EQA and/or IQC schemes been evaluated? Yes No
- iii. Has the method been assessed by an IQA scheme? Yes No
- iv. Has all or part of this work been published in a peer-reviewed journal? Yes No
- v. Are there any other reports related to the method available, eg project reports, manufacturers literature? Yes No
- vi. Are test results available for samples which challenge the performance of the method? Yes No
- vii. Are work books cross referenced? Yes No
- viii. Has the test been validated by collaborating laboratories? Yes No
- ix. Are comparisons with alternative methods available? Yes No
- x. Are MiDAS reports available for this test? Yes No
- xi. Has the assay been costed? Yes No
- xii. Is the assay to be distributed outside the organisation that created it? Yes No
- If YES, has CE marking been affixed to the reagent? Yes No

2) Have the following method characteristics been evaluated:

- i. Sensitivity Yes No
- ii. Specificity Yes No
- iii. Reproducibility Yes No
- iv. COSHH assessment of method Yes No
- v. Risk assessment of the new procedures, equipment etc. Yes No

3) Have customers been informed of significant changes in method performance: eg sensitivity, specificity, turn-around times Yes No

Has the User Manual been updated? Yes No N/A

Comments:

REFERENCES

1. Department of Health NHS Executive: The Caldicott Committee. Report on the review of patient-identifiable information. London. December 1997.
2. Clinical Pathology Accreditation (UK) Ltd. Standards for the Medical Laboratory. Sheffield 2004. p. 1-56
3. Diagnostics and Laboratory Technology Evaluation Reports Switzerland: WHO; 2006.
4. BS EN 13612:2002 *Incorporating Corrigendum No.1* - Performance evaluation of in vitro diagnostic medical devices. BSI; 2002.
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