

# Benchmarks

A regular feature covering topical issues for microbiology laboratories, compiled by Valerie Bevan

## Provision of a microbiological device evaluation service

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### Background

Evaluation of *in vitro* diagnostic medical devices (IVDDs) and associated instrumentation is essential for the delivery of a high quality laboratory service. Diagnostic, National Reference, and National Blood Service laboratories depend on the supply of a range of commercial devices for their operation, and should take into account available validation evidence when selecting and purchasing devices<sup>1</sup>. Evaluations compare the performance of a range of devices for the same intended purpose and independently verify manufacturers' claims, so helping users decide which devices are most suitable for their needs.

The breadth and depth of available evaluation information can vary considerably depending on the diagnostic marker. Some subject areas are intensively evaluated, e.g. HIV kits, while other areas are neglected. Evaluation programmes are often not resourced to keep abreast of developments in all device categories. This should lead us to question how much we actually know about devices that are being used on a day-to-day basis. The *Getting Ahead of the Curve*<sup>2</sup>

strategy for combating infectious diseases highlights the need to develop a co-ordinated system for evaluation followed by managed introduction of new technology. To achieve this we need to consider how we can build upon existing evaluation programmes.

### Evaluation centres and partnerships

Most service laboratories do not have the resources or time to undertake in-depth evaluations of the devices they use. In the UK, microbiological evaluations have been carried out by two dedicated evaluation centres and by individual laboratories with interests in evaluating particular products.

MiDAS (the Microbiological Diagnostics Assessment Service), based at the Health Protection Agency - Colindale, has a remit to undertake virology/serology kit evaluations. MiDAS works in a partnership between the HPA and the Medicines and Healthcare products Regulatory Agency (MHRA) and also undertakes work with the World Health Organisation (WHO), the National Blood Service (NBS) and sometimes carries out commercial evaluations for manufacturers. MiDAS also advises the NHS Purchasing and Supply Agency (PASA) on the performance and quality of kits at the time of procurement.

The need for formal evaluation of virology kits was highlighted in 1986, when the PHLS Virus Reference Laboratory assessed the

first commercial HIV kits. The evaluation programme later evolved to include hepatitis B and C kits, aligning itself with the interests of the Sexually Transmitted and Bloodborne Virus Laboratory (SBVL) where the group first developed. In February 2003 the work was transferred to the new Evaluations and Standards Laboratory (ESL), and within the same year three other changes affected our work, namely the creation of the Health Protection Agency, the incorporation of the Medical Devices Agency (MDA) into the newly formed MHRA, and the implementation of the European Union IVDD directive.

The second dedicated MHRA evaluation centre, based at Leicester Royal Infirmary, conducted bacteriological method evaluations. Unfortunately this centre closed at the end of March 2004 due to withdrawal of funds. It is to be hoped that this does not signal a future lack of regard for the value of effective evaluations.

### Benefits of evaluation

Information gained from evaluations helps laboratories select the best kits for their needs. The devices that are chosen for evaluation and the data produced should be relevant to important public health concerns, such as improving the diagnosis of acute and chronic infection, the safety of blood for transfusion, and the monitoring of immunisation programmes.

In addition to identifying the best performing products, evaluations will also identify poor and unacceptable performers. Also, if a kit or piece of equipment is found to be defective in routine use the information is reported to the MHRA and the ESL Standards Unit, where it undergoes a technical adverse incident investigation. In the absence of such evaluations, the risk is that little or no objective data are available for users involved in the selection of kits and equipment. Without this users rely on information produced by companies or licensing systems. This information may be biased and it fails to place results in the context

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of competitors' products.

Evaluation results are normally published in evaluation reports aimed at users of IVDDs such as laboratory personnel, laboratory managers, and policy-makers. Importantly, the results contained in the reports must be unbiased and independent. The MHRA evaluation reports are probably the best known output of our unit, and recent examples are cited<sup>3-7</sup>. In addition, we are involved in publication of WHO reports on the operational characteristics of kits, and submit reports to the NBS Kit Evaluation Group committee and to companies. The evaluation reports are recognised for their thoroughness and the extent of product comparisons. Once they are published, manufacturers are able to compare their products' performance with that of competitors' products. This may encourage them to develop their products.

### Basic evaluation principles

Evaluations need to be relevant, accurate, efficient, and timely. Success depends on a number of principles including good planning and project management, a challenging specimen panel, minimised bias, good technical quality, a complete safety and quality system, and comprehensive documentation. To achieve this we need to have a well trained team with an array of skills related to management, organisation, project planning, audit, process improvement, laboratory competency, data analysis, report and scientific writing, database and web development, presentation, and customer service. Currently, six people are involved in providing our evaluation service (three evaluation microbiologists, one evaluation laboratory assistant, one evaluation coordinator, and the unit head).

An evaluation involves about 30 steps before completion and demonstrates awareness of potential problems and pitfalls throughout the process. Of crucial importance is the choice of specimen panel, the panel size, the characterisation of the samples, the reasoning for

including particular groups of samples, and the relevance of the results to routine use. For diagnostic kits the panel needs to be designed to challenge specificity, clinical sensitivity, seroconversion sensitivity (ability to detect early infection), and reproducibility; also if appropriate, analytical and subtype sensitivity. HPA guidance note Q SOP 23 provides detailed advice<sup>8</sup>.

Evaluations are usually undertaken at one point in the life of the product. It is therefore important that once a kit has been accepted for use laboratories continue to monitor its performance by batch pre-acceptance monitoring and regular use of quality control samples. Minor as well as major adjustments to and developments of kit reagents and procedures by manufacturers need to be kept under scrutiny.

### Impact of the IVDD directive

Since December 2003 it has been mandatory for diagnostics manufacturers to comply with the European Union IVDD directive<sup>9</sup> which lays down harmonising rules for the safety, quality and performance of IVDDs. As a consequence of the IVDD directive and the role of MHRA as the Competent Authority for the UK, MHRA considered that it was no longer appropriate for them to conduct evaluations and produce MHRA evaluation reports on kits that detect markers of HIV, HTLVII/II, hepatitis B, or hepatitis C. These kits are within a special category of the directive, Annex IIa, and only certification organisations known as Notified Bodies are licensed to issue a CE Mark and subcontract organisations to test these products according to Common Technical Specifications (CTS)<sup>10</sup>. MiDAS could not be a notified body because of potential conflicts of interest. These developments have given MiDAS the opportunity to broaden its evaluation programme.

Although kits now marketed in the UK must be CE marked, it is important to recognise that the CE Mark process is not a substitute for the previous evaluations. Organ-

isations such as the NBS continue to require fully comparative kit evaluation data of Annex IIa kits to make sure that kits are 'fit for purpose'. By providing this service to the NBS, MiDAS has been able to continue to use its expertise in evaluating Annex IIa kits.

### New evaluation opportunities

Dedicated evaluation centres should be viewed as a resource amenable to all laboratories. We now have an opportunity to develop the range of evaluations undertaken in particular beyond the products that fall into Annex IIa. This will require a coordinated approach involving better communication and feedback between laboratories, evaluation centres and manufacturers. There are several ways to improve the service:

- 1) Microbiology laboratories can influence evaluation priorities by telling us what kits or equipment should be evaluated. (please help us to do this by completing the table (table 1) and sending it back to us).
  - 2) Difficulty in accessing specimens hampers evaluations. We are seeking to liaise with clinics and laboratories that can provide anonymised patient specimens. For evaluation of serological assays we ideally need specimens of 3-5 ml of sera/plasma. We particularly need positive specimens from recent and clinical cases of infection, pre- and post-vaccination specimens, and the less easy to acquire negative specimens (e.g. rubella antibody negative ones). The Department of Health's interim guidance on 'The use of human organs and tissue'<sup>11</sup> is before Parliament, and this bill needs to provide clear advice on collecting specimens for evaluation and test improvement.
  - 3) We need improved interaction with and feedback from manufacturers so that we are aware of developments and can plan evaluations appropriately.
  - 4) We are keen to hear from laboratories with particular interests that are willing to collaborate with evaluations.
- Finally, our MHRA evaluation

TABLE 1 Prioritisation of evaluations

Kits	Total or IgG serology	IgM serology	Antigen	Nucleic acid tests	Contact details
Adenovirus					Name
Chlamydia				in preparation - MiDAS	
Cytomegalovirus					
Epstein Barr virus					Position
Hepatitis A					
Herpes I/II					
HHV-6					
Influenza					Laboratory
Legionella					
Measles					
Mumps					Contact details - email
Mycoplasma					Please fill in details above. This will help prevent duplications.
Papillomavirus					
Parvovirus B19					
Rotavirus					
Respiratory Syncytial Virus					
Rubella					
SARS					
Syphilis	in progress - MiDAS				
Toxoplasma					
Varicella Zoster	in progress - EVU				
<i>Other markers</i>					
<b>Equipment</b>	<b>Equipment</b>				
'Open' serology processors					
'Closed' automated analysers					
NAT robotics					
Microplate washers					
<i>Other instrumentation</i>					

To make the scoring as simple as possible, please put up to five stars in the boxes in the table to indicate those evaluations that you consider high priority (no stars would indicate that you do not consider the evaluation worth doing).

MiDAS = Microbiological Diagnostics Assessment Service; EVU = Enteric Virus Unit

Evaluation of syphilis 'total', VZV IgG serology kits, and chlamydia NAAT kits are in already in progress or planned, so therefore do not need to be scored. In addition, HIV, hepatitis B, hepatitis C, and HTLVII/III kits have intentionally been omitted from the list as we particularly need to know which other markers or instrumentation are considered priority areas for evaluation.

Please photocopy this table and fax your scores to Dr Keith Perry (fax number 020 8358 3130) or post to the Evaluations and Standards Laboratory at the Health Protection Agency, Colindale.

centre is undergoing a strategic review. We would be grateful for your views on the need for evaluation services or any other comments that you would like to make as a result of reading this article.

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