

Device Bulletin

In Vitro Diagnostic Medical Devices Used in Combination

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1 Executive summary

In vitro diagnostic medical devices (IVDs) are often used in combination with other devices and equipment. Combining IVDs with other devices and equipment needs to be carefully planned and managed so that the combination does not impair the performance of any of the individual devices.

If you are planning to use IVDs in combination, you should be familiar with any restrictions and requirements set out by the manufacturers in the instructions for use. You may also choose to perform additional testing to support and supplement available evidence about the performance of the combination.

This Device Bulletin sets out:

- information that should accompany a CE marked IVD that is intended by the manufacturer to be used in combination with other devices and equipment
- some product characteristics to consider for general laboratory equipment
- actions to consider in order to verify that a combination is safe and does not impair the performance of any of the devices involved.

It is not intended to give advice on the use of IVDs in combination with other devices and equipment where such use is not intended by the IVD manufacturer.

This document does not constitute legal advice. If you have any doubt about your legal or professional obligations, you should consult your own advisors.

1.1 Who this document is for

This document is aimed at all professional staff who are responsible for using, purchasing, supplying, maintaining and replacing in vitro diagnostic medical devices (IVDs) including those used at the point of care.

It should be of particular interest to:

- all healthcare professionals performing point of care testing (POCT)
- ambulance trusts
- biomedical scientists
- chief executives and managers of primary care trusts
- clinical scientists
- directors of nursing
- directors of quality
- general practitioners
- healthcare scientists
- laboratory managers
- leads for clinical governance and clinical governance general managers
- medical directors
- nurse practitioners
- pathology directors
- pharmacists
- POCT co-ordinators

- purchasers of IVDs and general laboratory equipment
- scientists, technical and clinical staff in all disciplines of pathology laboratories.

2 Introduction

Following discussions with device users and manufacturers and from the analysis of adverse incident reports, the MHRA is aware that the use of IVDs in combination causes concerns and problems for some device users.

The MHRA has prepared this document to provide guidance on some of the issues that purchasers and users may want to consider when assessing whether devices can be used in combination with other devices and equipment. The bulletin advises on what steps you can take to verify that the combination has been validated for safety, quality and performance. As no guidance can cover all possible scenarios, you should always consider whether there are additional factors that you need to take into account.

This bulletin builds on and provides an update to previous MHRA publications, including:

- DB 2002(02) Management of in vitro diagnostic medical devices [1]
- DB 2002(03) Management and use of IVD point of care test devices [2]

Examples of device combinations

- Point of care blood glucose meters/strips with lancing devices.
- Reagent kits and automated laboratory analysers.
- Containers intended for storage and transport of samples including replacement caps.
- Sample collection and sample pre-treatment devices and reagents.
- 96-well ELISA plate used with an analyser.
- Blood grouping cards read using an automated card reader.
- Software interface between a laboratory analyser and a laboratory.

Manufacturers of IVDs that must be used in combination with another device or equipment have obligations under the In Vitro Diagnostic Medical Devices Directive (the IVD Directive) [3] relating to the information that they should supply to you.

The manufacturer must also retain evidence in their technical files to demonstrate that the IVD complies with the relevant essential requirements of the In Vitro Diagnostic Medical Devices Directive [3] when they intend the device to be used in combination with other devices and equipment.

3 Information provided by the manufacturer

3.1 The IVD Directive

The IVD Directive [3], which is implemented into UK law by the Medical Devices Regulations 2002 [4], details regulatory requirements dealing specifically with the safety, quality and performance of IVDs, thereby bringing them into line with other medical devices. In outline, the Directive is intended to ensure that IVDs do not compromise the health and safety of patients, users and third parties and that they attain the performance levels attributed to them by their manufacturer.

Performance

This document includes references to performance which is a term used in the IVD Directive [3] to include diagnostic sensitivity; diagnostic specificity; accuracy; analytical sensitivity; analytical specificity; repeatability; reproducibility and measurement range.

Definitions for these various terms can be found in various standards and the common technical specification. Full references are included in the bibliography.

Products for general laboratory use are not IVDs unless, in view of their characteristics, they are intended by their manufacturer to be used specifically for in vitro diagnostic examination (see article 1(b) of the IVD Directive).

Annex I of the IVD Directive [3] lists various 'essential requirements' with which IVDs must comply before being placed on the market/put into service. These essential requirements aim to ensure that IVDs:

- do not compromise the health and safety of patients, users and others
- are designed and manufactured so that they are suitable for the purpose specified by the manufacturer
- achieve the performances stated by the manufacturer.

Not all the essential requirements will apply to all devices and it is for the manufacturer of the device to assess which are relevant to the particular product. In determining this, account must be taken of the intended purpose of the device.

The CE marking on an IVD represents the declaration by the manufacturer that the device meets all of the relevant provisions of the Medical Devices Regulations [4].

3.2 Information supplied by the manufacturer of the IVD

If the device must be used in combination with or installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, then the manufacturer must provide sufficient details of its characteristics to identify the correct devices or equipment to use in order to

obtain a safe and proper combination (article 8.7(m) of Annex I of the IVD Directive [3])

Examples of good information provision by manufacturers

- The instructions for a syphilis enzyme immunoassay kit states that it can be used manually or with an automated pipetting station. The IVD manufacturer states the tolerances that have been determined for the kit for pipetted volume and incubation temperature so that a compatible pipetting station can be selected.
- The information for users of a manual immunoassay states that a water bath for incubation is required but not provided. The manufacturer states that the water bath used must be capable of maintaining 37 +/- 2 °C.
- An analyser used for processing an assay can take samples from various blood collection tubes. The manufacturer states the size range of sample tubes that are suitable for use on the analyser, as well as the types of tubes that are not compatible and cannot be used with the test.

If there is any uncertainty about the use of a particular combination, you should ask the manufacturers for advice. You can also ask for information on how the performance claims were generated to guide you in choosing a safe and effective combination.

3.3 Characteristics of the other device or equipment

The characteristics of the other device or equipment referred to in Annex I, section B 8.7(m) of the IVD Directive [3] might include:

- pipetting precision and accuracy
- temperature tolerances
- pH tolerance
- dimensional specification
- software version
- electric current/voltage
- timer accuracy
- compliance with standards specified by the device manufacturer
- spectral performance including:
 - wavelength accuracy
 - bandwidth
 - optical sensitivity
 - stray light
 - identity of monochromator and detector
- lux level and temperature of artificial lighting
- standardisation methodology
- voltage and current tolerance levels
- name and model number

If you intend to combine an IVD with general laboratory equipment to which the IVD Directive does not apply, then you should request this information from the IVD manufacturer or supplier.

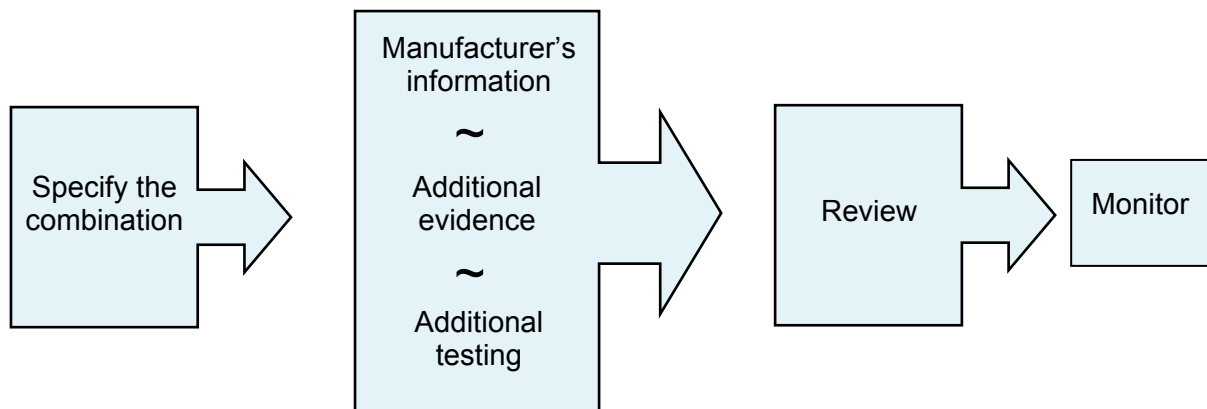
If you cannot ascertain the characteristics of the other devices or equipment, you will not be able to verify that it meets the requirements set out by the IVD manufacturer.

4 Verifying a safe combination

To verify that a combination is safe and does not impair the performance of any of the devices involved, you should consider the following actions:

- specify what combination will be used
- record and document the information provided by each manufacturer
- seek additional evidence
- determine the need for any additional validation and verification
- review the available evidence
- monitor the performance of the combination.

Flowchart



4.1 Specify what combination will be used

The combination can include any or all elements of the test system from obtaining the sample to releasing the result i.e. devices and equipment intended to be used for sample collection, sample storage, pre-analytical processes, analysis and post-analytical processes. It may include items that are regulated as medical devices and some that are not.

Example – sample collection tubes

Incorrect results have been reported when using blood collection tubes in combination with laboratory reagents and analysers. Some devices can be sensitive to the concentration of chemical agents including anticoagulants, surfactants and gels that are used in some blood collection tubes. Sample tubes may also have dimensions which make them unsuitable for use with some analysers. It is important to select a blood collection tube that is intended by the manufacturers for use with the test system.

Example – use of inappropriate swabs with a chlamydia test

False positive chlamydia results have been reported to the MHRA. The cause was found to be the swab used to take samples. The swab type was not recommended for this use either by the assay manufacturer or by the swab manufacturer.

Device Bulletin DB 2002(02) [1] sets out the need to draw up a technical specification prior to purchase. For devices used in a point of care setting, Device Bulletin DB 2002(03) [2] advises that there should be close liaison between users and the local hospital pathology laboratory on all issues relating to point of care testing. This should include issues related to point of care test devices that are used in combination with other devices and equipment.

4.2 Record and document the information provided by each manufacturer

If you are planning to use devices in combination you should be familiar with any restrictions and requirements set out by the manufacturers in the instructions for use.

If you need to use a device in combination but are unable to find the information, you might want to request this from the manufacturer. If the manufacturer is unable to provide you with this information, then consult the MHRA. If a product is CE marked and intended to be used in combination with other devices or equipment, failure by the manufacturer to provide certain information may be in breach of their obligations under UK law.

When you write your standard operating procedure (SOP) you should take full account of the procedures detailed in the manufacturers' instructions and operator manual.

Training and technical support

When the manufacturer gives you any training on how to use or set up the combination it is essential that you follow this advice and keep central records. It may be that the manufacturer gives you technical advice over the telephone rather than providing written instructions and this should also be logged. You should ask the manufacturer for written confirmation of any instructions or recommendations given either over the telephone or face to face.

Example – user-defined test programme

A laboratory based coagulation meter has the facility to allow the user to set up locally defined test programmes using different manufacturer's reagents. In one case, an incorrect and potentially fatal result was generated by the user-defined test programme. Although these parameters had been checked and agreed verbally with the meter manufacturer, neither the user nor the manufacturer had kept written records of the advice. It was not possible to confirm the cause of the incorrect result.

4.3 Seek additional evidence

Additional evidence regarding the use of the specified combinations might include safety warnings, evaluation studies, procedures and guidelines on the use of devices in combination and might be found in:

- MHRA publications (see www.mhra.gov.uk)
- peer reviewed journal articles
- Centre for Evidence-based Purchasing (NHS PASA) publications [5]
- national standard operating procedures
- national guidelines
- independent evaluations.

4.4 Determine the need for any additional validation and verification

You may choose to perform additional validation and verification in order to support and supplement the evidence that you have gathered.

Validation confirms that the test system is suitable for your intended purpose. Device Bulletin DB 2002(02) [1] provides more information on the validation of laboratory assays. Device Bulletin DB 2002(03) [2] provides more information on the validation of point of care tests.

Validation is defined as ‘confirmation through the provision of objective evidence that the requirements for a specific intended use or application have been fulfilled’ (ISO 9000:2005 [6])

Validation confirms that the test system* is suitable for your intended purpose. For example, you may wish to screen for viral infections in a particular patient group. For this population, you may have chosen an assay that meets your minimum performance criteria for diagnostic sensitivity and specificity for the detection of viral antibodies. You may also need to validate that the test system (including the assay) meets your requirements for screening for viral infections in your test population.

Device Bulletin DB 2002(02) [1] provides further information on validation of an assay for use in the laboratory.

*Elements of the test system might include sample collection, sample storage, pre-analytical processes, analysis and post-analytical processes and associated procedures. It may include items that are regulated as medical devices and some that are not.

Verification confirms that the device meets the requirements that you drew up in your specification. You can use additional testing to verify that the performance of the combination is comparable to the IVD manufacturer’s performance claims.

Verification is defined as ‘confirmation through the provision of objective evidence that the specified requirements have been fulfilled’ (ISO 9000:2005) [6]

Verification confirms that the device meets the requirements that you drew up in your technical specification. You might wish to verify that the actual performance of the device is comparable to the claims set out by the manufacturer. This might include requirements for diagnostic performance.

Device Bulletin DB 2002(02) [1] provides further information on drawing up a technical specification.

Examples of verification tests

Cross check critical settings loaded into an analyser against manufacturers’ instructions for use.

Run the new device in parallel with the old device. This could include several variables (e.g. different assays on a new instrument or different analysers in the same laboratory).

Run samples with known results – e.g. internal quality control samples, external quality control samples and sample panels to assess for discrepant results, cross reactions and carryover.

Run replicates to determine the accuracy of the new device.

Determine test specificity against samples known to be negative for the marker.

If the combination or components of the combination are altered after you have verified them then you may need to repeat the verification. You may also need to have a system in place to ensure that you are aware of any significant changes to components of the combination that could significantly affect the performance of the IVD.

It is essential that you keep records of all verification work. This should include any process carried out by you and any information provided by the manufacturer.

Device Bulletin DB 2002(02) [1] gives further advice on acceptance testing and user verification. This advice is particularly important if you need to establish new reference ranges for an assay. For devices used in a point of care setting, DB 2002(03) [2] advises that there should be close liaison between users and the local hospital pathology laboratory on all issues relating to point of care testing. This should include issues related to point of care test devices that are used in combination with other devices and equipment including the need for verification.

4.5 Review the available evidence

Before implementing the combination, you will need to review the available evidence.

You may decide that the combination meets your requirements or that further work is needed before the combination can be verified or that the specified combination does not meet your requirements. You should document your final decision.

4.6 Monitor the performance of the combination

You should monitor the performance of the whole combination as part of the normal requirements stated in your quality manual.

5 Adverse incidents

An adverse incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

The MHRA has two parallel reporting systems for device-related adverse incidents, one for manufacturers and another for users (<http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Devices/index.htm>)

We strongly encourage device users to report all adverse incidents to us. Analysis of adverse incident reports can help to reveal problems with IVDs that are used in combination with other devices and equipment.

By reporting to us we can:

- enable manufacturers to find solutions to device related problems
- disseminate advice to the healthcare professions to prevent adverse incidents and promote good practice for use and maintenance of devices
- collate information to identify trends in device safety and performance.

Manufacturers of IVDs are obliged, under the Medical Devices Regulations [4], to report certain adverse events to the MHRA.

See Medical Device Alert MDA/2008/001 'All medical devices' [7] for details on how to report incidents. This MDA is republished annually.

6 References and bibliography

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- 3 'The IVD Directive' Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices, Official Journal L 331 , 07/12/1998 P. 0001 – 0037 (available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:331:0001:0037:EN:PDF>)
- 4 The Medical Devices Regulations 2002. Statutory Instrument 2002 No. 618. ISBN 0110423178. <http://www.opsi.gov.uk/SI/si2002/20020618.htm> as amended by the Medical Devices (Amendment) Regulations 2003 (S.I. 2003 No. 1697)
- 5 Centre for Evidence-based Purchasing (NHS PaSA) <http://www.pasa.nhs.uk/PASAWeb/NHSprocurement/CEP/outputs/Labmed.htm>
- 6 ISO 9000:2005 Quality management systems – Fundamentals and vocabulary. ISO 2005. http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=42180
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BS EN ISO 13485:2003 Medical devices. Quality management systems. Requirements for regulatory purposes.

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Galen R.S., Gambino S.R. 'Beyond normality: the predictive value of medical diagnoses' John Wiley & Sons 1975

Sources of information

MHRA

<http://www.mhra.gov.uk>

European Commission medical devices homepage

http://ec.europa.eu/enterprise/medical_devices/index_en.htm

Health Protection Agency – National Standard Methods

<http://www.hpa-standardmethods.org.uk>

Clinical Pathology Accreditation (UK) Ltd

<http://www.cpa-uk.co.uk/index.htm>

United Kingdom Accreditation Service (UKAS)

<http://www.ukas.com>

British In Vitro Diagnostics Association (BIVDA)

<http://www.bivda.co.uk/Home/tabid/36/language/en-GB/Default.aspx>

US Clinical and Laboratory Standards Institute (CLSI) formerly NCCLS

<http://www.clsi.org>

Websites last accessed September 2008.