

REVIEWS
BULLETIN



*Management of
In Vitro Diagnostic
Medical Devices*



*An Executive Agency of the Department of
Health, Social Services and Public Safety*

*Áisíneacht Feidhmeannach don Roinn Sláinte,
Serbhísí Sóisialta agus Sábháilteacht Phoiblí*

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The Medical Devices Agency helps safeguard public health by working with users, manufacturers and lawmakers to ensure that medical devices meet appropriate standards of safety, quality and performance and that they comply with the relevant Directives of the European Union.

Our primary responsibility is to ensure that medical devices achieve their fullest potential to help healthcare professionals give patients and other users the high standard of care they have a right to expect.

The Medical Devices Agency is an Executive Agency of the Department of Health



The key objective of the Northern Ireland Adverse Incident Centre (NIAIC), part of Health Estates, is to record and investigate reported adverse incidents involving Medical Devices and equipment used in Health and Personal Social Services in Northern Ireland and to issue warning notices and guidance to help prevent recurrence and avert patient or user injury. NIAIC has direct links with MDA who co-ordinate across the adverse incident centres in England, Scotland, Wales and Northern Ireland. NIAIC also disseminates non-device related safety information in Northern Ireland.

Health Estates is an Executive Agency of the Department of Health, Social Services and Public Safety.

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1. EXECUTIVE SUMMARY

1.1 Who this document is for

The Northern Ireland Adverse Incident Centre (NIAIC) and the Medical Devices Agency (MDA) has produced this bulletin to address issues in the management of *in vitro* diagnostic medical devices (IVDs). It builds on and provides additional information to the NIAIC publication DB 9904 (NI) 'Medical device equipment management for hospital and community-based organisations'¹ but can also be used as a stand-alone document.

This document is aimed at all professional staff who are responsible for purchasing, supplying, using, maintaining and replacing *in vitro* diagnostic medical devices. This includes staff such as:

- Pathology Managers.
- Scientists, technical and clinical staff in all disciplines of pathology laboratories.
- Purchasers.
- NIAIC liaison officers and Trust Risk Managers (for onward distribution).

1.2 Scope

This bulletin addresses aspects that are important in the procurement of IVDs and in their safety, quality and performance. Purchasing and supply guidance is outside the scope of this document. This may be obtained from the Regional Supply Service of the Central Services Agency²

A number of the decisions involved in the management of IVDs can have an impact on the quality of the results produced and their usefulness in the clinical management of patients. This document particularly considers the importance of:

- obtaining meaningful performance evaluation data prior to making a purchasing decision;
- adequate in-house validation before a new testing system is introduced into routine use.

Reports received at NIAIC's and MDA's Adverse Incident Centres demonstrate that these two areas still continue to produce problems for some users.

This bulletin addresses issues surrounding the management of both CE marked IVDs (covered by the *In vitro* Diagnostic Medical Device Directive³ and the Regulations that implement it⁴) and, since this legislation will not be fully enforceable until 7 December 2003, those that in the meantime are not yet CE marked.

It identifies some of the different challenges that the new legislation brings. For example, under the IVD regulations, the responsibility of manufacturers increases, particularly with regard to clearly stating the performance claims for the device and where distributors are involved, in clarifying the respective responsibilities of the manufacturer and distributor.

The application of legislation is also complicated by different arrangements for the supply, ownership and use of IVD instrumentation, which may be lent or leased by suppliers.

When negotiating contracts for reagent rental, purchasers need to be aware that, depending on the length of the contract, it may cover the period during which CE marking becomes mandatory.

The Bulletin is focused on IVDs which, in the main, do not come into direct contact with patients but may nevertheless cause patients harm if they do not perform as intended. IVDs used in point-of-care testing are outside the scope of this device bulletin and are referred to in a separate NIAIC and MDA publication ⁵.

1.3 Key points

The user organisation should ensure that:

- **Users of IVDs and healthcare providers who use test results have appropriate input into purchasing decisions.**
- **The performance claims, maintenance, servicing arrangements, and software compatibility are considered at the stage of selection.**
- **Adequate levels of staff training are maintained.**
- **Appropriate user validation is undertaken prior to introduction for routine use.**
- The instructions for use are applicable to the user's situation.
- There is a system in place to manage device repair and maintenance.
- Adverse incidents are reported promptly to NIAIC.

2. INTRODUCTION

In vitro diagnostic medical devices (IVDs) can be described as the test kits and instrumentation that are used to carry out testing on human samples in order to assist in the making of a clinical diagnosis or decisions concerning clinical management. A European Union Directive was published in 1998 with the primary aim of creating a single market for such products³. Within the IVD Directive, definitions are given for a medical device, an *in vitro* diagnostic medical device, and manufacturer and supplier, which are applied throughout this document (see Glossary).

The following are some characteristics of IVDs that are pertinent to their management:

- The term IVDs covers a diverse range of products from individual reagents to testing systems that consist of reagents, instrumentation and software. Also included are accessories such as dedicated software, and control and calibration materials. IVDs differ from most general medical devices in that many do not come into direct contact with patients. Therefore they cannot cause direct harm to the patient if they fail to perform as intended. **However, if the results that are produced from testing are incorrect and are not recognised to be so, indirect harm can occur to patients through incorrect diagnosis or inappropriate treatment.**
- Where IVDs are used within a testing system and changing one component of the system may affect the performance of other parts of the system. Such a change therefore, requires reconsideration of whether it is appropriate to continue to use all the other components of the testing system. For example, when testing kits are changed do the swabs for patient sample collection also need to be changed? Is the Laboratory Information System (LIS) still fully compatible after analyser software upgrades have been obtained?

The UK regulations implementing the IVD Directive came into force on 7 June 2000 and include a transitional period until 7 December 2003, after which date manufacturers **must** comply with the legislation. IVDs which conform with existing national legislation already in the distribution chain at the end of the transitional period can continue to be supplied to the end user for a further two years (i.e. until 7 December 2005)⁶. Further information on the implications of CE marking to IVD management is given in section 3.

2.1 Best practice

Several principles of best practice should be applied in the use of IVDs:

- **Suitability for the intended purpose**
Until the IVD Directive is fully enforceable, IVD manufacturers are not required by law to state the performance characteristics of their device. It is, therefore, very important that appropriate information is obtained in the pre-purchase or pre-contract stages. In addition, it is important to be aware that, even with CE marked devices, there is not necessarily a requirement that clinical utility is demonstrated as a condition of placing an IVD on the market. This means that the onus is on the customer to assess whether the product is suitable for the use to which the results will put in the clinical management of patients. These aspects are covered further in sections 4, 5, 6 and 7.
- **Maintenance in a safe and reliable condition**
Device management includes not only strategies for the routine maintenance carried out by users and on behalf of the manufacturer but also monitoring and replacement of devices and appropriate training of all users. This is covered in more detail in section 8.
- **Reporting of adverse incidents that arise during use is covered in more detail in section 9.**

3. CE MARKING AND ITS IMPLICATIONS IN THE MANAGEMENT OF IVDs

3.1 CE marked and non-CE marked devices

The IVD Directive is the third of three New Approach European Directives aimed at creating a single market and reducing technical barriers to trade for medical devices. It introduces common regulatory requirements for IVDs across Europe, bringing them in line with other medical devices. It was published in the Official Journal of the European Communities in 1998³. It is implemented in the UK via the IVD Regulations 2000⁴. These new regulations introduce for the first time legislative controls dealing specifically with the safety, quality and performance of IVDs.

The IVD Regulations 2000⁴, came into force on 7 June 2000. Manufacturers have a transitional period of three and a half years until 7 December 2003 in which to continue to comply with the existing national requirements, or to comply with the Regulations and CE mark their devices. IVDs that are already in the distribution chain at the end of the transition period can continue to be supplied to the end user until 7 December 2005. This means that CE marked IVDs may be available at any time after 7 June 2000 but may be sold alongside IVDs that are not CE-marked. Manufacturers may not place on the market any IVD that is not CE marked after 7 December 2003, although distributors may continue to sell non-CE marked IVDs until 7 December 2005.

Further information about the implications of the IVD Directive can be found in the MDA bulletin⁶.

3.2 Implications of CE marking

3.2.1 No previous specific legislation for IVDs

In the management of IVDs it is important to understand the implications of CE marking. Prior to CE marking there has been no pre-market approval system for IVDs in the UK, although certain customer groups, such as the National Blood Authority, have introduced their own system for approving products that they deem appropriate to purchase for their own use. NIAIC along with the MDA operates a post-market surveillance system which relies heavily on users to report problems that they find in the use of IVDs (see section 9). In addition, the MDA funds an evaluation programme for medical devices that are already on the UK market. This provides independent third party assessment of the performance of the IVD, often carried out as a comparative evaluation between different products having the same intended purpose, with the aim of informing users' purchasing decisions.

3.2.2 What CE marking means with respect to performance claims

a) Claims must be made

The IVD Directive introduces certain requirements on manufacturers of IVDs. Essential requirements include the following criteria:

"[IVDs] must achieve the performances, in particular, where appropriate, in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer."³

b) Data must substantiate the claims

For any CE marked IVD the manufacturer must have data to demonstrate how the performance claims in terms of the above criteria have been established. In purchasing a CE marked IVD, therefore, the customer can expect clear performance claims to have been made and that the manufacturer has supporting data to demonstrate the claim. If customers have any concerns in this area then the MDA should be advised immediately. In the absence of CE marking the possibility exists that manufacturers may not make clearly defined claims concerning the performance of the product. In addition, the possibility exists that extensive validation data demonstrating an acceptable level of performance may not be available.

3.2.3 CE marking involves different conformity assessment routes

CE marking involves different levels of regulatory control for different IVDs.

For CE marked IVDs, the implications of CE marking may differ depending on the conformity assessment route that the manufacturer is required to use prior to CE marking the device. The Directive groups IVDs into four categories according to the risks associated with the relative dangers to public health and/or patient treatment by an IVD failing to perform as intended:

- General
- Self-testing
- Annex II List B
- Annex II List A

(Full details of which IVDs are to be found in which category are given in Appendix 1.)

Although the essential requirements are the same for all risk categories of IVDs, the route to obtaining a CE mark may be different.

a) General IVDs

For general IVDs, the manufacturer self-declares conformity with the relevant essential requirements of the directive. For the other three categories a third party independent assessment body, a Notified Body, will have been involved in assessing the product. The level of involvement is different for the different categories.

b) Self-test IVDs

A Notified Body must be involved in the assessment of aspects of the design and of the labelling of IVDs for self-testing.

c) Annex II List B

A Notified Body must be involved in the assessment of the manufacturer's Quality System and the design of the product. Common Technical Specifications (CTS) may be available.

d) Annex II List A

These are the most highly regulated IVDs. For these devices, a specification for evaluating both the performance of the product and of each batch is described in the Common Technical Specification (CTS) (to be published in the Official Journal of the European Communities). As a general rule manufacturers are required to comply with the CTS. An appropriately designated Notified Body is required to be involved in pre-market assessment and its agreement is required for the release of every batch. Further information can be obtained from the MDA. (See Appendix 2)

3.2.4 Suppliers who assign an IVD purpose to a product

Users should also be aware that where a supplier is purchasing products that do not fall within the definition of an IVD (eg because they are items of general laboratory equipment) but is providing them for IVD use, he may be changing the assigned use of the products to that of an IVD. During the transition period such products may or may not be CE marked. However, for any new contracts drawn up after the end of the transition period, where the supplier is assigning an IVD use to a product manufactured for general use, the supplier will be assuming the role of the manufacturer as defined under the IVD Regulations 2000⁴. It will, therefore, be the supplier's responsibility to ensure that the IVD is CE marked in demonstration of conformity with the relevant essential requirements of the IVD Regulations 2000⁴.

3.2.5 The CE marking process does not demand clinical utility

One aspect that is not necessarily demanded by the Directive is demonstration of clinical utility. It is therefore for the purchaser to assess whether the IVD, CE marked or not, is clinically useful.

4. IVD PROCUREMENT – SAFETY, QUALITY AND PERFORMANCE

This section addresses aspects of the selection process during procurement decision-making that may impact on the safety, quality and performance of the devices. It does not attempt to address wider issues of best procurement practice such as regulations implementing EU purchasing requirements, financial evaluations and purchasing specifications. Advice on such matters should be sought from the Regional Supplies Service of the Central Services Agency (see Appendix 2). Procurement or acquisition may be by, for example, purchasing, reagent rental or leasing.

4.1 Factors to be considered in the decision making process

4.1.1 Collecting data

The decision-making process of relevance to safety, quality and performance of IVDs is presented diagrammatically in Figure 1.

4.1.2 User experience

It is important to ensure that those who make purchasing decisions take account of the implications of all the relevant technical information.

This may be particularly relevant where devices such as swabs or specimen receptacles are purchased centrally eg within a Trust, because they may be:

- used by a large number of different healthcare professionals for different purposes;
- used with patients having different clinical conditions.

In addition, their performance characteristics may contribute to issues in

- their safe handling;
- the reliability of results of diagnostic testing.

(see Examples 1 and 2).

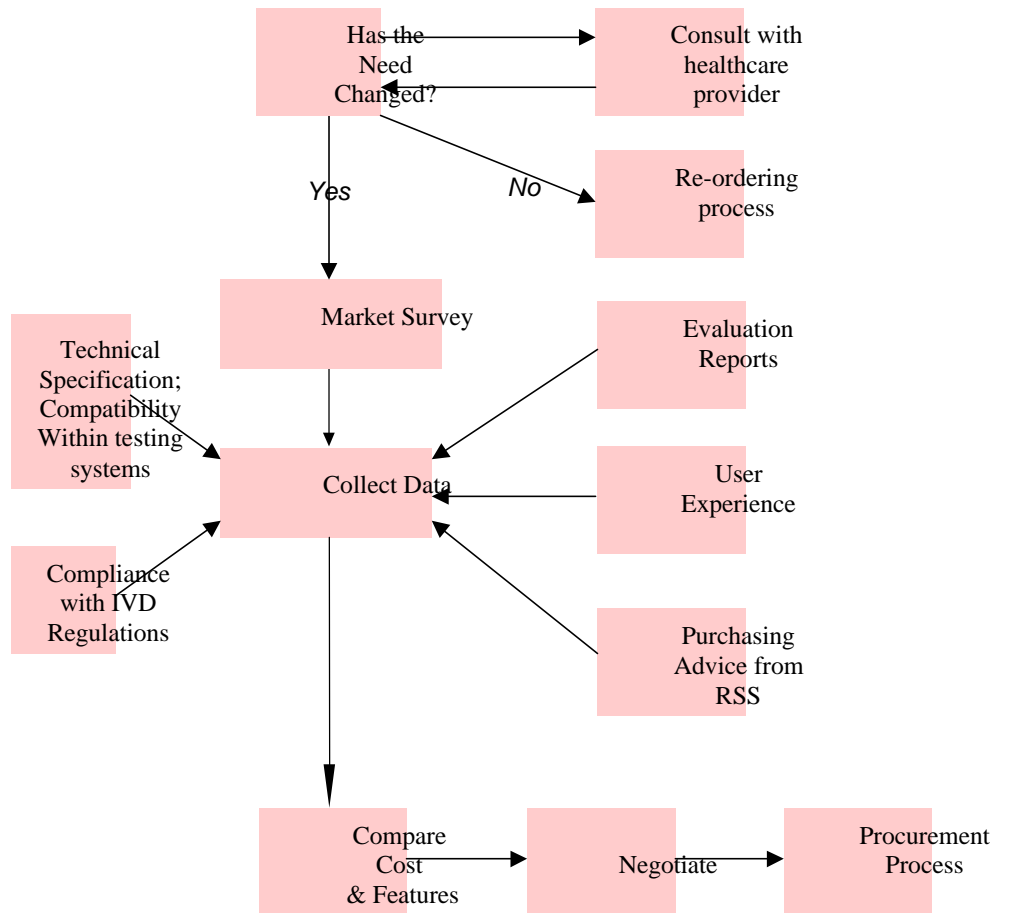
Example 1**Leaking specimen receptacles**

A central purchasing group introduced into the hospital specimen receptacles with which the laboratory had previously experienced leakages. The purchasing group, which did not include a laboratory representative, was resistant to the laboratory's requests to change supplier despite the laboratory reporting an unacceptable level of specimen leakages with use. The laboratory's perspective was not influential in the purchasing decision despite health and safety implications to laboratory staff of the use of unsatisfactory products.

Example 2**Swabs inappropriate with test kit**

A laboratory became aware of an increased number of chlamydia positive results with the chlamydia EIA assay that they had used for a number of years. The kit insert recommended a particular swab for sample collection but the laboratory had, for years, chosen to use a swab of its own choice without being aware of any problems. Investigation identified the cause of the false positives to be adhesive used to bind the swab to the stick. The swab manufacturer did not claim that the swab was suitable for this use and consequently did not control its raw materials for suitability with EIAs. The swab manufacturer amended the labelling to clarify that these swabs were not appropriate for such use. NIAIC issued a Safety Notice advising that appropriate swabs should be used.⁷

Figure 1: The decision-making process of relevance to safety, quality and performance of IVDs



* Regional Supplies Service - see Appendix 2

Healthcare providers who request testing for their patients should also be consulted to ascertain whether there are particular formats or tests that they require that may not otherwise be catered for.

4.1.3 Technical specification

The desired technical specification should be drawn up and compared with the performance claims made by the manufacturer. It may also be helpful to compare the manufacturer's claims with the actual data from which the claims have been derived. This is particularly recommended for IVDs on sale before the end of the Transition Period for the IVD Regulations and which have not been CE marked. A record of the claimed performance at the time of the purchasing agreement should be kept. [See section 5, Example 6]

It is also important to assess the instructions for use prior to purchasing to ensure that the method advised and therefore validated by the manufacturer is appropriate to the use to which the device is intended to be put in the laboratory (see Example 3). Further detail is provided in section 5 on Instructions for Use.

Additionally, the US organisation the National Committee for Clinical Laboratory Standards (NCCLS) produces standards and guidelines that may also prove helpful (see Appendix 2).

Example 3

Open system analyser with test kit designed for manual use

A supplier provided a laboratory on a reagent rental scheme with an open system analyser, designed by its manufacturer to automate EIA testing, and an EIA test kit manufactured by a different company for manual testing. The supplier did not have instructions for automated use of the kit nor validation data demonstrating the performance characteristics of the kit using an automated protocol. The laboratory thought they were buying a testing system that could be put straight into use to test patient's samples. Instead they inadvertently spent many months themselves developing and validating an appropriate automated protocol.

During the procurement process, it is important to consider carefully the implications of the servicing and response times on offer, the implications of this to the testing service, and whether there are alternative ways in which the testing service can be provided during unavoidable down-time.

Where an IVD has a software component, it is important to ensure that it is compatible with other software with which it may be required to interface (such as Laboratory or Hospital Information Systems (LIS or HIS)). The costs of such interfacing also need to be considered during the initial tendering process. See Example 4.

Example 4

An incident was reported which related to the interface between a LIS and an analyser, where data travelling along the interface had become corrupted and had blocked the interface. This resulted in delays in recognising clinically significant results. The incident was found to be connected with a recent software modification in the interface. The LIS manufacturer had not validated the modification for use with the analyser.

4.1.4 Commercial advice

Purchasing and supply guidance is outside the scope of this document. This may be obtained from RSS (see Appendix 2). Figure 1 represents a decision making process before consideration of the next stages of procurement and the development of collecting data. RSS will be able to provide best practice advice on specific areas of pathology. This will include offer documentation, specification templates, market knowledge, benchmarking and evaluation of offers.

4.1.5 Compliance with product specific regulations

Employers have duties to their employees. Medical devices must comply with the Medical Devices Regulations and, after 7 December 2003, IVDs must comply with the IVD Regulations 2000⁴. Further details of the IVD Directive³ and its implications are discussed in section 3.

Details of other relevant legislation (eg The Low Voltage and Electromagnetic Compatibility Directives^{8,9}, The Health & Safety at Work Order (Northern Ireland) 1978¹⁰, The General Product Safety Regulations¹¹, The HIV Testing Kits and Services Regulations 1992¹², The Radioactive Material (Road Transport) (Great Britain) Regulations 1996¹³) can be found in the MDA guidance document 'Sale and Supply of *In Vitro* Diagnostic Medical Devices.'⁶

4.1.6 Lease-purchase

Many of the pre-purchase processes are equally applicable to the operating lease of IVDs or to reagent rental.

5. INSTRUCTIONS FOR USE

Good clear instructions have a crucial role in the safe and effective use of IVDs.

5.1 Legal requirements

The General Product Safety Regulations 1994¹¹ apply to non-CE marked IVDs. They impose safety requirements on any consumer product for which there are no specific provisions in European law governing all aspects of the safety of the product. Under these regulations, IVDs may not be placed on the market unless they are safe. They include a requirement on producers to provide information to consumers. Requirements are also placed on distributors. For CE marked IVDs, the IVD Regulations 2000⁴ place clear requirements on the manufacturer in respect of supplying appropriate instructions for use and labelling.

Under the IVD Regulations 2000⁴, if a user reassigns the intended use of a CE marked IVD or modifies the instructions for use without the agreement of the manufacturer, they themselves become liable for any resultant performance failure that arises from such use of the device.

It is, therefore, essential that any Standard Operating Procedures (SOPs) that give instructions for use, exactly reproduce the manufacturer's instructions for how the device should be used, particularly for CE marked devices, and that all existing copies are updated as appropriate.

Clear responsibilities should exist for ensuring that essential information is given to all users (see Example 5). Situations where it may be particularly important to ensure that the users are aware of the current instructions for use include:

- where the device is used by individuals who may not routinely have access to the instructions for use;
- on-call staff.

In the event of litigation by a patient or their representative, user organisations may need to be able to call upon evidence that instructions were given to users in respect of equipment and upon documentary evidence that crucial steps in the process were, in practice, carried out (see Example 5).

Example 5

A laboratory entered into a contract with a supplier to provide a particular test kit. After some time, the performance characteristics of the test kit were found to have shifted giving rise to false negative results that were issued to patients. The manufacturer had made no specific claims for the performance of the product in the Instructions for Use. The laboratory could not find the evaluation data that they had used in the purchasing decision. In addition, although the laboratory believed it had followed the manufacturer's instructions for use, there was no clear laboratory record documenting crucial stages in the testing process. If legal action had been taken, the laboratory could have been in a vulnerable position.

5.2 Suitability of manufacturer's information

For CE marked IVDs, information supplied by the manufacturer is addressed in the essential requirements.

Whether the IVD is CE marked or not, users are entitled to instructions that are comprehensible in their national language. It is unsatisfactory for instructions to be provided in a poor translation which may obscure the meaning. See Example 6.

5.3 Manufacturer's revisions to instructions

It is important to:

- Ensure that manufacturers have the correct contact details for users of the device. Users should automatically be sent copies of revised instructions.
- Check with the manufacturer that revised instructions are appropriate to the products in service – there may have been software upgrades or changes.
- Have a procedure for keeping track of all the sets of instructions in use, and for replacing them with revised versions when necessary
- Ensure that all instructions deemed necessary by the manufacturer are provided in written form by the manufacturer using a formalised mechanism.

Increasingly, manufacturers of automated systems may provide revised instructions on-line. As with any revised instructions it is important to ensure that all users are fully conversant with the revision.

Revised instructions may arise out of problems with the previous instructions or changes to the product. It may be necessary to ensure, particularly for non-CE marked IVDs that, not only have the revised instructions a sound and adequately validated justification but that the possible implications of any problems in respect of test results previously obtained have also been assessed.

Possible implications for training needs in relation to instructions for use are considered in section 6.

Example 6

Poor translation of instruction manual into English

An analyser that was manufactured by a European manufacturer was distributed in the UK by four different companies. Although the instrument was sold under different names by the distributors in each case it was supplied with the manufacturer's own translation of the manual. This was poorly translated into English and none of the distributors had persuaded the manufacturer to obtain an improved translation. In a number of places the manual was very difficult to comprehend. The original manufacturer appeared unaware of the deficiencies in the translation and agreed to have the manual re-translated.

6. TRAINING

Guidance on the management of IVDs would not be complete without consideration of training. The effects of training in relation to the overall issues of laboratory performance are outside the scope of this document. However, the role of training in the safety, quality and performance of IVDs themselves is considered. Consideration has been given to instructions for use in the previous section where the importance of users following the manufacturer's instructions has been stressed and the need for appropriate and comprehensive training in following the manufacturer's instructions has been raised.

The obligation to provide appropriate training lies with the manufacturer. For CE marked IVDs this is identified in the essential requirements of the IVD Directive.³

However, the following aspects also require consideration:

- which individuals within the laboratory (out of the total number of individuals who will be working with the IVD) should receive the training offered by the manufacturer or supplier;
- how the remaining individuals will be trained, by whom and the timescale;
- when retraining is indicated;
- training of temporary or locum staff;
- training of on-call staff;
- future training needs in the event that those trained directly by the manufacturer/supplier change jobs;
- training updates in the event of instrument/software upgrades.

There is a separate NIAIC Device Bulletin that deals with IVDs used in a point of care setting⁵

If samples for which the method of collection is critical to IVD performance are collected by ward staff, it is important to ensure that ward staff are adequately trained and that retraining follows significant changes in the ward staff.

Users of IVDs should also be trained in the local system for identifying and reporting adverse incidents to NIAIC (see section 9)¹⁴.

7. ACCEPTANCE TESTING AND USER VERIFICATION

Inappropriate storage conditions can render devices unserviceable – inappropriate physical conditions (such as temperature, humidity, and presence of sunlight for some reagents) and stock rotation failures are some examples. Apart from possible dangers to the end users of the equipment, poor storage conditions also put the organisation at legal risk. Manufacturer's information and instructions both on storage conditions and shelf life should be followed.

Tests that need to be applied on delivery of a new product fall into three categories:

- Acceptance testing.
- Commissioning.
- User verification.

7.1 Acceptance testing

It may be particularly useful to carry out acceptance testing on instrumentation. It can weed out faulty product items which may have slipped through the manufacturer's quality assurance process, or which may have been damaged in transport or storage. They do not aim to test whether a given device model is suitable for its intended use – this must be done **before** purchase (section 4).

Laboratory instrumentation, such as analysers, which need to be installed and commissioned should have a comprehensive set of prescribed acceptance tests. Manufacturers may recommend certain forms of acceptance testing in the device manual. Electrical testing will also be necessary.

All equipment new to an organisation (on loan as well as newly purchased) should be checked before it is put into use for producing results on patient samples that will be issued to the attending clinician.

Figure 2 outlines the main aspects of acceptance testing, the main purposes of which are:

- to ascertain whether the device that was intended to be purchased is the same as the device that has been delivered;
- whether all the appropriate components have been delivered;
- whether in practice it is compatible with other aspects of the testing process;
- whether the instructions are adequate;
- whether any training that was given was adequate.

7.2 Commissioning

For complex instrumentation such as laboratory analysers this is usually carried out by the manufacturer, supplier or his representatives. In some instances the Trust's medical engineering department or pathology laboratory may be involved.

The purpose of commissioning is to set up the instrument so that it is in good and safe working order to put into service. Checks to ensure recommended practice in the installation of the device and to ensure electrical safety should be covered.

7.3 User verification

This process is described in Figure 3. It is the stage during which the user verifies that the performance of the device in his hands is comparable with the manufacturer's claims. This stage also provides the opportunity for comparing the performance of the newly delivered device with that of the testing system that has previously been in use to ensure that appropriate and reliable results are achieved with the new product. It provides the opportunity to assign QC ranges, assess training, write SOPs and determine consumable requirements. It is essential that this stage is carried out prior to introducing the new testing system for use in reportable patient sample testing. The new system can be compared with the previous system whether this previously involved in-house testing, using a different method, or sending samples away to another laboratory. Ideally, this should involve comparison with a recognised gold standard. Investing resources at this stage can minimise costly blunders in the future. For example, if the new system contains flaws that have not yet been identified and it is used for testing patients' samples, results may be issued before the problem is recognised. This may necessitate retesting of stored patients' samples or recalling patients (see Example 7).

Example 7

False results on introduction of a new testing system for rubella

A laboratory changed from a manual method for testing for antibody to rubella, to an automated system. They ordered the new system to be delivered before they had used up all the manual test kits so that the two testing systems could be compared. However, there were unanticipated delays in the delivery of the new testing system and the old product ran out just as the new product arrived. The laboratory switched from one system to the other without any period of assessing the performance of the new system against the performance of the old system. Within one month they had obtained 12 false negative results out of 48 patient samples, some of which had been issued to patients. Parallel testing of the new system with the previous one would have prevented these false results from being issued and would have allowed the teething problems with the new system to be sorted out without patient results being affected.

Similarly, software needs to be tested to ascertain whether in the local situation it behaves as intended by the manufacturer. With software there is the possibility that issues may not come to light immediately. The device software may interface with other software (such as LIS or HIS) and these may have been modified locally. The designers of either software may not have fully anticipated all the implications to other software with which communication is made. The supplier may also not have anticipated the full extent of validation testing required under these particular circumstances. This may hold for initial releases and for upgrades.

7.4 The role of a local specialist

It is important to bear in mind that, where a laboratory has a local specialist, that this individual makes a formal record of all strategic actions taken and leaves this behind if they leave the post. Some of the strategic actions that should be recorded include:

- introduction/modification of device;
- training needs;
- acceptance testing;
- connecting systems.

Such records can be important if there is a need subsequently to understand modifications that have been made in the past that may impact on IVD performance.

For example, incorrect patient results may arise where software designed by its manufacturer for a defined use is locally modified to broaden its application. Responsibility lies with the user to rigorously validate the performance of the software (including subsequent updates) in respect of use beyond that of its manufacturer's intended purpose. Where modifications have been made locally, the Trust will bear any liability issues.

Figure 2: Acceptance Tests

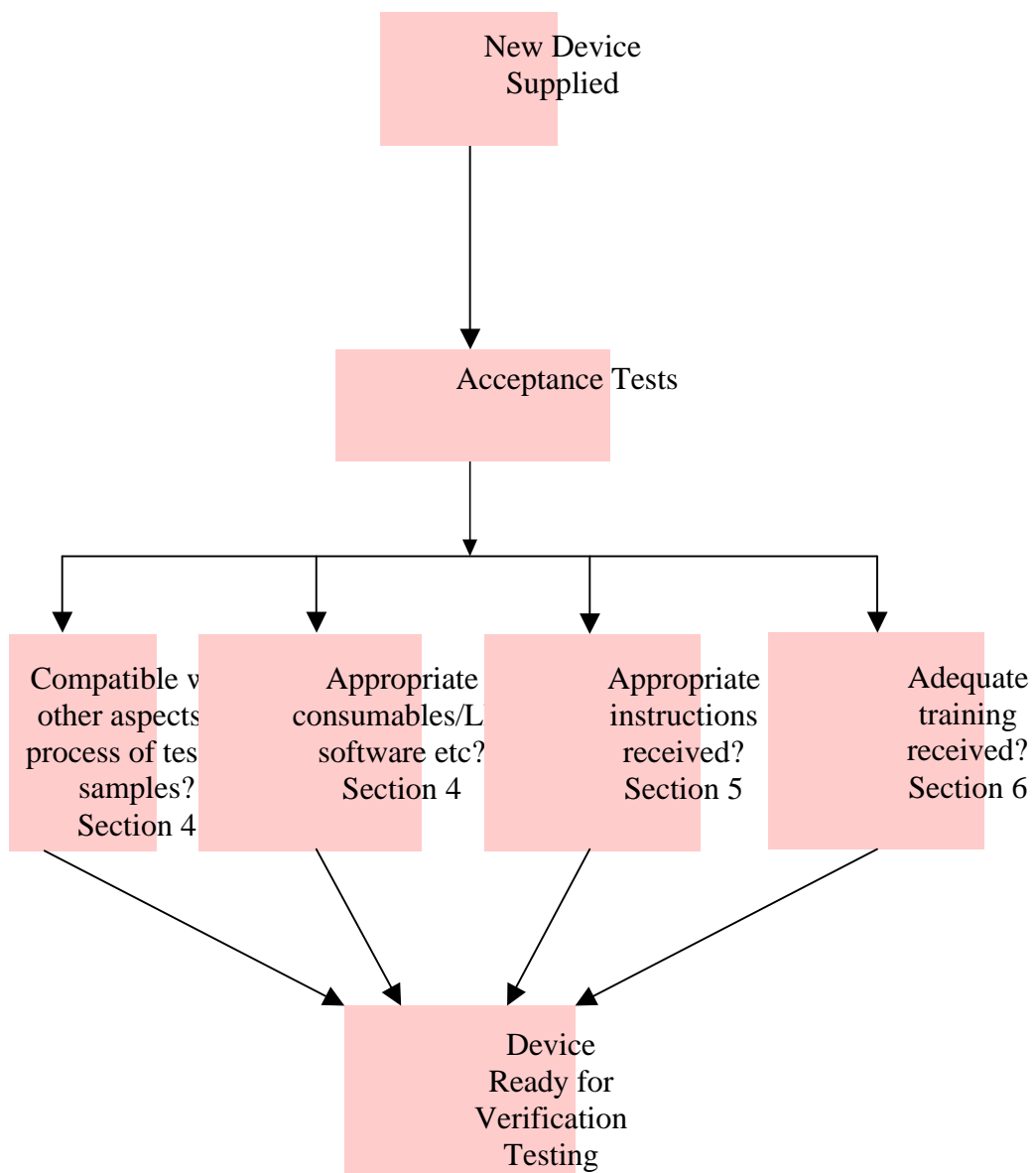
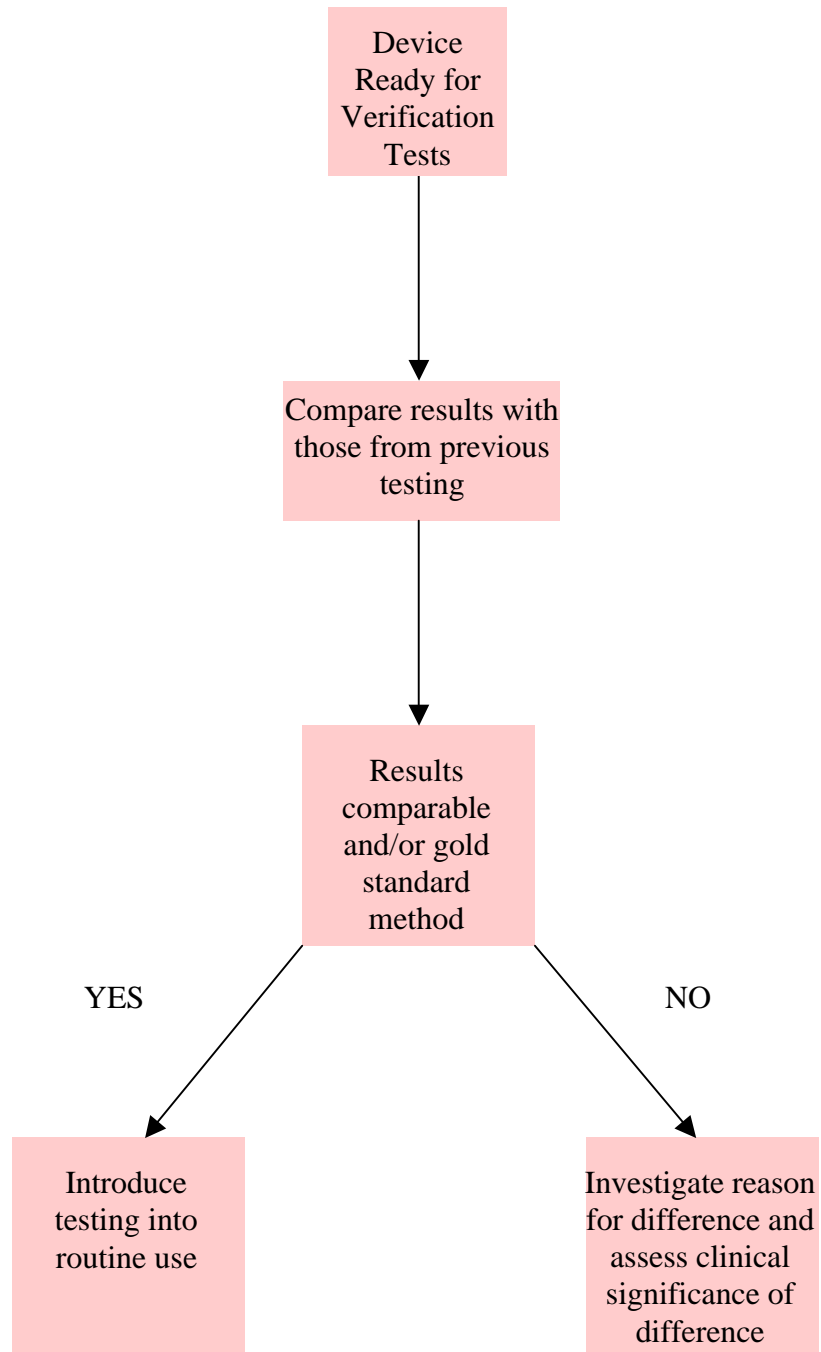


Figure 3: Verification Testing



8. MAINTENANCE AND REPAIR

Planned preventative maintenance should follow manufacturer's guidance on procedures and staff training. If this is not practicable for some reason, the manufacturer should approve changes, preferably before purchase.

Equipment that has been used for testing patient samples and which needs maintenance work must be cleaned and, where relevant, decontaminated before release. A failure to have effective procedures in place will put staff at risk and create a danger of legal liability being incurred. The Department of Health, Social Services and Public Safety has issued guidance on this subject¹⁵. Any departure from the manufacturer's recommendations will inevitably carry a risk of increased liability in the event of an adverse incident.

Where manufacturers or distributors themselves subcontract maintenance and servicing operations to a third party, it may be useful to clarify whether the subcontracted organisation is contractually obliged to report instrument failings to the distributor or manufacturer. If not, it may be possible for repeated problems to escape the attention of the manufacturer's design team.

Similarly, any contract with a third party servicing organisation should specifically address compliance with the manufacturer's recommendations by:

- the third party agreeing to follow the manufacturer's recommendations;
- including evidence that the manufacturer approves the recommendations;
- the third party accepting full liability for inadequate maintenance and maintenance induced faults.

8.1 Replacement of IVD instrumentation

A strategy is needed to help identify when to replace IVD instrumentation. Criteria suggested include:

- unacceptable levels of wear and damage;
- chronic unreliability;
- obsolescence;
- consumables no longer available.

8.2 Breakdowns

An efficient servicing organisation aims for rapid recovery from breakdowns. The simplest method is often to substitute a similar device in working order, although this is not always possible. However, increased stock levels can be set against the likely costs of, for instance, paying a third part servicing organisation for 24-hour fast response cover, or manufacturer's call-out fees for engineers.

Prior consideration can be given to the provision of an alternative verified testing service for periods of time when instrumentation may be out of action. This will help to safeguard against a backlog of untested specimens arising in the unexpected event of instrument failure. Alternative testing strategies to consider include out-sourcing, the use of a familiar and verified manual test, the use of alternative instrumentation including that held in a different local pathology discipline. Appropriate testing should, however, be carried out prior to introduction into service.

9. ADVERSE INCIDENT AND VIGILANCE REPORTING

9.1 Reporting adverse incidents

NIAIC along with MDA operate a voluntary adverse incident reporting system. This, along with the MDA-funded programme of evaluation of devices that are on the market, constitutes the post-marketing surveillance system that is operated as a means of safeguarding public health. It relies on users of all medical devices, including IVDs, to report adverse incidents to NIAIC in the first instance who then inform the MDA.

Adverse incidents have been defined as:

'incidents which produce, or have the potential to produce, unwanted effects involving the safety of patients, users and others'¹⁴.

The user organisation should ensure that there is a procedure for identifying adverse incidents and reporting them to NIAIC, that it is clearly documented in relevant policies and procedures, and that it is easily available to all staff. Detailed information concerning reporting to NIAIC and to other organisations involved with adverse incidents is available from NIAIC¹⁴.

With IVDs, it may not be immediately obvious to those observing an unusual result that the problem is with the device. The problem may only become apparent when several different laboratories are found to be experiencing the same phenomenon. For this reason, it is important to bear in mind, when reporting incidents, that the prompt reporting of incidents may be very important in preventing large-scale problems, and that other laboratories may have similar findings. NIAIC therefore strongly encourages all IVD users to report problems as they come to light even if the cause has not been clearly identified, so that NIAIC is aware of potential problems that may have nation-wide implications.

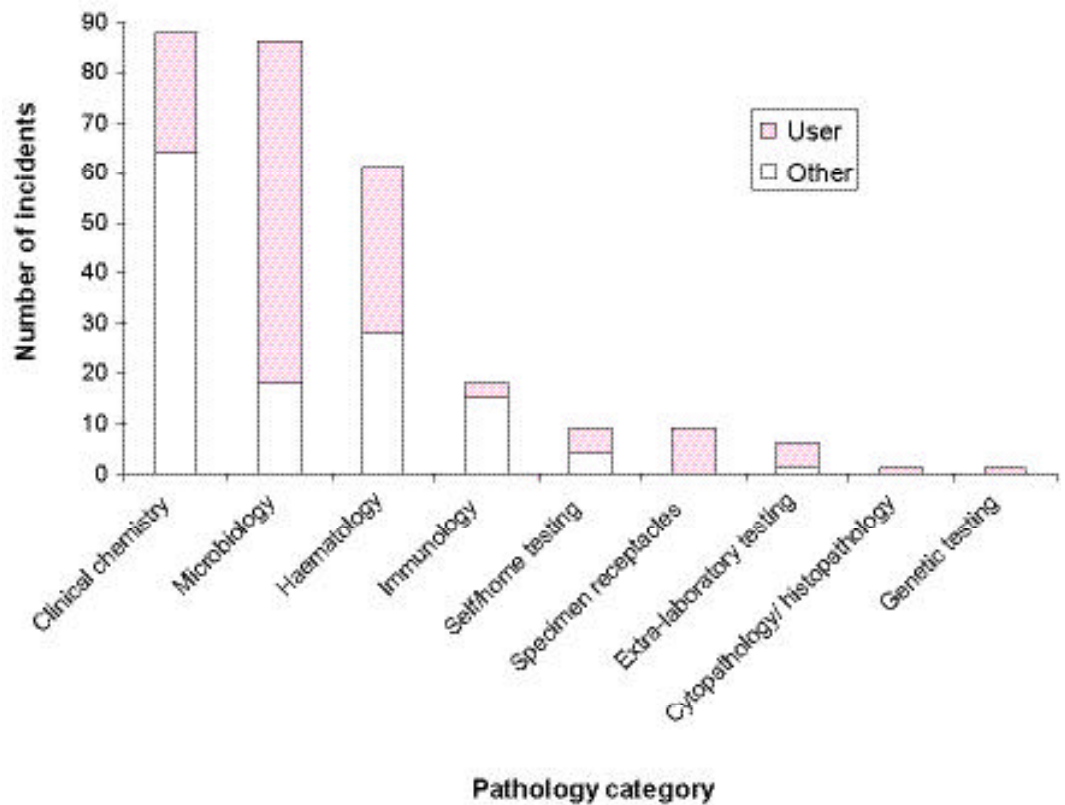
On receiving a report, NIAIC employs a risk assessment to identify which investigations clearly need a medical device specialist to carry them out and which can be pursued using standard letters to the manufacturer.

Of over 7896 adverse incidents reported to MDA in 2001, 279 concerned IVDs (approximately 3.5%). Figure 4 gives a breakdown per pathology discipline. Of the 279 IVD reports, 149 (53%) were received from IVD users. Of the remainder (shown as 'other' on figure 4), 63 were from manufacturers (22.6 %) and 57 from other regulatory bodies (20 %). Evidence to date suggests significant levels of under-reporting of incidents by IVD users. One of the implications of this is that individual laboratories may be using scarce resources to try to investigate problems themselves or negotiate solutions with the supplier when these activities could instead be addressed locally by NIAIC and at national level by the MDA.

A sample IVD Adverse Incident Reporting form is provided at Appendix 3.
A new on-line reporting facility is available on our website:
<http://www.dhsspsni.gov.uk/niaic>.

Further information on reporting adverse incidents concerning medical devices can be obtained from NIAIC (Details are provided in Appendix 2).

Figure 4: Number of incidents reported to the MDA for different IVD categories



9.2 Vigilance reporting under IVD Regulations

In addition to voluntary user reporting which covers all types of adverse incident related to medical devices, for CE marked IVDs the IVD Regulations 2000 contains reporting requirements for incidents that fall under the criteria of 'Vigilance'. If a manufacturer is aware of an incident involving a CE-marked IVD that has the potential to cause death or serious injury (whether to a patient, user or third party), there is a legal requirement for the manufacturer to report such an incident to the Competent Authority. In the UK the Competent Authority is the MDA.

Some differences between the user reporting system and the vigilance reporting system are listed below:

User Reporting System	Vigilance Reporting System
<ul style="list-style-type: none"> • Users report • Voluntary • Broad scope • No time limit on reporting 	<ul style="list-style-type: none"> • Manufacturers report • Required by law • Limited to cases where death or serious injury or the potential for these • Legal requirement for 'immediate' reporting

The MDA's experience with vigilance reporting under two previous medical device directives (covering active implantable medical devices¹⁶ and general medical devices¹⁷ respectively) has demonstrated that even with vigilance reporting, the MDA learns about a significant number of incidents, including ones that fulfil the vigilance criteria, initially through the user reporting system. It is, therefore, NIAIC's and the MDA's intention to continue to actively promote the importance of the user adverse incident reporting system to all users of medical devices.

10. CONCLUSIONS

In the management of IVDs the following aspects are critical:

- Choice of the IVD including critical assessment of the adequacy of performance data provided by the supplier.
- Appropriate use of the device, including:
 - adequate user verification prior to installation into routine use;
 - strict adherence to the instructions for use;
 - adequate training;
 - appropriate maintenance.
- Timely reporting of adverse incidents to NIAIC and the supplier.
- Recognition of legal liabilities including understanding of the implications of CE marking.

The commercial aspects of procurement and purchasing, though of fundamental importance, are outside the scope of this publication and advice should be sought from Regional Supplies Service (see Appendix 2).

Inadequate performance validation by the manufacturer has, on occasion, resulted in users finding themselves validating the product prior to being able to use it for routine testing. This may make unanticipated demands on the laboratory. Failure to report adverse incidents to NIAIC in a timely manner may give rise to wider continuing use of an inappropriate product.

The introduction of CE marked IVDs to the European market should result in clarification of the performance characteristics of IVDs and will introduce specific legislation for this device sector. The legislation covers both pre-market criteria and post-market vigilance reporting.

Consideration of laboratory management and the provision of the laboratory testing service are outside the scope of a NIAIC publication.

11. GLOSSARY

Competent Authority

The Competent Authority is the body responsible for implementing the requirements of a European Directive in each Member State. In the UK, the Competent Authority for the IVD Directive is the Secretary of State for Health acting through the MDA. The Competent Authority's main role is to ensure that manufacturers comply with the IVD Regulations, to evaluate adverse incident reports received from manufacturers, and carry out pre-clinical assessment of devices intended for clinical investigation.

CE mark

The CE mark means that a manufacturer is satisfied that his product conforms to the relevant essential requirements of a European Directive and that it is fit for its intended purpose.

Common Technical Specification (CTS)

For products in List A of Annex II of the IVD Directive (and some products in List B) conformity assessment may involve the use of Common Technical Specifications (CTS) to establish performance evaluation and re-evaluation criteria, reference methods and reference materials. CTS are drawn up by an expert Group convened by the European Commission. Manufacturers are expected to comply with the CTS. If they have duly justified reasons for not doing so they must adopt solutions that they can prove are at least equivalent to the CTS in terms of the above criteria.

Hospital Information System (HIS)

A database application used for managing hospital information.

***In vitro* diagnostic medical device (IVD)**

The term '*in vitro* diagnostic medical device' means 'any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures^{3,4}

Manufacturer

An organisation with responsibility for the design, manufacture, packaging and labelling of a device. (A more detailed definition can be found in the *In vitro* Diagnostic Medical Device Directive 98/79/EC³).

Medical device

The term 'medical device' means: 'any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process,^{3,17}
- control of conception

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.'

Laboratory Information System (LIS)

A database application used for managing laboratory information.

Notified Body

A Notified Body is a certification organisation which the Competent Authority designates to carry out one or more conformity assessment procedures described in the annexes of the Directive. Notified Bodies must be qualified to perform the functions for which they are designated and are monitored by the designating Competent Authority.

Supplier

The manufacturer, or their authorised representative.^{3,4}

Transition period

The period of time allowed in the Directive before CE marking is fully enforceable and during which manufacturers may start to CE mark their products.

12. REFERENCES

1. Device Bulletin DB 9904 (NI) 'Medical Device and Equipment Management for Hospital and Community-based Organisations'.
2. Regional Supplies Service
77 Boucher Crescent
Belfast
BT12 6HU
3. Official Journal of the European Communities L331, 7.12.98 p1-37 Directive 98/79/EC of the European Parliament and of the Council of 27th October 1998 on *in vitro* diagnostic medical devices.
4. The *In vitro* Diagnostic Medical Device Regulations 2000, Statutory Instrument 2000 No 1315 ISBN 0110992601.
5. Device Bulletin DB(NI)2002/03 Management and Use of IVD Point of Care Test Devices.
6. MDA Directives Bulletin No. 12 Sale and Supply of *In vitro* Diagnostic Medical Devices (IVDs).
7. NIAIC Safety Notice SN(NI)98/40. Swabs for Sample Collection. July 1998.
8. The Low Voltage Directive – Official Journal of the European Communities L77, 26.3.73 p29-33 Council Directive 73/23/EEC of 19 February 1973 on the harmonisation of the laws of the Member states relating to electrical equipment designed for use within certain voltage limits.
9. Electromagnetic Compatibility Directive – Official Journal of the European Communities L139, 23.5.1989 p19-26 Council Directive 1989/336/EEC of 3 May 1989 on the approximation of the laws of the Member states relating to electromagnetic compatibility.
10. The Health and Safety at Work Order (Northern Ireland) 1978
11. The General Product Safety Regulations 1994, Statutory Instrument 1994 No.2328 ISBN: 011045328X
12. The HIV Testing Kits and Services Regulations 1992 Statutory Instrument 1992 No. 460 ISBN: 011023460X
13. The Radioactive Material (Road Transport) (Great Britain) Regulations

1996 Statutory Instrument 1996 No. 1350

14. NIAIC publications that give further information about our role and responsibilities include:
 - DB(NI) 2002/01 Adverse Incident Reports 2001
 - Safety Notice SN(NI)2002/01 Reporting Adverse Incidents Relating to Medical Devices, Non-Medical Equipment, Buildings and Plant, January 2001
15. PEL(94)34 'Decontamination of Equipment prior to inspection, servicing and repair.'
16. Official Journal of the European Communities No. L189, 20.7.1990, p17-36 Council Directive 1990/385/EEC of 20 June 1990 on the approximation of the laws of the Member states relating to active implantable medical devices.
17. Official Journal of the European Communities No. L169, 12.7.1993, p1-43 Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

APPENDIX 1 CATEGORIES OF IN VITRO DIAGNOSTIC MEDICAL DEVICES:

- General IVDs.
- IVDs for self-testing.
- Annex II List B IVDs i.e.
 - reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd;
 - reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies;
 - reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis;
 - reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria;
 - reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia;
 - reagents and reagent products, including related calibrators and control materials for determining the following HLA tissue groups: DR, A, B;
 - reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA;
 - reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy 21;
 - the following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar.
- Annex II List A IVDs i.e.
 - reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell;
 - reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV1 and 2), HTLV I and II and hepatitis B, C and D.

APPENDIX 2 CONTACTS

NIAIC

Health Estates
Estate Policy Directorate
Stoney Road
Belfast
Tel: 028 90 523704
Fax: 02890 523900
E-mail: NIAIC@dhsspsni.gov.uk
<http://www.dhsspsni.gov.uk/niaic>

Current guidance for reporting such incidents is contained in NIAIC's Safety Notice SN(NI)2002/01, dated 7 January 2002.

Regional Supplies Service of the Central Services Agency

77 Boucher Crescent
Belfast
BT12 6HU
Tel: 02890 667799
Fax: 02890 668989

National Clinical Chemistry Laboratory Standards (NCCLS)

940 West Valley Road
Suite 1400
Wayne
PA 19087
USA

Tel: +1 610 688 0100
Fax: +1 610 688 0700
Website: <http://www.nccls.org>

APPENDIX 3 ADVERSE INCIDENT REPORT FORM

FORM A3 ISSUE 1 OCTOBER 2001 – *IN VITRO* DIAGNOSTIC MEDICAL DEVICES

Please tick the appropriate boxes

Origin of report

Hospital / Institution
Address
Laboratory.....
Reporter
Position
Telephone number.....
Consultant-in-charge.(if known).....
Local reference number (if available).....
.....
This report confirms a telephone report <input type="checkbox"/> a fax report <input type="checkbox"/> neither <input type="checkbox"/>

Device description (tick one box only)

<input type="checkbox"/> Clinical Chemistry	<input type="checkbox"/> Microbiology	<input type="checkbox"/> Self/Home Testing
<input type="checkbox"/> Haematology	<input type="checkbox"/> Cytopathology/Histopathology	<input type="checkbox"/> Genetic Testing
<input type="checkbox"/> Immunology	<input type="checkbox"/> Extra-Lab Testing	<input type="checkbox"/> Specimen Receptacle
Product		
<input type="checkbox"/> Test kit - Colorimetric	<input type="checkbox"/> Instrumentation/ Software	<input type="checkbox"/> Calibrators
<input type="checkbox"/> Test kit - Immunoassay	<input type="checkbox"/> QC Materials	<input type="checkbox"/> Reagent
<input type="checkbox"/> Test kit - Other		<input type="checkbox"/> Reagent strip

Details of device - Instrumentation

Product Name		
Model		
Manufacturer		
Supplier	Telephone no:	
Serial No	Approximate age	
Is there a CE mark? Yes <input type="checkbox"/> No <input type="checkbox"/>		

Details of device - Kits, reagents and specimen receptacles		
Brand Name		
Analyte / Marker		
Manufacturer		
Supplier		
Batch No		Expiry date
Is there a CE mark? Yes <input type="checkbox"/> No <input type="checkbox"/>		

Nature of defect / details of incident	
Contact name for further details	
Telephone number	

Action taken by staff / manufacturer / supplier

Further details can be given on additional sheets if necessary

FORM A3 OCTOBER 2001

Please send completed form to: NIAIC, Health Estates, Estate Policy Directorate, Stoney Road, Dundonald, Belfast BT16 1US Tel: 02890523704, Fax: 02890 523900, e-mail: NIAIC@dhsspsni.gov.uk

DISTRIBUTION

This Device Bulletin should be brought to the attention of all professional staff with responsibility for purchasing, use and maintenance of *in vitro* diagnostic medical devices. This will include: managers of scientific, technical and clinical staff; scientists, clinicians, and those with technical roles in all disciplines of pathology laboratories; purchasers of IVDs; NIAIC liaison officers (for onward distribution) and Trust Risk Managers.

TECHNICAL ENQUIRIES

Enquiries regarding the content of this Device Bulletin should be addressed to:

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FURTHER COPIES

Further copies of this Device Bulletin are free to Health and Social Care providers and may be obtained on written request from:

Northern Ireland Adverse Incident Centre (NIAIC)
Estate Policy Directorate
Health Estates
Estate Policy Directorate
Stoney Road
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Fax: 028 9052 3900

This document is also available on the NIAIC Website at: www.dhsspsni.gov.uk/niaic

Health Estates

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Áisíneacht Feidhmeannach don Roinn Sláinte, Serbhísí Sóisialta agus Sábháilteacht Phoiblí*

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