BIVDA

Safe and consistent? The regulation of pathology testing

The first audit of in-house testing in pathology laboratories across the NHS

November 2012

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Executive summary

70% of clinical decisions in the NHS are based on the results of laboratory or point of care tests, using in vitro diagnostic (IVD) products. The accuracy and reliability of such tests is therefore central to the successful diagnosis, treatment and management of patients.

However, current regulation only applies to those IVD tests which have been developed by commercial manufacturers. Tests developed by the NHS in-house i.e. within pathology laboratories of individual NHS trusts, are exempt from regulation. As such in-house tests are not subject to the same regulatory requirements as commercially developed tests. There is, therefore, not the same guarantee of quality, performance or safety.

As the trade association representing the IVD industry, the British in Vitro Diagnostics Association (BIVDA), is engaging in a constructive dialogue with its members, pathology professionals, the NHS, the Department of Health and the Medicines and Healthcare products Regulatory Agency (MHRA) around the issue of in-house testing in order to develop workable proposals to ensure that quality, performance and safety of IVD tests are kept to a high standard.

BIVDA is not opposed to in-house testing. Many tests which have been developed in-house have gone on to be used widely throughout the NHS and have led to significant health benefits for patients. Several in-house tests have been developed as a result of innovative practice within pathology laboratories and BIVDA strongly supports the spread of innovation through the NHS. However, there is no central record of the extent of use of these tests in the NHS, or the safety and reporting mechanisms that are in place to promote their safe use.

To obtain a clearer picture of the extent of in-house testing in the NHS, BIVDA launched an audit during 2012 of NHS providers, asking them the extent of use of in-house tests in their pathology laboratory, as well as any guidelines or safety practices they have in place to manage their use. This report is based upon the results of that audit and it has been published by BIVDA as a contribution to the development of public policy about the future regulation of in vitro diagnostics.

Through this audit we found that half of NHS providers reported that they used tests which had been developed in-house. Based on the volumes of in-house tests which trusts reported that they had carried out over the past two financial years, it is evident that, at the very least, well over 1 million tests per year are carried out across the NHS which are not CE-marked. The actual figure is likely to be much higher as many trusts did not provide data.

We also found that in-house testing is also not restricted to a limited number of conditions or clinical areas. In-house tests are being used widely across many different testing areas. In addition, very few trusts had guidelines or safety reporting practices particularly tailored to in-house testing. This gives cause for concern as these tests are being used outside of the existing regulatory framework.

While we recognise that many trusts have developed their own standard operating procedures for tests developed in-house, there are inconsistencies in approach which makes it hard for clinicians and commissioners to have a clear picture of the tests which are being used.

The regulatory environment is currently being reviewed at European Union (EU) level, and it is clear that the exemption for in-house tests where there are no commercial alternatives is likely to remain. This could be the case when a disease is very rare or only newly discovered.

We believe that the results of this audit show that there is a need to put in place further and more robust measures around in-house testing to ensure that everyone whose care is based on an IVD can be confident in the service they are receiving.

Key findings

- Around half of NHS providers acknowledged that they used tests developed in-house
- Large volumes of tests across many different conditions are being used in the NHS without being subject to the same rigorous regulatory standards as those which are sold commercially to the NHS
- The extent of in-house testing varies widely across NHS providers both in terms of the numbers of tests but also the clinical areas and conditions where such tests are used
- There were no significant discernible variations in-house of in-house testing between trusts, which include teaching hospitals and trusts which were constituted by district general hospitals
- As in-house tests are being widely used outside of the regulatory framework, there is no guarantee of the safety, reliability or accuracy of test results for NHS patients

Recommendations

- Where providers take the decision to use in-house tests, this decision should be explained according to clear criteria. Commissioners of services, and clinicians requesting tests, should be made aware of the decision to use an in-house test and the reasons for it
- To ensure transparency, all providers should publish information on the in-house tests they use, including the reasons that the test has been used, in their annual quality accounts
- The Medicines and Healthcare products Regulatory Agency (MHRA) should establish a publicly accessible register of in-house tests, updated on a monthly basis and containing information on:
    - the type of test
    - the patient population for which the test will be used
    - the reason that an in-house test has been used
    - whether or not a risk-assessment has been carried out by the pathology laboratory
- All providers should be required to report safety incidents relating to in-house tests to the MHRA. Where an issue is identified with a particular in-house test its use should be stopped immediately, with full details provided to the MHRA
- Where a safety issue with an in-house test is reported, the MHRA should alert all pathology laboratories to prevent the same errors occurring

- Where tests are used without a CE mark, NHS providers should be required to develop standard operating procedures for their use to ensure that they are used in a consistent and safe way. The Medicines and Healthcare products Regulatory Authority should develop a template for providers to develop standard operating procedures for tests used without a CE mark

- Pathology laboratories should put in place an approach to the use of non CE-marked tests, setting out:
    - The circumstances in which they will be used
    - The guidelines which should be put in place for any newly developed in-house tests
    - Audit mechanisms to ensure the safety and performance of in-house tests

- Where test results are generated by the use of in-house tests, the clinician using the test should be made aware. Clinical commissioning groups should make this a requirement of providers in their contract negotiations

Introduction

In vitro diagnostic (IVD) tests are used for early detection or diagnosis of disease, screening for disease pre-disposition and for the monitoring of treatment and disease management. They are vital to the NHS in supporting the improvement of outcomes for patients and in enabling the efficient use of resources. 70% of clinical decisions are based on the results of laboratory or point of care tests, using IVDs.

Many IVDs are developed in regulated commercial manufacturing environments. Others are developed within NHS laboratories – these are called in-house tests. They are developed outside of the regulatory environment established by the European In Vitro Diagnostic Medical Devices Directive.

To ensure the quality, performance and safety of IVDs across the EU, the Directive on In Vitro Diagnostic Medical Devices (Directive 98/79/EC) set out a common regulatory environment. The Directive requires that tests hold a CE mark to demonstrate that they conform to the requirements set out in the directive.

In-house testing can include using combinations of reagents developed in-house, using commercially developed tests for uses other than those for which they are CE-marked, using tests intended for research purposes for general use or using commercial reagents and instruments in a combination that has not been regulated by CE-marked.

There is a place for the use of in-house testing within the NHS. Where existing CE-marked tests are not available the use of in-house tests can offer an opportunity to innovate and develop new diagnostics. This is particularly the case for rare conditions. Many commercial tests in fact have their origins in in-house testing.

The development and then marketing of in-house tests could therefore offer a potential financial income to the NHS in the future and could provide the basis of even more effective partnership working in the future between the NHS and industry.

However, it is important that the use of in-house tests does not compromise quality, performance or patient safety. We believe that there is, therefore, a need to more closely regulate and performance-manage the use of in-house testing within the NHS. In the same way that commercial tests must meet high standards of accuracy and safety, so should those that are used in-house.

The use of in-house testing is a long standing practice within the NHS, and yet the extent of the practice has never been fully assessed or quantified. This audit represents the first assessment of the use of in-house testing across the NHS in England, its scope and the safety and performance requirements that are in place at a local level.

About BIVDA

BIVDA is the national industry association for the manufacturers and distributors of IVD products in the UK. We represent more than 90% of the IVD sector in the UK. Our membership includes subsidiaries of multi-nationals, UK SMEs and a number of start ups. BIVDA member companies

employ more than 8,000 people directly in the UK and provide the tests and equipment to the NHS to allow rapid diagnosis.

70% of clinical decisions are based on the results of laboratory or point of care tests, using IVD products. IVDs also enable screening for disease, identifying, monitoring and managing treatment and are vital to ensure the safety of the blood supply for transfusion. Increasingly diagnostics are available for use in a primary care setting and to enable people to manage their own diseases from home. This reduces the need for hospitalised care and will improve quality of life for much of the population. IVDs can be used to predict and prevent onset of disease and they can help ensure the appropriate and effective use of drugs and other NHS resources.

Methodology

To develop a picture of in-house testing in England, BIVDA commissioned the health policy consultancy MHP Health Mandate to undertake a Freedom of Information Act 2000 (FOI) audit of local NHS organisations. In order to be clear to NHS organisations about the scope of the research the definition of in-house tests used was: 'pathology laboratory tests developed in-house that are not regulated by CE marking'.

To test the level of information which might be held across the NHS, MHP sent a pilot FOI request to a small sample of primary care trusts (PCTs) and NHS providers. These were selected on the basis of a geographical, urban and rural spread across the NHS in England. The purpose of the sample FOI was to establish the level of information held by PCTs as commissioners and NHS providers and to enable the scope of the research to be refined.

Questions were sent to five PCTs and to five NHS providers. PCTs were asked about the processes they have in place to ensure quality, and the guidance that they provide to NHS trusts on the use of in-house tests. NHS providers were asked about the extent to which they use tests that are not regulated by CE marks, use of tests off-label and use of tests intended for research purposes only for general use.

No further questions were sent to commissioning organisations, as the findings of the sample audit suggested that the amount of relevant information held by commissioners was limited. None of the commissioners we asked directed us to guidance they have in place on the use of in-house testing by their providers.

A revised set of questions was sent to 167 NHS providers in August. These were structured around three themes:

- Extent of practice
- Information on safety incidents
- Guidance for pathology testing

The full questions are included in Annex 1.

In total 137 NHS providers out of 167 to whom we sent questions responded to the FOI[1]. This represents a response rate of 82%. 30 providers did not provide any response to the request for information. 14 providers responded that they do not perform pathology testing, and so have been excluded from the analysis.

This report represents the analysis of these questions. It is important to note that public organisations are not duty-bound to provide information in a set format. The information provided has therefore been subject to analysis and interpretation by BIVDA and MHP Health Mandate.

The regulation of in vitro diagnostic testing

In the early 1990s it was agreed that there should be a pan-European Union regulatory system for IVDs. Regulations were developed under the umbrella of the Medical Device Directives with the In Vitro Diagnostics Medical Device Directive (98/79/EC) coming fully into force across the EU in December 2003. The Directive (98/79/EC) was implemented into UK legislation by the Medical Devices Regulations Act 2002.

The Directive (98/79/EC) defines an IVD as:

"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

The Directive also includes essential requirements with which IVDs must comply before being placed on the market. The essential requirements aim to ensure that the products do not compromise the health and safety of patients and users, and are designed and manufactured to achieve the performance specified by the manufacturer for the stated medical purpose. According to the MHRA's guidance[2], not all the essential requirements will apply to all devices and it is up to the manufacturer of the device to assess which are appropriate for their particular product.

The Directive contains an exemption for in-house tests which states "reagents which are produced within health-institution laboratories for use in that environment and are not subject to commercial transactions are not covered by this Directive"[3]. This allows the NHS to continue to produce tests without regulation, as long as they are for use within the same healthcare institution.

The Directive is now under revision. A recent Department of Health consultation set out that the aim of the revision is to address acknowledged weaknesses in the current regulatory system. This includes weaknesses brought to light during recent events with faulty breast implants and metal-on-metal hip replacements. The consultation acknowledges that there is a need improve the quality and safety of devices by strengthening controls on the organisations which assess the safety of devices, increasing transparency and making the surveillance of the safety of devices more robust[4].

CE marking

The CE mark is a declaration by the manufacturer which denotes that the product conforms with the requirements of relevant legislation stemming from EU Directives. Under the Directive, all IVDs

must be CE-marked before they may be placed on the market.

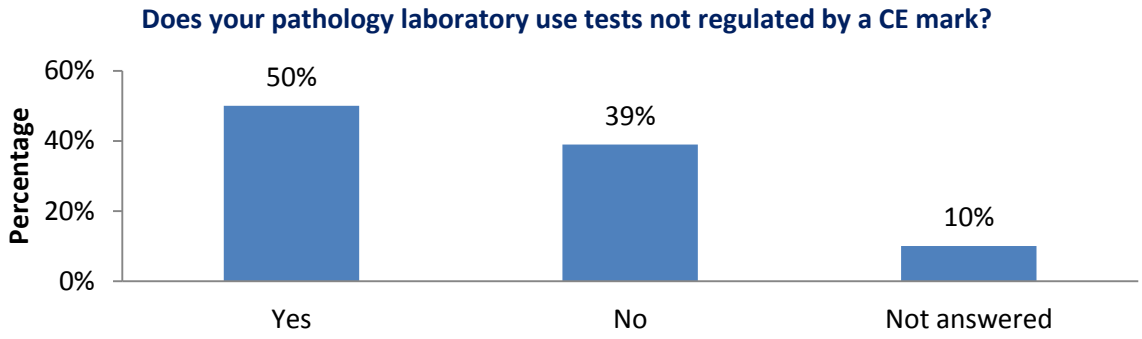
The extent of in-house testing in the NHS

BIVDA has been aware that NHS pathology laboratories have been producing diagnostics in-house for some time. Concerns have been expressed that such tests are being used in the NHS without being subject to the same rigorous standards as those tests that are manufactured commercially. In the absence of a CE mark on these in-house tests, there is no guarantee of the safety, reliability or accuracy of test results for NHS patients.

To date there has been no attempt made to quantify the extent of the use of in-house tests within the NHS. Therefore, BIVDA's intention in this research has been to investigate the extent to which tests without CE marks are being used in NHS trusts, in which condition areas they are being used and whether there were signs of an increase in the extent of this practice.

As Figure 1 below demonstrates, 50% of providers confirmed that they use tests that have been developed in-house. 39% confirmed that they do not use in-house testing.

Figure 1: Use of tests not regulated by a CE mark



The number of providers using in-house testing is lower than may be expected from our experience of working with the NHS and anecdotal evidence. Of the 50% of providers that confirmed using in-house developed tests, the scale and scope of use, and detail of collected information, varied considerably.

For some providers, the practice of modifying CE-marked tests was common. For example, Newcastle Upon Tyne Hospitals NHS Foundation Trust said that:

> "In many cases the products used in Laboratory Medicine are CE-marked but then used in modified in-house procedures that are essential for local service provision. The CE-marked products are then only components of an analytical procedure that is not in entirety CE-marked"[5].

The trust argued that the reason for this was "essential for local service provision." [6]

Brighton and Sussex University Hospitals NHS Trust demonstrated a similar approach, showing that some trusts are validating the testing processes themselves:

> "All of these assays are analysed using 'in-house' methods which have been validated / published within the laboratory."[7]

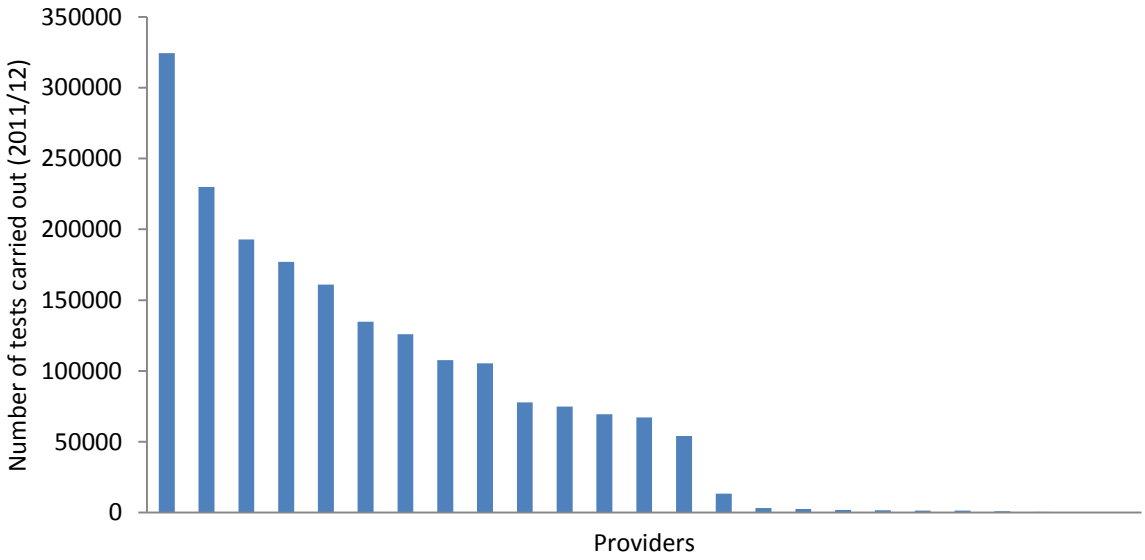
As set out in Figure 1, some providers do not use in-house tests at all. Croydon Health Services NHS Trust said that:

> "The pathology services use commercial kits and chemical reagents which are regulated by CE marking. All tests results reported are CE-marked and regulated."[8]

Volume of testing carried out in-house

To understand the scale of in-house testing, we asked providers how many tests they had used that were not regulated by CE marking in 2010/11 and in 2011/12. The detail of responses varied, with some providers providing information on the number of different types of tests they carried out and others the absolute number of tests that were used. Figure 2 shows the variation between those providers that gave information on the total number of tests carried out.

Figure 2: Number of tests carried out in-house



As the graph shows, there is significant variation in the scale of testing taking place across the NHS. Of those providers using in-house testing, the number of tests varied from 343 at South Tees NHS Trust to 324,334 at St George's Healthcare NHS Trust. Across the providers that reported that they use in-house testing, the average number of tests carried out was 77,199 in 2011-12. This was an increase from 2010-11, when 76,178 tests were carried out on average.

To illustrate the variation in practice across trusts, Figure 3 shows the in-house tests used in the financial years 2010-11 and 2011-12 by those trusts that responded.

It is not clear why the variation in the number of in-house tests across different trusts is necessary. Some providers do not need to use any in-house tests, while some are using hundreds of thousands every year. While the use of in-house tests can sometimes be appropriate, it is surprising that providers are using them to such different extents.

The types of tests used in-house

97% of those providers that confirmed that they use in-house tests provider further details of the types of tests used. Some broke these down by disease area, while others provided information on the assays used or areas of medical practice. The most common responses referred to the following areas of practice: immunology, haematology, biochemistry and histopathology. The spread of particular diseases where in-house tests were used was board and a selection is provided in Figure 3.

Figure 3: Selection of tests carried out in-house

Cross-section of in-house pathology testing disease areas:

Breast cancer	Thrombophilia
Cystic fibrosis	Fetomaternal haemorrhage
Prolactinoma	Lactose intolerance
Muscle disorders	Characinoid syndrome
Drug abuse	Pheochromocytoma
Metabolic disorders	Endocrine disorders
Sarcomas	Pyruvate kinase deficiency
Porphyria screening	Respiratory viral infections
Neonatal screening	Haematoxylin and Eosin

The conditions set out are just a selection of where trusts reported they are using in-house tests in practice. Responses received indicated that across a very wide range of diseases and conditions, tests developed in-house are being used. Some more detailed answers are provided below in Figure 4.

Figure 4: Examples of conditions and clinical areas where trusts are using in-house tests

"Thyroid tumours marker; Endocrine disorders; Fertility disorders; Gastrointestinal disorder screening; Immunosuppressant drug monitoring; Cushing's Syndrome; Vitamin D deficiency; Adrenal tumour marker; Carcinoid Syndrome; Haemostatic and Thrombotic disorder." University Hospital of Birmingham NHS Foundation Trust[9]	"Haematology, haemostasis, immunological disorders (monitoring and diagnostic), oncology, molecular haematology, molecular immunology, HLA disease association, endocrine, metabolic, toxicology and trace elements." Southampton University Hospitals NHS Trust[10]
"Respiratory illness, diarrhoea, immunodeficiency, opportunistic infections, hepatitis, meningitis, encephalitis, skin rashes."	"The disease areas of the Molecular Haematology would include, Haemoglobinopathy, Thrombophilia,

University College London Hospitals NHS Foundation Trust[11]	Haemophilia, Oncology, Haemochromatosis...At least part of all the process of all of the Molecular Haematology tests uses a non CE-marked Test." Oxford University Hospitals NHS Foundation Trust[12]

In contrast, Royal Berkshire NHS Foundation Trust listed breast cancer as the only disease for which in-house testing was used in the trust[13] and Royal Marsden NHS Foundation Trust reported in-house tests as only being used in the detection of fusion genes in sarcomas[14]. From these findings, it is clear that not only are there wide variations in volume of in-house tests implemented across trusts the range of conditions, clinical areas and conditions where such tests are used also varies significantly.

In addition, we looked at the responses to see whether there were any discernible variations in the use of in-house tests between trusts which were comprised of teaching hospitals and those which were comprised of district general hospitals. The proportion of teaching and non-teaching trusts which responded that they used in-house tests was almost even.

The reasons for using in-house tests

This chapter has set out significant variations in the scope and scale of in-house testing. While some providers use in-house tests in a relatively small number of areas, and relatively few times a year, others are carrying out large numbers of tests across a variety of medical areas.

There are strong reasons to use in-house testing in some cases. This is particularly true in those areas where there are no CE-marked reagents or tests available. Oxford University Hospitals NHS Trust explained that "non CE-marked reagents are used where no appropriate CE-marked reagents are available in a rapidly developing field"[15]. The Royal Marsden said that in-house tests are used as the exception, where other tests are not available: "The one exception is molecular diagnostics where exceptions are permitted for rare tests which cannot be purchased commercially and have to be developed by leading experts in the field, in-house".

Developing tests in-house can therefore contribute to research and development and is a demonstration of innovation. They can allow for testing that would not otherwise be possible. Once identified, these tests can be professionally manufactured, and then shared with the NHS as a whole. This has the additional benefit of potentially creating a revenue stream for the NHS at a time of financial challenge.

Despite the potential benefits of in-house testing in some situations, their use is not always appropriate. Our audit has shown vastly different usage of in-house tests between providers. It is unlikely that this variation can be explained solely by the need to use in-house tests where CE-marked tests are not available.

Recommendation 1: Where providers take the decision to use in-house tests, this decision should be explained according to clear criteria. Commissioners of services, and clinicians requesting tests, should be made aware of the decision to use an in-house test and the reasons for it

Recommendation 2: To ensure transparency, all providers should publish information on the in-house tests they use, including the reasons that the test has been used, in their annual quality accounts.

Recommendation 3: The Medicines and Healthcare products Regulatory Agency (MHRA) should establish a publicly accessible register of in-house tests, updated on a monthly basis and containing information on:

- **the type of test**
- **the patient population for which the test will be used**
- **the reason that an in-house test has been used**
- **whether or not a risk-assessment has been carried out by the pathology laboratory**

Ensuring the safe use of in-house tests

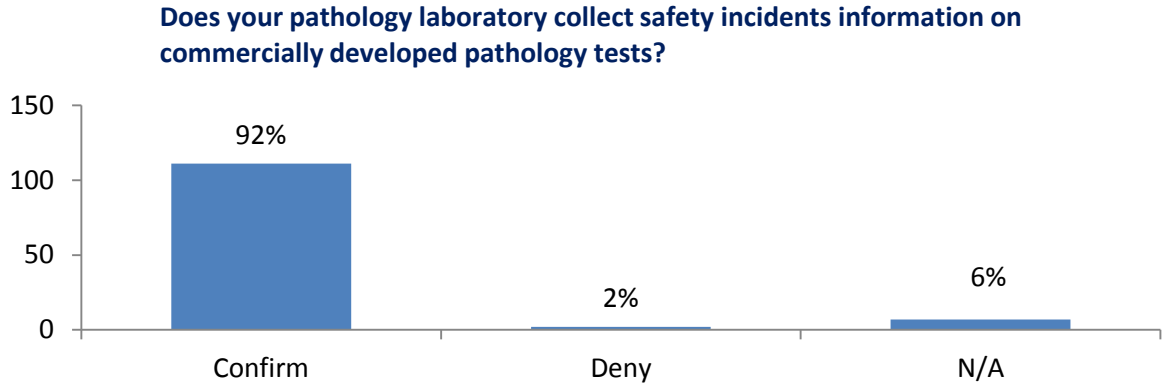
Given the scale of in-house testing in some pathology laboratories, it will be important to ensure that safety is ensured. As set out above, the European IVD Medical Devices Directive includes an exemption for tests developed in a healthcare setting for use only within that setting. We therefore wanted to find out what additional safeguards providers have in place to record and manage any safety incidents that arise. In particular, we wanted to know how practices vary between those tests developed commercially and those developed in-house.

The majority (92.5%) of providers responded that they collect safety information on commercially developed tests. For example, Great Ormond Street Hospital for Children NHS Trust stated that they:

> "collect data reports on any incidents related to safety...this is a requirement for the laboratories to retain full accreditation with CPA (UK) ltd." [16]

Other providers, including County Durham and Darlington NHS Foundation Trust[17] and Liverpool Heart and Chest NHS Foundation Trust[18], stated that they do not collect information on safety incidents, but rather rely on alerts from the Medicines and Healthcare products Regulatory Agency (MHRA).

Figure 5: Collection of safety incidents for commercially developed tests



However, few providers told us that they have separate mechanisms for reporting safety incidents relating to in-house tests from those mechanisms that they use for tests that have a CE-mark. The following response from Plymouth Hospitals NHS Trust suggests that this was one of the few trusts which indicated that it differentiated between in-house and commercially developed tests in the collection of data concerning safety incidents:

> "...The Pathology laboratory also collects information on safety incidents related to in-house tests not regulated by CE marking. These are recorded as Trust Datix reports or departmental Non Conforming Work Reports in local Quality Management Systems.[19]"

Similarly, Royal Brompton & Harefield NHS Foundation Trust indicated that "we do collect information on safety incidents related to both commercially developed and in-house tests.[20]"

For example, University Hospitals of Morecambe Bay NHS Trust stated that it records all safety incidents relating to any testing that is carried out in the Trust irrespective of whether they are CE-marked or not[21].

Only a small number of providers were able to distinguish between their safety reporting for tests developed in-house and those that were commercially manufactured. This is an area of concern as, given the unregulated nature of such tests, and the fact that they are being developed on an evolving basis within trust's pathology laboratories, it is important to be able to tell whether a safety incident was attributable to a test which had been developed in-house or not. This should support providers to respond to any issues.

The extent of safety reporting was not always consistent, with some providers pointing only to their own internal validation methods. The following three examples illustrate variations in approach between trusts when asked to set out how they collect information on safety incidents in relation to in-house. Papworth Hospital NHS Foundation Trust confirmed that it undertook internal validation and assurance of the in-house tests which it carried out: "...the Immunology Dept performs tests which are not CE-marked. These are internally validated and quality assured."[22]

Lancashire Teaching Hospitals NHS Foundation Trust reported as follows:

> "All safety incidents whether related to in-house tests or commercially available assays are recorded. These are reported on a monthly basis to the department management team and are also discussed during the monthly laboratory meetings. Any significant safety issues are recorded following the Trust's governance protocol and using the online reporting tool named Datix. In conjunction with the Trust's local reporting protocol there is also RIDDOR [Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995] and MHRA that are informed if appropriate."[23]

Brighton and Sussex University Hospitals NHS Foundation Trust gave the following response:

> "The Trust can confirm that its laboratory collects information on safety incidents relating to both commercially developed pathology tests and pathology tests developed in-house that are not regulated by CE marking. Quality control and quality assurance is monitored, audits are regularly carried out in work areas and any incidents or non compliance are recorded appropriately on the CPA and audit modules of Qpulse."[24]

From the responses we received it is clear that providers follow different procedures in relation to collecting data on safety incidents – some refer to reporting mechanisms to the MHRA, while others use different recording systems including Datix and Qpulse. As set out above, few providers stated that they would be able to differentiate between information on CE-marked and non CE-marked tests. We believe that clearer mechanisms should be put in place so that trusts are able to separate such information.

Recommendation 4: All providers should be required to report safety incidents relating to in-house tests to the Medicines and Healthcare products Regulatory Agency (MHRA). Where an issue is identified with a particular in-house test its use should be stopped immediately, with full details provided to the MHRA

Recommendation 5: Where a safety issue with an in-house test is reported, the MHRA should alert all pathology laboratories to prevent the same errors occurring

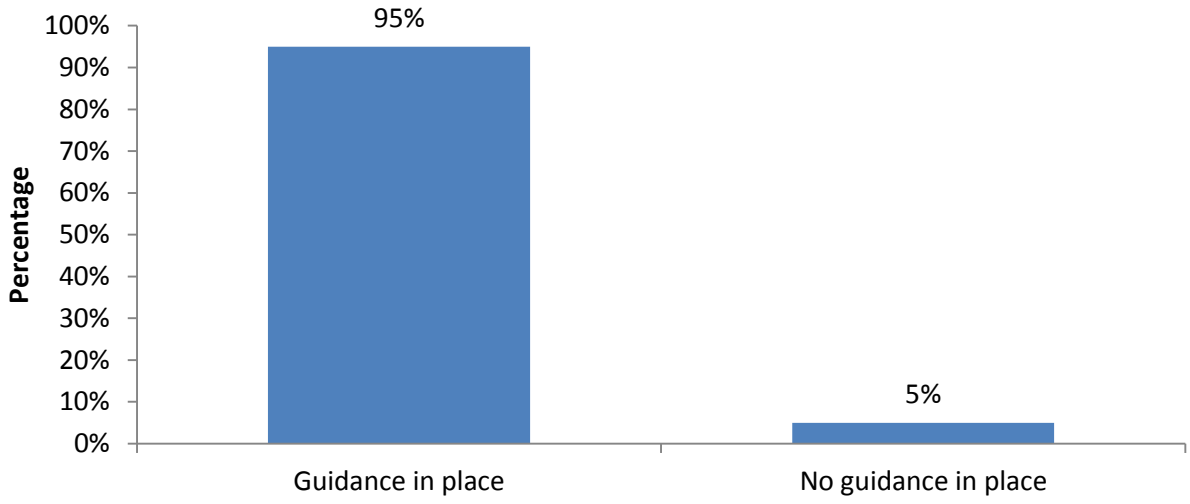
Guidance

Given the significant role that IVDs can play in the diagnosis and care pathway, it is important that local NHS pathology laboratories have appropriate guidance in place to manage the use of the tests. This should be the case for both commercially developed, CE-marked tests and those that are developed in-house or used without a CE-mark. It is particularly important for non CE-marked tests, where, as set out above, there is a comparative lack of information and scrutiny on their use. In addition, the fact that they are used outside of the regulatory framework increases the rationale for robust and implementable guidelines.

Clear guidelines can help to ensure that patient safety is protected, and help professionals to ensure that tests provide accurate results that can inform diagnosis or treatment. We therefore asked providers whether they have guidance in place for the appropriate use of pathology testing and whether there is separate guidance available for the use of commercially developed tests and in-house tests.

As shown in Figure 6, 95% of providers said that their pathology laboratory has guidance in place for the use of commercially developed tests. 5% were not able to confirm that they had such guidance in place.

Figure 6: Guidance for commercially developed testing



The guidance that providers have in place for the use of IVDs varied from their own standard operating procedures to guidance from the Royal College of Pathologists. The wide scope of available guidance was demonstrated in the response we received from Imperial College Healthcare NHS Trust which set out that it takes into account:

> "guidance provided by all governing bodies including the Medicines and Healthcare products Regulatory Agency (MHRA), Clinical Pathology Accreditation (CPA), the Human Tissue Authority (HTA), European Federation for Immunogenetics (EFI), the Human Fertilisation and Embryology Authority, Association of Clinical Biochemists (ACB), the Royal College of

> Pathology (RCPath) and the Institute of Biomedical Science (IBMS) with regard to the appropriate use of tests performed within the laboratory."[25]

Plymouth NHS Hospital Trust provided a similar response demonstrating the range of guidance and accreditation regimes which trusts consider in this area:

> "The Directorate is subject to audit by regulatory and accreditation bodies including, but not limited to; CPA, MHRA, HTA, EFI, JACIE. Quality Management Systems are in place and designated Quality Assurance personnel are members of the Association for Quality Management in Laboratory Medicine (AQMLM) and the Research Quality Association (BARQA)."

The most common response from providers was that they follow the standard operating procedures for tests. Standard operating procedures contain the manufacturer's guidance on use, control, calibration, storage, disposal, health and safety and risk assessments[26]. At some providers, including Burton Hospitals NHS Foundation Trust[27], compliance with standard operating procedures is subject to both internal and external audit.

As with the collection of safety information, very few providers noted that they have separate policies in place for the management of tests carried out without CE-marks. The Dudley Group of Hospitals NHS Foundation Trust gave the following answer, which was typical of responses received:

> "Guidance is in place for all assays, either commercial or developed in-house. These take the form of Standard Operating Procedures for each individual assays and general procedures for the assessment or development of new assay."[28]

The response from Brighton and Sussex University Hospitals NHS Trust also suggested that although guidance was available for both commercially developed and non CE-marked tests, it was not clear that the guidance was tailored:

> "The Trust can confirm that the laboratory has in place guidance for the appropriate use of commercially developed pathology tests and pathology tests developed in-house that are not regulated by CE marking."[29]

Doncaster and Bassetlaw Hospitals NHS Foundation Trust was one of the few trusts which referred to a set approach to the management of the use of in-house tests, distinct from that use for tests that have been CE-marked. The trust set out in its response that:

> "in the situation where a CE product is not available the 'in-house' test is validated to ensure that it is 'fit for purpose' following MHRA guidelines and will be subject to quality assurance[30]."

Shrewsbury and Telford Hospital NHS Trust is the only trust that confirmed having guidance in place for the appropriate use of commercially developed tests, but denied having guidance in place for pathology tests developed in-house that are not regulated by CE marking[31].

Given the range of guidance in place, further clarity is needed on the requirements for the use of tests that are used without a CE mark. There should be a consistency of approach across both CE-marked and non CE-marked tests.

Recommendation 6: Where tests are used without a CE mark, NHS providers should be required to develop standard operating procedures for their use to ensure that they are used in a consistent and safe way. The Medicines and Healthcare products Regulatory Authority should develop a template for providers to develop standard operating procedures for tests used without a CE mark

Recommendation 7: Pathology laboratories should put in place an approach to the use of non CE-marked tests, setting out:

- **The circumstances in which they will be used**
- **The guidelines which should be put in place for any newly developed in-house tests**
- **Audit mechanisms to ensure the safety and performance of in-house tests**

Informing clinical decisions

As set out above, 70% of clinical decisions are based on the results of laboratory or point of care tests, using IVDs. Figure 7 below provides practical examples of how diagnostics can be used to inform treatment decisions, for women with breast cancer and for people who present with symptoms of possible bowel disease.

Figure 7: Diagnostics in action

Targeting breast cancer treatment

- Around 20% of women with breast cancer are positive when tested for the HER2 gene, which is associated with aggressive cancer cell growth. Herceptin is a treatment designed specifically to target the HER2 protein
- Before beginning treatment, patients are required to be tested for their HER2 status. Clinical trials have shown that HER2 positive individuals receiving Herceptin as a treatment experience show substantial improvements in survival and quality of life compared to treatment with conventional chemotherapy alone
- The highly-targeted nature of the treatment means that response rates are good, and wastage is minimised. HER2-normal tumours will not derive any benefit from Herceptin. It is therefore vitally important that patients who are positive for the protein are identified accurately to ensure that they will benefit from the treatment, and that those who are negative do not receive the treatment unnecessarily

Distinguishing between Inflammatory Bowel Disease and Irritable Bowel Syndrome

- Patients who present with symptoms of possible bowel disease are often required to undergo further examination to obtain a diagnosis, usually involving an invasive and unpleasant test such as a colonoscopy or small bowel radiology
- One such test is a quick and simple diagnostic test that can be performed on a stool sample to differentiate between organic intestinal diseases such as Inflammatory Bowel Disease (IBD) and functional bowel diseases such as Irritable Bowel Syndrome (IBS) enabling a swift diagnosis and allowing the correct treatment to be initiated
- The benefits of this test to the NHS are simple, non-invasive and low cost. It is ideal for serial monitoring of disease activity and treatment success. It also allows disclosure of treatment failure allowing patients to avoid prolonged courses of steroid drugs when these are not proving effective. For patients, the test allows for quick diagnosis and screening, thereby avoiding unnecessary referrals and anxiety

In both examples set out above, the result of a diagnostic test can have a significant impact on the treatment that will be offered to a patient. Through informing treatment diagnostic tests can improve patient outcomes and experience while also leading to more efficient care. Given the impact of these decisions, on treatment as well as individual resources, it is important that pathologists and clinicians can be confident in the results that are generated. To ensure this they should be carried out in accordance with quality guidelines and safety procedures, as set out in the chapters above.

Where use of a test differs from regulated CE-marked tests, clinicians should be made aware of this when they receive a patient's results. This will allow them to have the widest possible context for the results and therefore to gain the best possible understanding of a patient's condition.

Recommendation 8: Where test results are generated by the use of in-house tests, the clinician using the test should be made aware. Clinical commissioning groups should make this a requirement of providers in their contract negotiations

The future of IVD regulation

The imminent update to the IVD Medical Devices Directive offers an opportunity to ensure that additional safeguards are put in place to promote the safety, performance and accuracy of diagnostics that are not regulated by a CE mark. One solution would be to place the same requirements on all tests used in pathology laboratories, regardless of whether they have been developed commercially or in-house. This would have the benefits of providing a level playing field, and creating confidence in all test results.

Given the essential role that diagnostics play in a care pathway, there should be no complacency about their regulation. The exemption should not apply to those tests which can have a significant impact on the treatment of an individual.

A number of other safeguards have been set out in this report, and we hope that these can be introduced to ensure parity not only across Europe but between diagnostic tests. We believe that requirements must be put in place to ensure that:

- In-house tests are produced and used under a common quality management system within the healthcare institution
- All in-house tests should be subject to reporting of safety incidents and that, within the UK, the MHRA should be responsible for collecting information on any safety issues. This should be compiled into an annual report so that the potential safety implications of in-house tests are presented in a transparent way

Conclusion

It is clear that there will be a need to retain the in-house exemption from EU regulation for tests where there are no commercial alternatives. These could be because the disease is very rare or only newly discovered. However, we believe that a number of steps should be taken to ensure that in-house testing meets minimum standards of quality and safety and to ensure that its benefits can be maximised across the NHS.

A register of in-house testing

BIVDA believes that the MHRA and the Department of Health should implement and manage the collection of a publically available database of information concerning in-house testing. This should ensure that there is a clear record of which tests are being developed in-house and for what clinical purpose they are being used. This kind of database or 'register' of in-house testing is essential for:

- enabling innovation – so that innovative practices can be highlighted and communicated more widely
- tackling health inequalities – by demonstrating variations across the NHS

Information could be shared among clinicians in order to raise the level of practical knowledge in some areas and in order that regulators could have a better view of which tests were being developed across different trusts.

Safety testing

It is also important that in-house tests undergo the same rigorous safety tests as any other commercial counterpart, in order to avoid hampering innovation due to any problems which may occur outside of established regulatory approvals.

GP awareness

BIVDA sees it as important that GPs are informed when their clinical decisions depend on a result generated by an in-house test so that they are able to make the best-informed decision about care for their patients. This is legally required in the USA but it is not widely known in the UK that in-house testing is common practice.

Commercialisation of in-house testing

The NHS could benefit from increased commercialisation of novel and innovative tests where a health benefit is clearly demonstrated. This process of commercialisation could extend to providing either an income stream locally by offering a testing service (such as at City Hospital in Birmingham[32]) or working with a commercial partner so that the royalty for the test sales would benefit the NHS financially.

Many tests which have been developed in-house have gone on to be used widely throughout the NHS and have led to significant health benefits for patients and financial benefits to the NHS. BIVDA strongly supports the spread of innovation through the NHS and has played a key part in the development of the NHS Chief Executive's innovation review *Innovation, Health and Wealth.*

However, although innovation around the development of diagnostic tests must be supported, robust measures must be put in place to ensure that the safety, accuracy and reliability of in-house tests is ensured, in the interests of patients.

Annex: Freedom of information (FOI) questions

The following FOI requests were sent to NHS providers:

1. Please confirm or deny whether your pathology laboratory uses tests developed in-house that are not regulated by CE marking. If confirmed, please provide details, including:

    i. For which disease areas tests are used that have been developed in-house and are not regulated by CE marking
    ii. How many of the tests developed in-house that are not regulated by CE marking were used in a) 2010/11 and b) 2011/12

2. Please confirm or deny whether your pathology laboratory collects information on safety incidents relating to:

    i. Commercially developed pathology tests
    ii. Pathology tests developed in-house that are not regulated by CE marking

3. Please confirm or deny whether your pathology laboratory has in place guidance for the appropriate use of:

    i. Commercially developed pathology tests
    ii. Pathology tests developed in-house that are not regulated by CE marking

The following FOI requests were sent to a sample of five NHS providers:

1. Please confirm or deny whether your pathology laboratory uses tests developed in-house that are not regulated by CE marking. If confirmed, please provide details, including:

    i. For which disease areas tests are used that have been developed in-house and are not regulated by CE marking
    ii. How many of the tests developed in-house that are not regulated by CE marking were used in a) 2008/09 b) 2009/10 c) 2010/11 and d) 2011/12

2. Please confirm or deny whether your pathology laboratory uses tests off-label. If confirmed, please provide details, including:

    i. For which disease areas tests are used off-label
    ii. How many tests were used off-label in a) 2008/09 b) 2009/10 c) 2010/11 and d) 2011/12

3. Please confirm or deny whether your pathology laboratory uses tests intended for research purposes only for general use. If confirmed, please provide details, including:

    i. For which disease areas tests intended for research purposes only are used for general use

ii. How many off-label tests intended for research purposes only were used for general use in a) 2008/09 b) 2009/10 c) 2010/11 and d) 2011/12

4. Please confirm or deny whether your pathology laboratory collects information on safety incidents relating to:

   i. Commercially developed pathology tests
   ii. Pathology tests developed in-house that are not regulated by CE marking
   iii. Pathology tests used off-label
   iv. Tests intended for research purposes only that were used for general use
   v. Commercial reagents and instruments used in a combination that has not been regulated by CE marking.

   If confirmed, please provide details, including:

   i. What information is collected
   ii. How many safety incidents were recorded for
   iii. Commercially developed pathology tests
   iv. Pathology tests developed in-house that are not regulated by CE marking
   v. Pathology tests used off-label
   vi. Tests intended for research purposes only that were used for general use

5. Please confirm or deny whether your pathology laboratory has in place guidance for the appropriate use of:

   i. Commercially developed pathology tests
   ii. Pathology tests developed in-house that are not regulated by CE marking
   iii. Pathology tests used off-label
   iv. Tests intended for research purposes only that were used for general use
   v. If confirmed, please provide details

6. Please confirm or deny whether your trust has made or received communication on the use of i) commercially developed pathology tests, ii) pathology tests developed in-house that are not regulated by CE marking, iii) pathology tests used off-label, iv) tests intended for research purposes only that were used for general use, v) commercial reagents and instruments used in a combination that has not been regulated by CE marking with:

   i. The Department of Health
   ii. The Medicines and Healthcare products Regulatory Agency
   iii. Other NHS organisations

References

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31 Shrewsbury and Telford Hospital NHS Trust, Response to Freedom of Information request, September 2012
32 Sandwell and West Birmingham Hospital NHS Trust, New Oral Fluid Drug Testing Services. Accessed on 22 November via www.cityassays.org.uk