

The IVD Directive and Genetic Testing Problems and proposals

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Our research

Our research team have spent the last three years exploring the policy issues around the evaluation and regulation of genetic tests for common, complex diseases. We have explored two key questions: What are the incentives test developers need to generate good evaluative data on new tests? And what are the appropriate regulatory mechanisms for evaluation of such data? Underlying these two questions is our fundamental concern that patients, doctors and healthcare decision-makers should be able to make informed decisions about the use of new genetic tests based on high-quality, rigorously-evaluated clinical data.

We have looked at the regulatory regimes in Europe, the US, Canada and Australia and we have spoken to over 80 individuals from key stakeholder groups - policymakers, regulators, diagnostics companies, clinicians and patients groups.

Most of the people we have spoken to expressed the view that public confidence in genetic testing can only be maintained if there is a clear and coherent framework of regulation. There was general agreement in both the United States and Europe that the status quo is not adequate; that new tests should be subject to some form of systematic independent pre-market evaluation, and that regulatory reform is required to ensure such evaluation takes place.

However, stakeholders were also concerned that regulatory reform should not impede innovation by creating unnecessary regulatory burdens, nor was their general support for special regulations targeted specifically at genetic tests. Instead we found support for trying to make progress through modest incremental improvements in the mechanisms for pre-market review of new tests (focused on ensuring truth-in-labelling) and by enhancing other regulatory mechanisms. In particular, policymakers need to consider how to develop more systematic mechanisms for carrying out Health Technology Assessments on new genetic tests once they have been placed on the market.

This briefing outlines a series of issues in the IVD Directive which need to be addressed if it is to deliver the kind of systematic, independent pre-market evaluation we propose. Furthermore, regardless of whether there is support for the approach proposed, many of these issues still need to be addressed, as they are sources of ambiguity which require clarification. Of course, some level of confusion and ambiguity is inevitable with any new piece of legislation. This seems a particularly opportune moment to consider both the issues which require clarification, and other ways in which the Directive might be enhanced: the Directive is well-established in the member states; the Commission is now contemplating a revision of the Directive; and the development of IVD regulation is being actively pursued through the work of the Global Harmonisation Task Force.

Summary of policy proposals

Risk classification

1) EU should adopt new model developed by Global Harmonisation Task Force. This would ensure more tests are subject to pre-market review, and move EU towards its global partners, creating more consistency for manufacturers.

2) However, modification is required to the GHTF model which needs to recognise that *novelty* is a risk factor, and that novel Class B devices require independent pre-market review. This entails modification of both the classification model and the conformity assessment model.

Analytic and clinical validity

1) It should be mandatory for manufacturers to state the test's intended clinical purpose and to provide data on both analytic and clinical validity (although for clinical validity it may be sufficient to cite the existing scientific literature).

2) This could be dealt with through guidance or through revision of Essential Requirements 1 and 3. Since the Essential Requirements are in Annexe I, revisions can be made through comitology.

3) Clarifying the criteria for evaluation is not enough - manufacturers need more detailed guidance on evidence requirements – development of new standards are needed especially for highly complex tests.

In-house tests

1) Commission investigates how LDTs are being dealt with by member states and how they are interpreting the public health institution exemption. Need to ensure that LDTs put into service by commercial labs are regulated under the Directive.

2) Guidance is needed on definition of an LDT.

3) Guidance is needed on definition of a label for LDTs. This could draw on recent FDA guidance which addresses the same issue.

Encouraging transparency

1) Oblige test manufacturers to make information available to all stakeholders online – labels, sample results sheets with reference ranges etc.

2) Work is currently underway on publishing some information from assessment reports, scope of this should be widened. May be able to learn from other countries e.g. United States where review summaries are published.

Predictive testing

1) IVD Technical Group should clarify what they meant.

2) Predictive tests need to be defined.

3) It should be made clear that predictive tests which are intended for a medical purpose are IVDs and fall within the scope of the Directive. This could be done through guidance, but if Directive is revised, then the issue should be addressed in the revision.

4) GHTF document on IVD classification also needs to clarify status of predictive tests.

Scientific progress and clinical applications

We are now beginning to see robust, well-replicated associations between genetic markers and common, complex diseases in areas such diabetes and heart disease. These findings are coming from a new wave of large-scale genome-wide association studies each involving thousands of individuals.¹

However, caution still needs to be exercised. In the past, most genetic tests were for single gene disorders, in which having the gene variant was synonymous with having the target condition. However, common, complex diseases are multifactorial – environmental factors play a major role in disease risk and heritable risk will generally be determined by the small effects of a large number of different genes. Thus, most recently discovered variants merely convey degrees of risk, often moderate in size; in most recent cases odds ratios have been below 1.5 for allele phenotype associations in general population samples.

However, there is still a tendency for many people to overestimate the predictive power of genetics. Recent reports on the discovery of a gene linked to obesity, heralded the finding as “the fat gene”, as if it was the most important determinant of obesity. Yet in fact the conclusions of the study were far more cautious, reporting that those who carry two copies of the gene variant they identified only weigh about 3 kilograms more and have a 1.67-fold increased odds of obesity when compared with those not inheriting a risk allele.²

Furthermore, the new wave of genome-wide association studies are revealing that earlier research was often underpowered and poorly-designed and led to findings which have rarely been robustly replicated. A recent study looked at 85 gene variants which had been linked to acute coronary syndrome (ACS) in earlier work. The new study failed to confirm any of the 85 markers.³ Indicating how easy it is to cherry pick attractive results from studies of thousands of markers and the dangers that result if researchers do not seek to replicate the results in independent populations. Of greatest concern is the fact that at least six of these markers are being offered as clinical tests to assess risk of cardiovascular disease.

Even with more powerful, better designed studies, scientific research still faces the problem that nearly all gene-disease associations have been found in Caucasian populations and there is no data on whether they have the same significance in other ethnic groups. Genetic heterogeneity across populations means that the predictive value of tests is likely to vary enormously across ethnic groups.

Tests enter the market

Tests for susceptibility to heart disease are only one example of a more general trend: genetic testing is no longer a narrow specialism focused on rare diseases; it has moved into mainstream medicine and is beginning to have a broader impact on public health. For instance, pharmacogenetic tests are being used to guide treatment decisions. Gene expression tests are being used in applications such as estimating risk of breast cancer recurrence.

¹ See for instance Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls *Nature* 447, 661-678, 7 June

² Frayling, T *et al* (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity *Science* 316(5826):889-94.

³ Morgan TM *et al* (2007) Nonvalidation of reported genetic risk factors for acute coronary syndrome in a large-scale replication study. *JAMA* 297 1551-61

Predictive tests which assess susceptibility to common, complex diseases such as cancer, osteoporosis and heart disease are now on the market.

Such tests will often involve large panels of genes and complex interpretative algorithms. For instance the OncoVue test developed by the US company InterGenetics is a polygenic test for risk of breast cancer which examines 117 common polymorphisms located in over 100 genes. Although still an investigational device in the United States, this test is now available in the UK. The test illustrates an important regulatory issue inherent in these tests: to predict significant risk effects, tests will have to combine large numbers of genes and use complex interpretative algorithms to provide a risk score. These algorithms will generally be proprietary, making it very difficult for ordinary doctors to assess the value of the test. In general, regulators will be the only people with the power to open these ‘black boxes’ and subject them to independent scrutiny.

Some of these new tests are being offered direct-to-consumer. For instance, in the UK Genetic Health offer polygenic screening tests which promise to tell patients their heritable risk of a whole host of common, complex diseases such as cancer, osteoporosis and heart disease.

Perhaps the most dramatic development has been the advent of gene expression microarrays with a range of clinical applications such as tumour profiling. The Dutch company Agendia offer the MammaPrint test which profiles breast cancer patients to predict risk of recurrence and guide treatment decisions.

Yet this scientific and clinical progress has not been met with unconditional enthusiasm. There has been much concern about both the ethical, legal and social consequences of genetic testing and also about the clinical dangers which arise from the premature commercialisation of tests which have not always been properly evaluated and which enter clinical practice when their predictive power and clinical utility are still unclear.

Policy concerns

Professional and public concern that new predictive genetic tests were being introduced with insufficient evidence of their safety and effectiveness has been considered by a series of committees in the US, Europe and elsewhere. Concerns were first articulated as early as 1975 in a report from the National Academy of Sciences entitled *Genetic Screening Programmes, Principles and Research*. In the years since then, as experts began to predict that genetic testing would play a greater role in disease prevention, management and treatment, there have been growing concerns that some genetic tests continue to enter clinical practice prematurely:

“[There has been] a noticeable lack of consensus within the genetics community about exactly when a test for a new marker was sufficiently validated for it to enter into clinical service. Some labs rushed to provide testing after the first publication, while others waited until the result had been replicated in multiple studies or multiple ethnic groups.”

There has been a prolonged policy debate about how best to ensure the safe and appropriate use of clinical genetic tests; a number of committees and task forces have reviewed the

oversight of genetic testing and their reports have come to similar conclusions (the European policy debate is set out chronologically in the appendix to this briefing). For our purposes, the most important idea which has emerged from this debate is a general consensus that genetic tests should not enter routine clinical practice without thorough independent evaluation. Furthermore, it has become a well-established view that full evaluation requires evidence on four criteria set out in what has become known as the ACCE framework.

Analytic validity – accuracy of test identifying the biomarker

Clinical validity – relationship between the biomarker and clinical status

Clinical utility – likelihood that test will lead to an improved outcome

Ethical, legal and social implications

IVD sector - innovation and business models

There has been much discussion about the broader effects of the new wave of genetic tests; their public health impact and their ethical, legal and social consequences. There are concerns that rapid technological change is causing disruptions which need to be dealt with at a policy level. Less often observed is that fact that change is also coming to the business models for *in vitro* diagnostics and with it the IVD innovation process.

The IVD industry has traditionally held intellectual property (IP) in test platforms, not in biomarkers. This means it is a very competitive industry with low profit margins and little experience or infrastructure to undertake large-scale clinical studies. This model of weak IP in biomarkers has meant that no one party is responsible for developing the data on the clinical validity of a new test. Academic studies and professional advocates have filled the gap, often promoting tests on the back of ad hoc clinical experience. Policymakers must consider how to provide support for this business model, as, for those genes which are not patented, there is only limited incentive for the development of robust clinical data and public subsidy may be needed to plug the gap.

However, there is some evidence that the emerging field of molecular diagnostics has disrupted the traditional business model in a number of ways. A number of companies developing genetic tests based on patent protection of the gene and its association with disease have emerged. The emerging market for gene expression and proteomic tests is based on similar strong IP rights, in biomarkers and/or their interpretative algorithms. Higher reimbursement rates are being seen for some new tests, these include Agendia’s MammaPrint test which costs \$3,000.

Strong IP in biomarkers allows companies to charge higher prices for their tests because it gives them longer on the market before the arrival of competing products. When companies have greater certainty of a return on their investment, it is more likely that they will invest in substantial clinical studies to generate a proper evidence base for their tests. So IP has become an important incentive for funding clinical studies for new molecular diagnostics and this new model may help to address oversight concerns about lack of clinical data to support novel tests by offering clear incentives to generate that data.

But this new model may also present special regulatory challenges. IP in biomarkers can lead to monopolistic provision of tests. Many clinicians and laboratory directors have opposed

this, arguing that monopolistic provision circumvents the traditional (informal) methods of test evaluation, whereby in-house tests are subject to peer-review in the field. They are concerned that it creates a situation where the only people who can perform a new test are those with a vested interest in its promotion and this creates anxiety that in order to recoup their R&D investment, companies may make strong clinical claims for their tests at a stage when the evidence base is still developing.

Enhancing regulation

So this new business model presents regulatory challenges as well as providing potential advantages. And this brings us back to the unresolved issue of how to deal with the current gaps in regulation which prevent comprehensive and systematic pre-market evaluation of new genetic tests for common, complex diseases.

Why have we failed to achieve a goal that is so strongly supported? There are two key reasons:

- the need to strike a balance between ensuring proper evaluation and encouraging innovation and access;
- the lack of clarity on the respective roles of different gatekeepers.

These two issues are linked because clarifying the role of non-statutory gatekeepers is essential to creating a regulatory model which is not unduly burdensome, for either companies or regulators. In the past there has sometimes been a tendency to expect too much from the statutory regulation of medical devices. Many issues in the regulation of genetic testing cannot be dealt with through the IVD Directive – social issues such as genetic discrimination and aspects of clinical practice such as the confidentiality of personal data and the quality of genetic counseling.

Furthermore the evaluation of a genetic test might be conducted by a number of gatekeepers, for a number of purposes:

- statutory regulators (in Europe the Notified Bodies and Competent Authorities) may set standards for safety and effectiveness;
- reimbursers may conduct formal review through health technology assessment (HTA), resulting in the production of practice guidelines and/or coverage decisions;
- professional bodies also play an important role by developing their own practice guidelines which support the appropriate use of a test.

Understanding this multi-tiered approach to test evaluation allows us to focus on what can be best achieved at each stage. One approach to creating a minimum common requirement for pre-market review under the IVD Directive would be to focus on ensuring truth-in-labelling. We describe this approach as regulation by information disclosure: test manufacturers should provide patients and healthcare providers with evaluative data on the analytic and clinical validity of tests; and independent pre-market review can be used to evaluate whether this information is an accurate account of a test's strengths and weaknesses. Our research showed strong support for an approach focused on using pre-market review to ensure truth-in-labelling (and truth-in-promotion).

To return to the ACCE criteria for test review, this position was linked to the broadly-supported view that data on analytic and clinical validity are minimum data requirements but that it is both generally unrealistic to ask statutory regulators to evaluate the clinical utility of tests or their ethical, legal and social implications, and probably constitutes too high a barrier to market entry. Reviewing evidence on these criteria is more appropriately done after tests have entered the market, and handled by other gatekeepers, for instance through HTA mechanisms at the level of resource allocation and through clinical practice guidelines.

Such a model can be seen as a least burdensome mechanism for ensuring some form of pre-market review where none currently exists. Our research suggests that this least burdensome approach can satisfy both many of the concerns of stakeholders and the desire of test developers to gain rapid entry to the market. Finally, it should be noted that our proposals are primarily focused on genetic tests for common, complex diseases and that the regulation of rare disease genetics may require a different approach for a variety of reasons.

Issue 1 - risk classification

The primary reason that most genetic tests are not subject to independent pre-market review in the European Union is that they are classified as low-risk and therefore the manufacturer is not required to submit their technical file to a Notified Body. An international comparison of device regulations shows that the European approach is unique. In the United States, Canada and Australia genetic tests which fall within the medical device regulations are all treated as moderate to high risk – and so are generally subject to pre-market review (in Australia some genetic tests are Class II and exempt from pre-market review). There are a number of reasons for considering that many genetic tests are moderate- to high-risk:

1. They are often stand-alone, with no confirmatory test available.
2. They are used for relatively serious clinical purposes, such as pre-implantation genetic diagnosis and selecting treatments (pharmacogenetics).
3. They may have serious psychological impact (e.g. Huntington’s Disease).
4. Many new tests are highly complex involving multiple alleles or multiple genes, making interpretation more difficult.
5. If it is a test which is performed in a single reference laboratory, then it will not undergo informal peer-review by the pathology community.
6. New genetic tests carry the risks associated with all novel devices – unproven performance in the field and lack of familiarity on the part of users.

1. Lack of consistency

A major problem with the current approach in the Directive is a lack of consistency. The Directive sets out three criteria which would determine whether a test is in Annex II, List B:

“(i) whether total reliance has to be placed on the result obtained with a given device, this result having a direct impact on subsequent medical action, and

(ii) whether action taken on the basis of an incorrect result obtained using a given device could prove to be hazardous to the patient, to a third party or to the public, in particular as a consequence of false positive or false negative results, and

(iii) whether the involvement of a notified body would be conducive to establishing the conformity of the device.”⁴

But whilst there is a clear set of criteria, there appears to be little consistency as regards what is classified moderate-risk and what is low-risk. Thus Chlamydia tests are in Annex II, List B, but no other tests for sexually transmitted diseases; PSA is also on List B, but no other cancer tests such as the Pap smear and CA125, CEA etc.; there is one heritable disorder, PKU, but no others.

A list-based approach to classification is not an effective mechanism for risk classification of novel tests. The automatic assumption is that all new tests are low risk and this creates further

⁴ Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro medical devices

inconsistency. For instance, Gen-Probe’s PCA3 test quantifies the PCA3 mRNA in a patient's urine sample as a marker for prostate cancer and thus performs exactly the same clinical function as the PSA test, yet it has not been added to Annex II, List B.

2. The proposed GHTF model

By contrast the risk classification schema developed by the Global Harmonisation Task Force is both more comprehensive and more consistent.⁵ Largely modelled on the Australian system (itself a refinement of Canada’s model) it is a four-class system running from high- to low-risk. The risk of a test is assessed using a number of criteria, such as the intended use/indications for use, the skill of the user, the degree of reliance placed on the test result, and the potential impact on public health and the individual patient. Examples of existing tests have been assessed according to these criteria and placed in one of four categories and this guides manufacturers in how to classify their new tests.

The GHTF model places some genetic tests into the moderate-to-low risk category (Class B) and others in the moderate-to-high risk (Class C) category. The principle seems sensible, since it is clearly the case that some genetic tests pose greater risks than others. However, when linked to the conformity assessment model, this distinction creates problems, because tests in Class B are not subject to independent pre-market review.

This is a problem where a Class B test is a novel one. The GHTF model does not treat novelty as a risk factor. This is contrast to the US regulatory system which treats novelty as a risk factor - novel tests are automatically classified as Class III and subject to the most rigorous conformity assessment route.⁶ Experience would suggest that lack of familiarity with a new test - whether it is the testing platform, the biomarker/s, the interpretative algorithm or any combination of these three - can lead to errors. The true performance of a test, both its analytic and clinical validity, are not known until the test has been in routine clinical practice for some time. Furthermore, tests generally perform less well in routine use than they do in clinical investigations. For these reasons, novel tests are more likely to lead to incorrect results and so novelty should be formally acknowledged as a risk factor.

Risk classification - policy proposals

1) EU should adopt new model developed by Global Harmonisation Task Force. This would ensure more tests are subject to pre-market review, and move EU towards its global partners, creating more consistency for manufacturers.

2) However, modification is required to the GHTF model which needs to recognise that *novelty* is a risk factor, and that novel Class B devices require independent pre-market review. This entails modification of both the classification model and the conformity assessment model.

⁵ GHTF Study Group 1 (2007) *Principles of In Vitro Diagnostic (IVD) Medical Devices Classification, Proposed Document*

⁶ This classification can be appealed, and generally most new tests are reclassified as Class II, and subject to a less rigorous pre-market review (*de novo* 510K, roughly equivalent to Class C conformity assessment route in the GHTF model).

Issue 2 - analytic and clinical validity

Our research would suggest that most stakeholders believe that the Directive requires manufacturers to provide evidence of a test’s analytic validity, but only requires evidence of a test’s clinical validity if clinical claims are made by the manufacturer. An international comparison indicates divergence between the US and Canadian systems and those of the European Union and Australia in this regard.

Country/region	Analytic validity	Clinical validity
USA	Yes	Yes
Canada	Yes	Yes
Europe	Yes	Only if clinical claims made?
Australia	Yes	Only if clinical claims made?

However, there are a number of reasons to believe the common interpretation of the IVD Directive may be wrong, or at least in conflict with crucial aspects of the Directive:

1. Recent guidance on Research Use Only products states that IVD devices must have a clinical purpose.
2. You cannot classify risk without a clinical purpose.
3. You cannot fulfil Essential Requirements one and three without a clinical purpose and data on clinical validity

Discussion of this issue requires clarity on terms:

Analytic claim	This test identifies gene X.
Analytic validity	The accuracy of test in identifying the biomarker.
Clinical claim	By identifying gene X this test diagnoses disease Y.
Clinical validity	The relationship between the biomarker and clinical status.

1. Can you distinguish between research use and clinical use without an intended clinical use?

MEDDEV guidance issued in 2004 on research use only products highlights the issue of the distinction between research and clinical use. This guidance clearly states that an IVD test with no intended medical purpose is not a test under the IVD Directive, it is simply an RUO product.

“In summary for a product to be categorized as an RUO product it must have no intended medical purpose or objective ...When a medical purpose has been established based on sufficient and broadly agreed upon scientific, diagnostic and clinical evidence, then the

product must comply with the requirements of the Directive before the manufacturer can place it on the market with an intended IVD use.”⁷

Since the guidance states that the manufacturer must define the device’s medical (or clinical) purpose, then they must make a clinical claim, and if they make a clinical claim then they must support it with evidence.

2. Can you do risk classification without an intended clinical use?

Returning to the previous issue of classifying a test as higher risk, we might ask how points i) and ii) in the list of criteria which determine if a test might be added to Annex II can be considered in the absence of a specific clinical use. For instance, point i) requires one to consider “whether total reliance has to be placed on the result obtained with a given device, this result having a direct impact on subsequent medical action”. Since as noted above, risk-based classification is central to the Directive’s approach to regulation, then anyone who sets out to answer these questions can only do so in relation to a specific intended clinical use. Again, once a manufacturer has a stated clinical purpose for a test, then they must provide data on its clinical validity.

3. Can you fulfil the Directive’s essential requirements without an intended clinical use?

Finally we can turn to the Directive’s six essential requirements concerning safety, quality and performance which all IVDs must comply with before being CE marked and placed on the market. Is it possible to fulfil the Directive’s essential requirements by only providing data on a test’s analytic validity? GR Higson, a UK expert on device regulation closely involved in the development of the medical devices directives, commented on this issue, stating that:

final confirmation of the safety and performance of a medical device is normally provided by observation of the behaviour of the device in its intended use with patients ... Essential requirements 1 and 6, and in some cases 3, can only be satisfied by the evaluation of clinical data relating to the use of the device.⁸

The first essential requirement states that the test must not “compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons”. Furthermore, any risks conferred by the test must be outweighed by the benefits to the patient. Common sense suggest that one can only assess the benefits of a device in relation to an intended clinical purpose. Risk assessment also requires a clinical purpose for the device. Manufacturers must assess “any indirect risks which may be associated with their use”. For IVD devices the main indirect risks are the clinical consequences of an incorrect result. Since such false results might arise from either poor analytic validity or poor clinical validity, then comprehensive risk assessment must evaluate the clinical validity of the test in its intended use.

Perhaps the most relevant part of the Directive is the third essential requirement. Requirement three states that devices must meet the manufacturer’s specifications, taking into account “the

⁷ MEDDEV. 2.14/2 rev.1, February 2004 IVD Guidance: Research Use Only products. A guide for manufacturers and notified bodies.

⁸ Higson, G *Medical device safety – the regulation of medical devices for public health and safety* (Bristol, Institute of Physics, 2002) p49

generally acknowledged state of the art”. Performance criteria that may be appropriate include “analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity”. Common usage of these terms would lead one to understand analytical sensitivity and specificity as referring to analytic validity and diagnostic sensitivity and diagnostic specificity as referring to clinical validity. Unfortunately, the Directive does not define the terms analytical and diagnostic. However, in the common technical specifications for Annex II, List A devices published in 2002, the terms diagnostic sensitivity and analytic sensitivity are defined thus:

(Diagnostic) sensitivity - The probability that the device gives a positive result in the presence of the target marker.

Analytical sensitivity - In the context of the CTS it may be expressed as the limit of detection: i.e. the smallest amount of the target marker that can be precisely detected.

It would seem that diagnostic sensitivity has been defined as what would normally be considered analytic sensitivity. It should be noted that these common technical specifications only relate to Annex II, List A devices and are not part of the Directive. The CTS are currently being revised and this may be one opportunity to correct this problem.

Analytic and clinical validity - policy suggestions:

- 1) It should be mandatory for manufacturers to state the test’s intended clinical purpose and to provide data on both analytic and clinical validity (although for clinical validity it may be sufficient to cite the existing scientific literature).
- 2) This could be dealt with through guidance or through revision of Essential Requirements 1 and 3. Since the Essential Requirements are in Annexe I, revisions can be made through comitology.
- 3) Clarifying the criteria for evaluation is not enough - manufacturers need more detailed guidance on evidence requirements – development of new standards are needed especially for highly complex tests.

Issue 3 – in-house tests

Genetic testing is characterised by a high degree of dependence on tests developed in-house by laboratories (which we will refer to as laboratory developed tests or LDTs). These range from tests for very rare diseases where there is no commercial incentive for the development of kits, through to high-volume tests for common conditions where the test developer has chosen to operate as a reference laboratory rather than as a kit manufacturer (for instance InterGenetics in the United States and Agendia in The Netherlands).

The Directive takes a clearer approach to these tests than either the US or Canadian regulations, which do not explicitly define LDTs as medical devices. But there are

ambiguities concerning the regulatory status of such tests in the EU, in part because there is an exemption for some tests developed by health institutions (Article 1, para 5). The Directive's approach to LDTs thus raises a number questions:

1. What is a health institution?
2. What is an in-house test?
3. How to deal with complex chains of supply?
4. What is the equivalent of the product label?

1. What is a health institution?

In the UK the nature of the health institution exemption has been the subject of considerable debate, but the MHRA has produced some very clear guidance and its current interpretation is that the exemption applies if a device is:

1. made and used by a single health institution
2. used on the same premises as manufacture (or in the immediate vicinity)
3. legally owned (and probably controlled) by that health institution.

This raises the question - what is a health institution? The MHRA's guidance states it is:

6. ... a body whose primary purpose is the care and / or promotion of public health ...[such as] NHS trusts and bodies such as the National Blood Authority and the Health Protection Agency ... [and] private hospitals and bodies which provide private health care (for example, BUPA) ... provided that the primary purpose of those bodies is the care and / or promotion of public health.
7. ... free-standing laboratories which provide diagnostic services, (which are not part of a body which has as its purpose the care and / or promotion of public health) do not ... qualify as health institutions. Similarly, were a clinic to be established purely to provide diagnostic services, which did not have as its overall purpose the provision of health care (i.e. care and treatment of patients) or the promotion of public health, MHRA would not consider such a clinic to be a "health institution." This means that the exemption will not apply to such bodies even if they would otherwise fall within the exemption.⁹

Although the UK position seems clear, our research suggests that, at least in some member states, there is no regulation of in-house tests under the Directive, whilst in others all LDTs are regulated, i.e. no institutions covered by the in-house exemption. This lack of a consistent approach is a cause for concern.

2. What is an in-house test?

LDTs raise other issues which need to be addressed. For instance, what is a laboratory-developed test? We can distinguish between four types:

1. a test created from scratch in the laboratory;
2. a test where the components are bought in and then assembled by the laboratory;
3. a test kit which is modified by the laboratory

⁹ MHRA Guidance In-house IVDs 2004
<http://devices.mhra.gov.uk/mda/mdawebsitev2.nsf/0/A93D14B5548D628E80256EE000534595?OPEN>

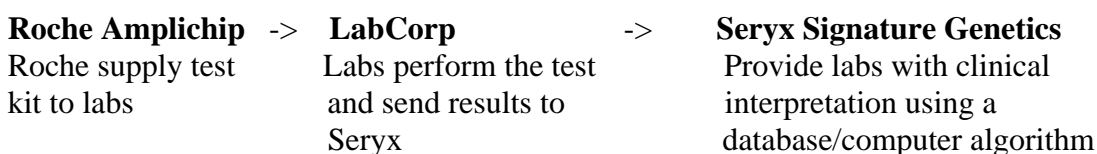
4. a test which is used off-label i.e. for a purpose other than that intended/indicated by the manufacturer

How many of these are covered by the Directive? In 1. and 2. the laboratory can clearly be considered the manufacturer. Yet some experts suggest that under the Directive the party which assigns a purpose to a device is deemed to be a manufacturer and that off-label use may constitute assigning a new intended purpose to a device.¹⁰ Under the New York State system for regulating clinical laboratories, laboratories which seek to use a test in a way other than that approved by FDA, must submit the new use for approval by NY State. Changes of use requiring approval include changing the test’s purpose, for instance from diagnosis to prognosis, or applying it in a different target population.¹¹ The justification for this approach is that modification of kits, and other forms of off-label use, can significantly alter the performance of a test and therefore require evidence of the test’s performance in its modified application. Clarification is needed on how this matter is to be dealt with under the Directive.

3. How to deal with complex chains of supply?

These issues become more complex when we consider some of the complex chains of supply which can be involved in genetic testing. We can illustrate this with a real-world example which involves three companies: a manufacturer, a laboratory and a company with a clinical interpretation service.

Roche Molecular manufacture the Roche Amplichip, a pharmacogenetic microarray which identifies CYP450 genes. Roche supply the test to LabCorp, the second largest reference laboratory in the US. LabCorp send test results to a Canadian company called Seryx, who use a computer database of clinical data and an interpretative algorithm to provide clinical interpretations of the test results. They send their clinical interpretation back to LabCorp who then pass this on to the ordering physician. Each of these parties in this complex supply chain may be making clinical claims for the test. If all these companies were operating in Europe, whose claims would be regulated under the Directive?¹²



4. What is the equivalent of a product label for LDTs?

Ensuring truth-in-labelling is a fundamental aspect of the Directive’s purpose. Yet there is currently no regulatory equivalent of a product label for LDTs. Although a significant move in this direction has been made in the United States as a result of a recent FDA guidance, in

¹⁰ King, S (2004) ‘In Vitro Diagnostics: the grey areas of the Directive 98/79/EC’ *Journal of Medical Device Regulation* p27

¹¹ NYS Department of Health, Clinical Laboratory Evaluation Program, Submission Guidelines for Test Approval accessed online at <http://www.wadsworth.org/labcert/TestApproval/submitguide.htm>

¹² In fact, the Amplichip is CE-marked and Seryx is providing its service to at least one European lab. FDA have stated that Seryx’s algorithm is a medical device and subject to their regulations.

Europe it is not clear how the concept of truth-in-labelling should apply to LDTs.¹³ Since the Directive covers promotional material as well as product labels, then the information which laboratories make available to doctors and patients in printed materials and on their websites, would be covered by the Directive. However, in the case of promotional material it is the manufacturer who decides which types of information to provide to the user; whereas with the product label, the Directive clearly sets out requirements about which types of information *must* be provided to the user. Guidance is required on how to apply these requirements to LDTs.

In addressing this issue European officials could consider the best practice of some leading commercial laboratories, who make considerable efforts to provide detailed information to doctors and patients on the performance of the test and its intended use. Consideration should also be given to the approach being adopted by FDA.

“...the manufacturer should make the labeling information available to users by providing a reference link to the 510(k) summary and/or decision summary documents posted at the publicly accessible FDA 510(k) database website in their test report form.”
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In-house tests - policy proposals:

- 1) Commission investigates how LDTs are being dealt with by member states and how they are interpreting the public health institution exemption. Need to ensure that LDTs put into service by commercial labs are regulated under the Directive.
- 2) Guidance is needed on definition of an LDT.
- 3) Guidance is needed on definition of a label for LDTs. This could drawn on recent FDA guidance which addresses the same issue.

Issue 4 – encouraging transparency

The issue of truth-in-labelling for LDTs is linked to the broader need to ensure the provision of accurate and comprehensive information to patients and doctors. We have advocated a model largely based on regulation by information disclosure, and transparency is particularly important in this model as it gives more responsibility for the safe use of tests to clinicians and lab directors. But they can only take greater control if they have the information on which to act, and in certain respects the Directive works against transparency of data.

It is possible for regulators to facilitate information disclosure by making public their device reviews and subsequent post-marketing data. However, whilst in the US the FDA publishes

¹³ HHS, FDA *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis*
<http://www.fda.gov/cdrh/oivd/guidance/1627.html>

¹⁴ HHS, FDA *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis*
<http://www.fda.gov/cdrh/oivd/guidance/1627.html>

review summaries on its website, in Europe evaluative data is treated as confidential and so the regulatory agencies are under an obligation not to reveal it, unless they have the agreement of the manufacturer. This issue is currently under review and it is expected that in future some categories of information from assessment reports will be made public in summary format, probably on a centralised European website, and that a simplified administrative procedure will be established to review whether additional categories of information should also be made public.¹⁵ However, this may only apply to high-risk devices and might thus exclude genetic tests.

A problem for the regulation of IVDs which extends beyond Europe is that truth-in-labelling may not assist if the end user does not see the label. In the case of prescription drugs, the doctor and patient will see the product label / instructions for use, but most tests are performed by laboratories and it is they who have this information, not doctors and patients. What is required is a broader concept of a label, once which ensures that all those offering tests make the necessary information available to clinicians and the general public. Test manufacturers should be obliged to keep their labels online, where they can be accessed by all. Samples of the results sheet for the test, which show reference ranges etc. should also be provided online.

Encouraging transparency - policy proposals:

- 1) Oblige test manufacturers to make information available to all stakeholders online – labels, sample results sheets with reference ranges etc.
- 2) Work is currently underway on publishing some information from assessment reports, scope of this should be widened. May be able to learn from other countries e.g. United States where review summaries are published.

Issue 5 – predictive testing

At the April 2005 MDEG meeting the IVD Technical Group was asked to analyse the Directive in the context of genetic testing, in particular issues of quality and performance assurance. They produced a note on this issue for the Competent Authorities. One of its conclusions addressed the question of which genetic tests would be covered by the Directive. It stated that:

“2. But, genetic tests that do not have a medical purpose, e.g. genetic tests for forensic or **predictive** purposes, are not covered by the Directive.”¹⁶

Since most genetic tests can be used for both diagnostic and predictive purposes, and a significant amount of genetic testing is predictive rather than diagnostic, then this conclusion may be highly significant. Predictive applications include the prediction of late-onset disorders such as Huntington’s Disease; risk assessment for common, complex diseases such

¹⁵ Interview with EC official 2006

¹⁶ IVD Technical Group Note to MDEG meeting 28 March 2006

as breast cancer and diabetes; prediction of response to therapy (pharmacogenetics); and prognostic tests such as Agendia’s MammaPrint test which predicts risk of breast cancer recurrence.

The intent of the Technical Group’s statement is unclear. Predictive tests are currently covered by the Directive, since at least one test in Annexe II, List B is predictive: “reagents for ... evaluating the risk of trisomy 21”. Furthermore, predictive tests meet the core requirements for definition of a medical device, i.e. they are “for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease” and they also meet the definition of an IVD, i.e. their purpose is “providing information concerning a physiological or pathological state”. Manufacturers of predictive tests clearly think they are covered by the Directive, since they are CE-marking them, e.g. Roche Amplichip and Agendia’s MammaPrint.

Predictive testing - policy proposals:

- 1) IVD Technical Group should clarify what they meant.
- 2) Predictive tests need to be defined.
- 3) It should be made clear that predictive tests which are intended for a medical purpose are IVDs and fall within the scope of the Directive. This could be done through guidance, but if Directive is revised, then the issue should be addressed in the revision.
- 4) GHTF document on IVD classification also needs to clarify status of predictive tests

Appendix

Chronology of major policy reports / recommendations at European level

2000 – European Parliament Temporary Committee on Human Genetics and New technologies in modern medicine

Task:

assess the ethical, legal, economic and social implications of human genetics

Recommendation:

a harmonized EU-wide regulatory framework, to guarantee the quality of genetic testing

2002 – European Commission publishes *Life Sciences and Biotechnology Strategy for Europe and Action Plan*

Recommendations

- play a leading role in the development of international guidelines, standards and recommendations
- science-based regulatory oversight (authorization procedure for products of public health interest)
- calls for the JRC/IPTS to enhance technology foresight in biotechnology for early identification of newly emerging issues and elements of a policy response.

2002 - European Parliament Report on EC’s Life Sciences and Biotechnology Strategy adopted by large majority of European Parliament and supported by Council of Ministers

- Calls on the Commission to draft a legislative regulation for the introduction of a standard for genetic tests, since these services lie outside the scope of existing legislation such as IVD Directive
- Calls on the Commission to take the necessary steps for an EU-wide regulation on DNA-testing, choosing, if possible, a legal basis (e.g. Article 152 (health) or Article 153 (consumer protection)) which leaves Member States free to introduce more stringent protection measures

2003 - JRC/IPTS publish *Towards quality assurance and harmonisation of genetic testing services*

“There seems to be a trend to overestimate clinical utility of the tests. It would be wise to set up a European (or International) review board to determine whether the specific criteria have been correctly fulfilled before a test is introduced in clinical practice or marketed as a commercial product. “

- The creation of an advisory body has been suggested, a European or International review board to determine whether the specific criteria have been correctly fulfilled before a test is introduced in clinical practice or marketed as a commercial product.
- An evaluation system at European level for cost/effectiveness and to prioritise the tests could eventually function along with the utility assessment. It might include determination of the indications of the testing, in which cases is the testing

recommended, and when it is not, or could even formulate guidelines on the clinical and laboratory management of these patients.

- a virtual European body that could mirror the role of the European Agency for the Evaluation of Medicinal Products (EMA) in reviewing the marketing of drugs in EU but it would do it for a given genetic test. It could start as a European Advisory Group that would slowly achieve consensus on validity and utility. Although EMA itself cannot provide the basis for this body, it would obviously be beneficial if it were to be linked to it.

2004 - Strata Expert Group publish *Ethical, legal and social aspects of genetic testing: research, development and clinical applications*

Recommendation 7

That:

- a. the European Union institutes a consistent regulatory framework to assure specific standards of quality for all genetic-testing services
- b. test providers ensure that the information provided is accurate, by conforming with internationally agreed quality standards;
- c. national healthcare systems establish consistent quality requirements for genetic testing.

Recommendation 17

That:

- a. the regulatory framework for genetic testing be further developed by the EU and other international organisations in a way that recognises both the need for new tests and the importance of safety, clinical validity and reliability;
- b. all newly developed tests must conform to the standards established before introduction into clinical use, based on a review process by an organisation or body independent of the test developer to ensure that the patient will benefit from the test;
- e. the EC actively promotes the regulatory framework on these topics.

Major policy reports on regulation of genetic testing¹⁷

US

1975 – *Genetics screening programmes, principles and research* (National Academy of Sciences)

1994 - *Assessing genetic risks* (Institute of Medicine)

1999 - *Promoting safe and effective genetic testing in the United States* (Task Force on Genetic Testing)

2000 - *Enhancing the oversight of genetic tests: recommendations of the Secretary's Advisory Committee on Genetic Testing* (SACGT)

2004 – *Reproductive genetic testing: issues and options for policymakers* (Genetics and Public Policy Center)

UK

1994 - *Genetic screening – ethical issues* (Nuffield Council on Bioethics)

2000 - *Genetics and health – policy issues for genetic science and their implications for health and health services* (Report for the Nuffield Trust)

2000 - *NHS Laboratory services for genetics* (Report for the Department of Health)

2003 - *Genes direct. Ensuring the effective oversight of genetic tests supplied directly to the public* (Human Genetics Commission)

EU

2000 - *Report of European Parliament's Temporary Committee on Human Genetics and New technologies in modern medicine*

2003 - *Towards quality assurance and harmonisation of genetic testing services in the EU* (Institute for Prospective Technological Studies)

2004 - *Ethical, legal and social aspects of genetic testing: research, development and clinical applications* (European Commission Expert Group)

Other countries

1995 – *Opinion and recommendations on 'Genetics and medicine: from prediction to prevention* (CCNE, National Consultative Ethics Committee for Health and Life Sciences, France)

2002 - *ALRC 96 Essentially Yours: the protection of human genetic information in Australia* (Australia Law Reform Commission and Australian Health Ethics Committee)

2002 – *Ontario report to Premiers: genetics, testing and gene patenting: charting new territory in healthcare* (Provincial Advisory Committee on New Predictive Technologies)

2001 - *Genetic investigation of healthy subjects – report on presymptomatic gene diagnosis* (Danish Council of Ethics)

2001 – *The application of genetics in the health care sector* (ZonMW, Netherlands)

International

2001 - *Genetic testing: policy issues for the new millennium* (OECD)

2005 - *Quality assurance and proficiency testing for molecular genetic testing: summary report of a survey of 18 OECD member countries* (OECD)

¹⁷ This list is not exhaustive and does not cover the many academic policy articles which have been published around this subject