

The regulatory framework for genomic tests

**Evidence to the House of Lords Science and
Technology Sub-Committee on Genomic Medicine**

April 2008

Summary

- 1) This submission addresses questions posed by the sub-committee relating to the regulatory framework for genomic medicine, in particular the regulatory framework for genomic tests. The committee asked questions about gaps in the regulatory framework, how this framework compares with regulation in other countries, what progress is being made in regulation of genetic tests that use genome variation data and the possible utility of a regulatory code governing the provision of medical advice based on genomics information. This submission focuses on the IVD Directive (enacted in the UK by the Medical Device Regulations 2002 and enforced by the Medicines and Healthcare Products Regulatory Agency (MHRA).
- 2) This submission draws on three years of research on the policy issues relating to the regulation of genetic tests for common diseases and addresses the growing concerns that some genetic tests are entering the direct to consumer market and clinical practice prematurely. It highlights a number of important areas where the current system of regulation in Europe needs to be improved.
- 3) In seeking to find a balance between improving regulation to protect public health and promoting the rapid adoption of useful new tests, we suggest that a focus on regulation by information disclosure should inform future approaches to the regulation of genomic tests. One of the primary goals of regulation should be to ensure that:
 - doctors and patients have sufficient information about a test's accuracy, utility and safety risks to make an informed decision about whether to use it; and
 - doctors and patients receive accurate and informative test results which can guide decisions about prevention or treatment.
- 4) The primary areas of the IVD Directive which require attention are its approach to risk classification, its lack of clarity on data requirements, undue level of secrecy over clinical data held by manufacturers and ambiguities surrounding the regulation of tests developed by commercial reference laboratories.
- 5) A number of EU member states are keen to address some or all of these anomalies and the forthcoming review of the IVD Directive will provide an opportunity to take action. The UK government should act with other countries to ensure that the European regulatory system is enhanced to provide more adequate safeguards for public health.

Introduction

- 6) This submission draws on three years of research on the policy issues relating to the regulation of genetic tests for common diseases.¹ In the course of our research we have looked at the regulatory regimes in Europe, the United States, Canada and Australia and we have spoken to over 80 individuals from key stakeholder groups - policymakers, regulators, diagnostics companies, clinicians and patients groups.
- 7) Over the past 15 years, genetic testing has begun to play a greater role in disease prevention, management and treatment. This has brought significant clinical benefits to many patients. However there have been growing concerns that some genetic tests are entering the direct to consumer market and clinical practice prematurely. There has been a prolonged policy debate about how best to ensure the safe and appropriate use of clinical genetic tests; a number of expert bodies have reviewed the oversight of genetic testing and their reports have come to similar conclusions:
 - public confidence in genetic testing can be maintained only if there is a clear and coherent framework of regulation;
 - the regulatory status quo is not adequate;
 - new genetic tests should be subject to independent evaluation of their analytic and clinical validity before they are offered as part of clinical care
- 8) Many participants in our research expressed support for the view that regulatory reform is required. However, not all stakeholders were convinced of the necessity of reform or that statutory regulation could provide useful additional safeguards for the public. More generally, nearly all stakeholders were concerned that regulatory reform should not impede innovation by creating unnecessary 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 statutory regulation of tests and enhancing other regulatory mechanisms, including a more systematic approach to Health Technology Assessments for new genetic tests.
- 9) This submission outlines a series of issues in the IVD Directive which need to be addressed if it is to facilitate the safe and effective use of genomic tests by doctors and patients. These include: using a “light touch” approach to premarket review of new tests focused on:
 - a. Access to all data on the performance of tests
 - b. ensuring truth-in-labelling
 - c. improving the risk classification system
 - d. providing clearer guidance on the regulation of laboratory developed tests
 - e. and facilitating transparency of data through mechanisms such as a test registry

- 10) This seems a particularly opportune moment to consider these issues: the EU IVD Directive is well-established in the member states; the Commission is now preparing for a revision of the Directive; and the development of IVD regulation is being actively pursued through the work of the Global Harmonisation Task Force. This provides an opportunity to strengthen both the explicit public health and free trade objectives of the IVD directive, without letting the latter undermine the former.

Pre-market review and minimum data requirements

- 11) Premarket review is the most powerful tool in the regulator's toolkit. This barrier to market entry is used to ensure that the manufacturer's intended use for the product is supported by the clinical data on the test's performance as set out in the technical file, and summarised in the product label and in promotional material and to ensure that the product label includes appropriate instructions for the user including any necessary warnings on the limitations of the test's performance.
- 12) Ensuring truth-in-labelling and truthful promotion - an honest account of the strengths and weakness of a test's performance - can be thought of as the fundamental function of premarket review in the medical devices sector, although for high-risk tests the process may be more onerous, with regulators setting out in some detail the types of clinical studies which will be required to gain premarket approval. 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.
- 13) 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. It presents a minimal evidence requirement since it is possible for a test developer to rely solely on the existing scientific literature rather than conducting costly clinical studies of their own (providing of course that the literature supports the test developer's intended use). Our research showed considerable support for an approach focused on using pre-market review to ensure truth-in-labelling (and truth-in-promotion) and full evidence disclosure.
- 14) This position was linked to the broadly-supported view that data on analytic and clinical validity are minimum data requirements for test developers 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 (see ACCE framework below). 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.

Clinical validity should be assured before putting a test on the market. Clinical utility will be very difficult because it may take years of exposure to the market with a specific test to get back clinical utility data that are anywhere near meaningful ... That is only possible if you expose the market to the test. You can never do that pre-clinically or pre-market. It costs too much time, too much effort, too much money that nobody will be able to pay that.

European IVD manufacturer (focus group participant)

- 15) However, there is some ambiguity regarding evidence requirements in Europe. Whilst in the United States and Canada the regulators require evidence on analytic and clinical validity of tests, there is currently disagreement amongst European member states about whether in fact manufacturers must provide data on clinical validity to fulfil the requirements of the Directive.² Some believe that manufacturers are only required to provide evidence on analytic validity (but must provide data on clinical validity if they make clinical claims). However, we have spoken to a number of member states who believe that the Directive goes further than this and that to fulfil its essential requirements manufacturers should provide data on both analytic and clinical validity. Clarification of this ambiguity is required.

ACCE framework for test evaluation

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

Risk classification

- 16) 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. 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:
- a. They are often stand-alone, with no confirmatory test available.
 - b. They are used for relatively serious clinical purposes, such as pre-implantation genetic diagnosis and selecting treatments (pharmacogenetics).

- c. They may have serious psychological impact (e.g. Huntington's Disease).
 - d. Many new tests are highly complex involving multiple alleles or multiple genes, making interpretation more difficult.
 - e. 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.
- 17) European officials have admitted that this approach to risk classification is problematic and have suggested they may adopt the model developed by the Global Harmonisation Task Force (GHTF) which is both more comprehensive and more consistent.³ Largely modelled on the Australian system, it is a four-class system running from high- to low-risk, and places some genetic tests into the moderate-to-low risk category (Class B) and others in the moderate-to-high risk (Class C) category. Adoption of the GHTF model in Europe would be a significant advance on the EU's current incoherent and inconsistent approach to risk classification and would ensure that a far greater proportion of genetic tests will be subject to independent pre-market review. The Dutch government has made its own proposals regarding reform of the European risk classification system which would create a more consistent four-class system in which predictive genetic tests would be classed as moderate to high risk (Class C).⁴

Creating greater transparency

- 18) 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, but in certain respects the Directive works against transparency of data.
- 19) Current law and practice involves an extraordinary level of secrecy in the regulation of genetic and other tests. Technical files, the dossier of evidence (including the clinical data) a manufacturer prepares to demonstrate they have fulfilled the requirements of the IVD Directive, are regarded as confidential, impeding the ability of health professionals to identify areas of concern and report them to regulators. The MHRA has also indicated that it is unable to inform professionals about any action taken when complaints are made about mismatches between test claims and performance. This lack of transparency is at odds with the climate in drug regulation and with the principals of quality improvement approaches in health care and very likely puts patients at unnecessary risk.
- 20) 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 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.⁵ However, this may only apply to high-risk devices and might thus exclude genetic tests.

It is bizarre that if I want a hip implant I can get info from FDA website but not in Europe ... If I am a concerned citizen wanting information on a medical device then you would have to have faith in the competent authorities that it exists.

Interview with European Commission official

21) A problem (which extends beyond Europe) for the regulation of IVDs 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 how tests are interpreted etc. should also be provided online.

Laboratory developed tests

- 22) 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).
- 23) 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 what are termed “health institutions”.
- 24) In the UK the nature of the health institution exemption has been the subject of considerable debate, but the MHRA’s current interpretation is that the exemption does not apply if the institutions offering the test are: “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)” Although the UK position seems clear, our research suggests that, at least in some member states, there is no regulation of LDTs 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.

I see absolutely no reason, if it is a regulated industry and industry has to be regulated, that a laboratory that makes its own test has crossed the line from a buyer to a maker, and they should fall under the maker rules.

US IVD manufacturer (focus group participant)

- 25) The market for genomic tests often involves complex chains of supply. For instance, there are an increasing number of companies who provide genomic tests as LDTs from reference laboratories outside the European Union. Sometimes they offer the tests direct-to-consumer over the internet e.g. the US company 23andme and the Icelandic company deCODE. Some companies prefer to partner with a European firm who take patient samples and report the results to the patient e.g. the US company Genomic Health is offering its Oncotype Dx test in Europe through a partnership with Medical Solutions, a UK firm based in Nottingham.
- 26) The advice we have received from both the MHRA and the European Commission suggests that in neither case would the tests provided by companies outside the EU be subject to the IVD Directive. Whilst there is no explicit reference in the Directive to such arrangements which would clearly cover such tests, we are not aware of any provisions within the Directive which clearly indicate that such tests are not covered by the Directive. We would suggest that since the Directive clearly covers commercial LDTs, then there is no reason to exclude these tests and that to do so would not only be a failure to protect public health but would also provide a perverse incentive for EU companies to locate their operation outside the EU, an outcome incompatible with the objective of developing the UK (and European) biotech sector.
- 27) 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. 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 it may be helpful to 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 which suggests companies should provide online information to test users.⁶

Guidance on standards

- 28) Regulators can assist test developers by making their regulatory requirements clearer. The regulation of diagnostic tests relies heavily on guidance documents to supplement the basic statutory requirements. Guidance is also important because regulation focused on ensuring truth-in-labelling requires agreement on what constitutes truth. This requires consensus on standards of evidence, amongst all stakeholders.

From a commercialisation point of view, the more clearly you can enunciate the path between idea to product and the cost associated with that, the better ...

Interview with US IVD manufacturer

- 29) The IVD Directive has been developed under the aegis of the EU's New Approaches framework of regulation. This seeks to deal with the problems encountered when regulating a range of rapidly developing technologies by setting broad essential requirements supported by more technology-specific standards which can be updated as required. However, there have been no guidance documents or other kinds of standards developed for genomic tests in Europe, an issue which some industry stakeholders suggested was a problem for them. Amongst medical device regulators, the FDA is the most advanced in its development of guidance on the evaluation of genetic tests.⁷ It is not unusual for regulators from other countries to adapt FDA guidance documents⁸ and it may be that Europe can learn from the FDA's experience. It also may be helpful if there could be greater international coordination in the development of guidance, as a more consistent approach would lessen the regulatory burden for companies.

... it's so open to interpretation. For the majority of tests apart from ... the high or moderate risk tests, it is up to the manufacturer to interpret whether they meet the requirements of the Directive and most companies had already gone through FDA approval with their products where it's much more 'this is what you have to do. Put in a submission and get approval for sale in the USA.' ... Whereas with the Directive it is very much open to ... There's a lot of uncertainty. Have I done the right thing?

European IVD manufacturer (focus group participant)

Independent information sources

- 30) Our research also found strong support for the idea of an *independent* web-based information tool which might provide details on both tests and quality information on laboratories. Existing examples of web-based information tools were cited as providing examples of what could be achieved, the Lab Tests Online⁹ website which is a resource for all kinds of lab tests and the two genetics sites – GeneTests¹⁰ in the US and OrphaNet¹¹ in Europe.

- 31) Discussion of such web-based data sources has taken on greater significance in the United States since the FDA has indicated it is to regulate some LDTs. Some of the companies who are affected by this development are advocating an alternative system of regulation which would require LDT developers to provide details of their company, their laboratory and their tests on a web-based registry. This system would not entail submitting tests for premarket review by FDA but would provide some controls to ensure that companies provide clinical evidence to test users.
- 32) Such a model is an intriguing one and offers either an alternative, or a supplement, to our model for least burdensome premarket review. However, this model raises two important questions: who guarantees the quality of information provided and who deals with complaints? The former problem is difficult to address without some form of independent evaluation of the evidence. The latter problem could also be addressed by the statutory licensing authority adopting the role of “meta-regulator”, allowing the market to operate with minimal controls but ready to step in where concerns arise. Clearly such a model has parallels with the EU’s current system, largely based as it is on reacting to complaints once a test is on the market. Its advantage over this system in which technical files are treated as commercially confidential, is that it introduces a high level of information disclosure.

Conclusion

- 33) Genomic science is moving at great speed. Genome-wide studies have recently identified many new variants associated with common diseases. Findings point mainly to sets of variants with modest effects, with many more markers still to be discovered. Some variants are shedding new light on disease mechanisms and on previously unsuspected parts of the genome. Much more work is needed, however, to define the clinical relevance and value to patients of testing for these new genetic markers.
- 34) It is worrying that in the absence of this knowledge, commercial genetic testing services are being marketed directly to the public. In an age of evidence based medicine, the marketing of genetic tests with little evaluation is an unwelcome anomaly. The UK has already made a significant contribution to progress towards the evidence-based evaluation of genetic tests through the development of the UK Genetic Testing Network and the gene-dossier process. It can provide further leadership by advocating reform of the IVD Directive towards a regulatory system that encourages clinical evaluation and makes the results (or lack of them) easily available to all.

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² For an analysis of the ambiguities see Hogarth, S and Melzer, D *The IVD Directive and Genetic Testing: Problems and Proposals. A Briefing presented to the 20th Meeting of Competent Authorities.* (Cambridge University, (2007)) Disagreement amongst member states was clear in the discussion following this presentation.

³ Remarks made by EC official at EuroGentest meeting on IVD Directive and genetic testing in Leuven, April 2007. **NB** The GHTF is an international forum which brings together regulators and industry from the US, Canada, Australia, Europe and Japan to work towards harmonization of the regulatory frameworks for medical devices. GHTF Study Group 1 (2007) *Principles of In Vitro Diagnostic (IVD) Medical Devices Classification, Proposed Document*

⁴ M Hollestelle, and A de Bruijn *In Vitro Diagnostic Medical Devices. Decision rules for IVD-classification* (Bilthoven, 2006)

⁵ Interview with EC official 2006

⁶ HHS, FDA *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Gene Expression Profiling Test System for Breast Cancer Prognosis*
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⁷ For a broader discussion of FDA leadership in this area, see Hogarth, S. *et al.* (2006) *Regulating pharmacogenomics. an overview of developments in various countries and industry response to regulatory initiatives* (Cambridge,)

⁸ Interview with official from Medical Devices Bureau, Health Canada, August 2007.

⁹ <http://www.labtestsonline.org/>

¹⁰ <http://www.genetests.org/>

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