phg foundation
making science work for health

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Revision of Directive 98/79 of the European Parliament and of the Council of 27 October 1998 on *In Vitro* Diagnostic Medical Devices

Response from the PHG Foundation

Introduction

The Foundation for Genomics and Population Health (PHG Foundation) is a non profit making charitable company and the successor body to the UK Public Health Genetics Unit. Its overarching purpose is to foster and enable the application of biomedical science, particularly genome-based technologies, for the benefit of human health. Among its specific objectives is the promotion of a social and regulatory environment that is receptive to innovation, without imposing an undue or inequitable public burden. The Foundation has a particular interest in the way that new technologies are translated within health services, in genetic research and its impact upon clinical and public health services.

General Comments

The PHG Foundation has previously responded to the consultation on recast of the medical devices directives[1]. In our response we referred to the framework we have developed for evaluating DNA tests[2], and more recently have expanded this to a framework for evaluating and regulating consumer genetic tests[3].

Medical diagnostics are now moving away from individual kits and tests for specific targets towards multivariate investigations, such as genome scanning techniques. As this trend continues, the role of the regulator should be to focus on the technical accuracy of the technique and the competence of the institutions, companies and personnel responsible for delivering the service and interpreting the results. We believe that the primary purpose of the *In Vitro* Diagnostic Medical Devices Directive (IVDD) is to ensure that, when products are placed on the market, they are *safe* and *perform as intended*. With this in mind, we have the following three points to make with respect to the current revision:

(1) Unwarranted genetic exceptionalism should be avoided. Tests should be regulated in accordance with an evidence-based risk assessment, not simply by virtue of the particular analyte assayed.

(2) There is a balance to be struck between facilitating innovation (in providing for a regulatory environment that is not so oppressive that it stifles novelty) whilst protecting consumers and patients from harm. Thus any regulatory regime must be targeted, appropriate, and proportionate.

(3) The IVDD is not the sole means of regulating medical tests (see Figure 1), and revision of the Directive to widen its scope is misguided in our view. Specifically, we believe that it should be limited primarily to: (a) the analytical validity of the assay, which includes the technical competence of the laboratory (*e.g.* through ISO-15189 accreditation); and (b) the scientific validity of the claims made by the manufacturer. Issues around clinical performance and utility, whilst critical, cannot be

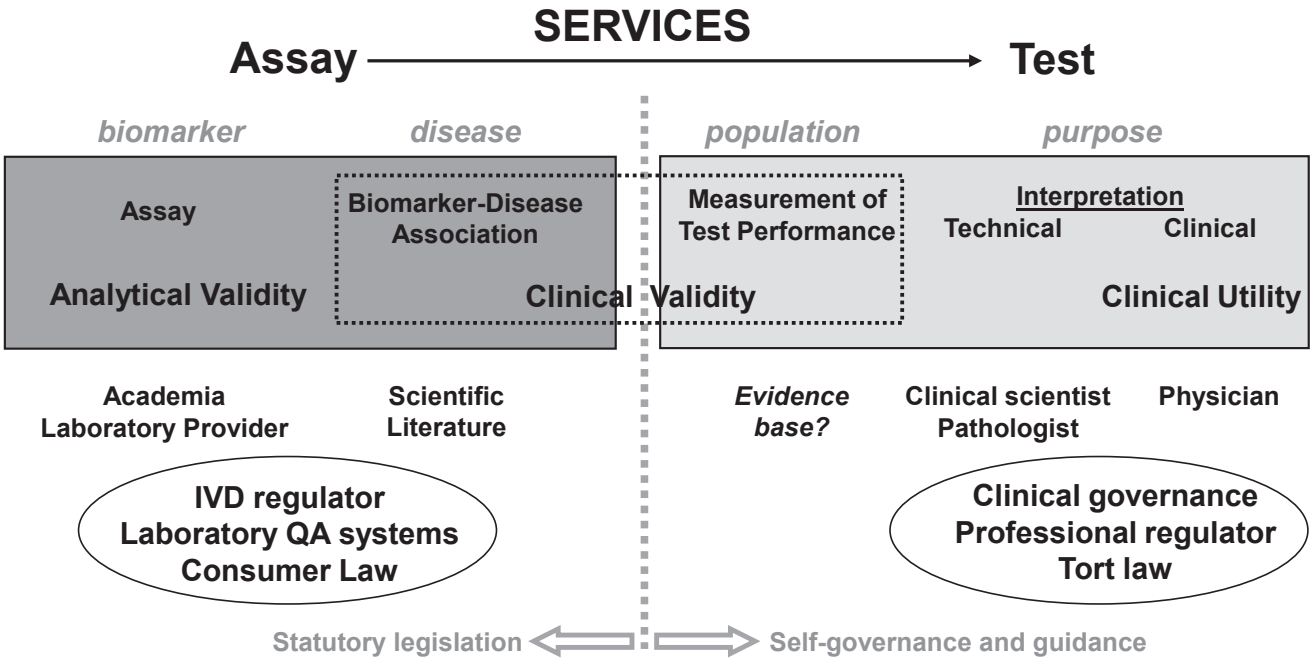
1 PHG Foundation (2008) Recast of Medical Devices Directives: Public Consultation. Evidence from the Foundation for Genomics and Population Health.

2 W. Burke, R. Zimmern. (2007) Moving beyond ACCE: An expanded framework for genetic test evaluation.

3 C.F. Wright, A. Hall, R. Zimmern (2010) Regulating direct-to-consumer genetic tests: what is all the fuss about? Genetics in Medicine (in press)

legislated in the same manner, as the interpretation of the test depends on professional judgement, health care services, the patient population, the clinical context and the exact purpose of the test. Rather, regulation through professional governance mechanisms should be used ensure that the individuals involved in each stage of the test are competent.

Figure 1: Outline of a model test evaluation framework, adapted from the ACCE model for genetics test evaluation, with the relevant regulatory vehicles indicatd at each stage[4]. We suggest that the scope of the IVDD should be limited to regulating everything on the left-hand-side of the dotted line.



Another important consideration is whether the desired outcome of increased regulation could be achieved by means which are either less oppressive or burdensome. For example, we question whether the proposed extension of the scope of conformity assessment procedures, or change to the definition of genetic tests would be more effective than alternatives which are less restrictive of free markets. For example, an alternative approach to concerns about consumers being mislead if genetic tests are marketed direct to the public is a response which combines robust sanctions for misleading advertising, coupled with a requirement for transparency so that evidence is made available to potential consumers from a publically accessible source (such as the Genetic Testing Registry recently proposed by US National Institutes of Health). Submission of evidence to such a database could be mandatory for testing companies, rather than voluntary as currently proposed, without necessarily extending the scope of the Directive. Therefore our starting point is to question whether other regulatory strategies might be more effective than some of the proposals that are the subject of this consultation (such as the removal of CE marking for 'in house tests').

4 C.F. Wright, A. Hall, R. Zimmern (2010) Regulating direct-to-consumer genetic tests: what is all the fuss about? Genetics in Medicine (in press)

Consultation questions

1. Classification

Q1: Should a risk-based classification be adopted and what would the public health consequences be?

We are in favour of a risk-based approach, such as that advocated by the Global Harmonization Task Force on the basis that it offers a proportionate model of regulation (in which the degree of oversight is commensurate to risk) whilst ensuring transparency, accountability and consistency. In particular, we are supportive of an evidence-based approach to classification, and oppose (for example) categorising all genetic tests as the same risk simply by virtue of the fact that they assay DNA.

However we have some concerns about how a risk-based approach may operate in practice (such that it may not be always be straightforward to discriminate between the safety of a device and the harm caused as a consequence of its use). It is important to be clear what harms the regulation is intended to prevent. For *in vitro* devices, the concern is not with the assay itself, but the consequential harms that might be caused by the result. All tests have false positive and false negative results, which can lead to incorrect and harmful treatments, and all tests cause anxiety. Therefore, the preventable harms are limited to protecting consumers and patients from inaccurate *interpretation* of test results. As stated previously, interpretation cannot be directly legislated, therefore the role of the IVDD in mitigating the risk to the public is ensuring that the assay result is accurate, and that any claims are backed up with robust scientific evidence.

In the UK, the majority of diagnostic and/or predictive genetic tests are administered in the context of receiving medical care from a health care professional, already regulated through professional bodies, who interprets the test result and has legal responsibility for ensuring that the standard of care conforms to customary medical practice. This might include providing that suitable pre-and post-test counselling is available if the results are likely to confer clinically actionable results, or advising on follow-on tests, interventions or treatments. Although some genetic tests are now available to the public on a direct-to-consumer basis (see Q11), there is little evidence of any harms being caused.

2. Conformity assessment procedures

Q2-6: In the context of a possible adoption of a risk-based classification, should conformity assessment procedures be amended (and how)?

No specific comments.

3. Scope

3.1 Specific exemption for 'in-house' tests

Q7: Would it be necessary to maintain the exemption provided for by article 1(5) of Directive 98/79/EC and why?

We are strongly in favour of the existing exemption provided for by article 1(5) of Directive 98/79/EC being maintained within the UK, on the basis that the great majority of tests are supplied via the National Health Service. It is the norm for hospital trusts to develop their own 'home brewed' tests, in their own laboratories and then for those tests to be used for within the local geographical area. This system appears to work well and we are not aware that any patients have been harmed as a result.

Q8: If this exemption should be limited, which of the following items should be limited or clarified?

(1) Definitions of 'in house test', 'health institution' or 'premises of a manufacturer or premises in the immediate vicinity'?

(2) Require essential requirements to be fulfilled without CE marking?

(3) Support exclusion of high risk items

(4) Require tests that are eligible for the exemption nevertheless are accredited or nationally regulated?

In view of the lack of evidence that patient safety has been compromised, and given the existing well-established hierarchy of professional accountability within NHS laboratories within the UK, we suggest that there is no justification for altering the existing scope of the exemption. We therefore oppose limiting or clarifying it by any of the measures suggested in paragraphs (1) to (4) above (by amending definitions, providing for fulfilment of requirements without CE marking, excluding high risk items or introducing other forms of accreditation or national regulation).

Q9: Should devices for monitoring of rare conditions (affecting less than 5:10,000 people) be exempted?

We strongly support the exemption of devices that monitor rare conditions (in preference to other regulatory strategies). This is particularly relevant to very rare genetic disorders where bespoke tests are necessarily used, in some cases for just a single family. There are a number of instances in which the EU already treats rare diseases as a special case and relieves manufacturers and regulators from the regulations that would ordinarily apply. Where conditions arise very infrequently, there is little commercial incentive to create or manufacture tests which will only be used by a small sub-population of affected individuals.

3.2 Genetic tests

Q10: The scope of genetic tests covered under Directive 98/79 and extension to include tests with an indirect medical purpose

We do not support an extension of the IVDD to include tests with an indirect medical purpose. Furthermore, we do not support a genetic exceptionalist approach that regulates all DNA-based assays without regard to their purpose. Moreover, because whole genome analysis is becoming more common, rather than individual genetic tests, both for medical and non-medical purposes, we believe that the competence of the organisations and personnel involved in providing these services should be regulated through laboratory accreditation and professional certification.

(1) Extension to include results obtained by analysis of the genome? Exclusion of some categories of tests?

We oppose the requirement that all forms of genomic analysis should be regulated under the Directive, for the reasons stated above. A genomic analysis which is used to answer a medical question (such as using array-CGH for diagnosing copy number changes underlying learning disability, for example) should be regulated as a medical device, whilst one that is used for non-medical purposes (such as SNP-genotyping for genealogical investigation) should not. Therefore, test purpose and the claims made by the test manufacturer/ provider should define whether a test is included in the scope of the IVDD, not the analyte assayed. Where there are multiple uses of the same device, only those tests for medical purposes should be within the scope of the IVDD.

Many types of genomic analysis serve no medical diagnostic purpose and much of the genome will therefore remain irrelevant for this use and thus should not require medical regulation.

(2) Direct or indirect medical purpose?

As stated above, we do not support the extension of the definition of genetic tests in the Directive to include indirect medical tests.

Q11: Additional requirements for direct-to-consumer genetic tests?

Although there are fears that direct-to-consumer genetic tests provoke anxiety in consumers, there is little evidence of harm. On the contrary, preliminary evidence suggests that even where individuals receive results that they have inherited a genetic variant that confers a small but non-deterministic increased relative risk, they may not change their behaviour as a result of learning of their increased risk. To the extent that genetic tests that are of direct medical purpose are already covered by the Directive, we see no purpose in extending this category to protect the interests of consumers.

However, we believe that improved regulation through the IVDD is relevant for those consumer tests that make medical claims:

(a) It should be a requirement that all tests are carried out in facilities which have formal laboratory accreditation, irrespective of whether they are provided to physicians, hospitals or consumers, in order to ensure analytical validity;

(b) Any claims made by the test providers should be supported by scientific evidence. Thus, for susceptibility testing, there should be robust epidemiological evidence that the gene-disease association is real.

3.3 Diagnostic services

Q12: Clarifying 'putting into service'

No further comments.

Q13: Other specific requirements

We believe that the IVDD could be strengthened to ensure "truth in labelling", which is particularly important for tests available direct-to-consumer. It should be a requirement that any medical claims used for advertising should be supported by evidence (as is already the case for drugs). Moreover, there should be a clear evidence base for recommending products as a companion to testing, or that are expressed to be contingent upon the test results (such as vitamin supplements or other nutritional product). Advertising standards regulations (such as those arising from the EU Unfair Commercial Practices Directive, *e.g.* the UK Consumer Protection from Unfair Trading Regulations 2008) might be relevant here.

3.4 Point of care/near patient in vitro diagnostic medical devices

Q14: Is there a need to add specific requirements for 'point of care' or 'near patient' testing?

No specific comments.

4. Clinical evidence

Q15: Clarification of the requirements regarding clinical evidence for IVDMD's

4.1 Clinical validity.

We believe that there is a need to clarify the requirements for clinical evidence, in particular the "demonstration of performance", in the IVDD. Although it is often taken to mean clinical validity, it is important to clarify exactly what this entails, as the concept of clinical validity can usefully be separated into two linked but independent factors:

i. *Scientific validity* – the robustness of the scientific or epidemiological evidence that the assayed biomarker is actually linked to the disease of interest. This is a necessary, though not sufficient, criterion for a test to be clinically useful, and could form a minimum evidentiary requirement for all tests.

ii. *Clinical test performance* – the performance of the test in the population and clinical context in which it will be used, for a particular defined purpose (e.g. diagnosis, screening, prognosis, etc). This is generally evaluated through standard measures such as sensitivity, specificity and positive and negative predictive values. Although such evidence is needed to know how a test will perform in a particular clinical context, due to the expense and collaborative nature of the trials required, we do not support this being a mandated requirement for a test to be available.

We therefore recommend that the terminology used within the IVDD should be clarified to make it clear that the requirement for "demonstration of performance" is confined to providing evidence of scientific validity.

4.2 Clinical utility

We do not support a requirement for clinical utility to be demonstrated as a prerequisite for a test being made available, not least because utility will differ between different contexts and be dependent upon many factors that are outside the scope of the Directive (e.g. healthcare infrastructure, presence of effective treatments, funding structures, acceptability of the test within a particular country, etc). While evidence of utility is desirable, healthcare systems must evaluate the potential utility within their own specific contexts. In particular, lack of evidence of utility should not prevent potentially valuable and innovative tests from being available. In the direct-to-consumer context, the absence of clinical utility does not necessarily imply that the test has no personal utility, or that an individual should not be free to access a test purely out of interest, in full knowledge that testing is unlikely to yield anything useful. Ancestry testing is a case in point: individuals may feel curious about their origins without feeling compelled to use that information in a clinically actionable way.

5. Others

5.1 Conditional CE marking (Q18)

There may be a public health justification for conditional CE marking in some cases. Emergency use in a pandemic is a good example of where the likely benefits of using a genetic test, outweigh the likely benefits, and where evidence as to safety, performance and utility may well emerge over a given time period. However, with very rare inherited conditions, manufacturers may not be in a position to submit evidence in support of a test, due to the rarity of the disease and our preference is for exempting rare conditions from the requirement for CE marking altogether.

5.2 Companion in vitro diagnostic medical devices (e.g. pharmacogenomic assays, biomarker assays) (Q19)

We believe that the focus for regulation should be the quality of the evidence that supports any medical claims that are made. Where medical claims have a direct impact on patient safety, then these claims should be supported by appropriate evidence: this is the case with the use of companion diagnostics and pharmacogenomic tests that together may dictate a particular therapeutic choice, and guide drug selection and dosage.

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9 September 2010

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