EuroGentest response to EC consultation on recast of Medical Devices Directive

EuroGentest is an EU-funded Network of Excellence (NoE) with 5 Units looking at all aspects of genetic testing - Quality Management, Information Databases, Public Health, New Technologies and Education. Through a series of initiatives EuroGentest encourages the harmonization of standards and practice in all these areas throughout the EU and beyond.

Issue 1 Scope, Item 2 Risk-based classification (and Issue 7. GHTF)
This issue is dealt with on pages 10 and 11 of the briefing. We argue that a risk-based classification system would be preferable to the current list-based system because it would be more coherent and consistent and would provide a greater level of protection for public health by subjecting a broader range of tests to independent pre-market evaluation. Regarding costs or savings resulting from this change, we have no data to provide. However, we would note that such a change would bring Europe more closely in line with the US and Canadian systems and the proposed new model for Australia. Such international harmonisation is of benefit to industry as it creates a more consistent regulatory landscape. Furthermore, bringing more tests into the moderate-high risk category, and subjecting them in effect to the equivalent of the FDA's 510k review should not pose an undue burden to industry.

However, we must stress the urgency of reform required on this matter. The range and number of new genetic and genomic tests coming on to the market is growing rapidly. Genomics is moving from its current place as a clinical specialty dealing largely with rare diseases to a broader role in healthcare. Past experience would suggest that the likely timetable for reform of the medical device directives is 2-3 years at a minimum. The pace and scale of innovation in molecular diagnostics does not permit us to wait that long. Serious consideration should be given to whether revision of risk classification can be done more swiftly through comitology since the current list based system appears in annexes to the directive.

Issue 1 Scope, Item 3 Medical devices currently not regulated at an EU level
a. LDTs outside EU
The market for genomic tests often involves complex chains of supply (see page 16 of the briefing). For instance, there are an increasing number of companies who provide genomic tests as Laboratory Developed Tests (also known as in-house or homebrew tests) 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.

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 the Commission's Life Sciences and Biotechnology Strategy which commits it to supporting the development of the European biotech sector.

b. Lifestyle tests

The UK's Competent Authority the Medicines and Healthcare Products Agency (MHRA), claim that so-called 'lifestyle' tests are not clinical tests, so would not be covered by the IVD Directive (*More Genes Direct*, Human Genetics Commission, 2007). The term 'lifestyle test' lacks a precise definition but is sometimes used to describe tests such as nutrigenetic tests, where the intended use of the test is to provide lifestyle advice such as dietary guidance. The MHRA draws a distinction between these and what it deems "tests for a medical purpose."

Consideration of this requires an understanding of what constitutes an IVD medical device. In Europe a medical device is defined as items "intended by the manufacturer to be used for human beings, for the purpose of…. diagnosis, prevention, monitoring, treatment or alleviation of disease" (European Commission, 1993) and the European definition of an 'in vitro diagnostic medical device' is any medical device which is … intended by the manufacturer to be used in vitro for the examination of specimens … derived from the human body, solely or principally for the purpose of providing information: concerning a physiological or pathological state …" (European Commission, 1998)

The Human Genetics Commission (HGC) have questioned the MHRA's position and suggested that 'lifestyle' tests may be considered IVD devices if their purpose is to help in the prevention of disease (HGC, 2007). Moreover, a number of regulatory authorities have indicated they agree with the HGC. At a congressional hearing largely devoted to the regulation of nutrigenetic tests, Steve Gutman, Director of FDA's Office of In Vitro Diagnostics was asked whether such tests were covered by FDA's regulations for medical devices, he answered in the affirmative (US Congress, 2006) and letters were subsequently sent to a range of nutrigenetics companies inviting them to meet with the FDA (Gutman, 2006). In Australia the Therapeutic Goods Administration (TGA) has issued guidance on the issue (TGA, 2007).

Whilst some DNA tests, such as forensic and paternity tests, clearly fall outside the IVD Directive, nutrigenetic tests, which are intended to improve health and prevent disease, and which often give risk predictions for common diseases such as cancer and heart disease, should be considered IVD devices.

3 Evaluation procedures Item 6 Changes needed to essential requirements

On pages 12-14 we deal with the issue of evidence requirements, specifically Essential Requirements 1 and 3. We conclude that 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). When we presented these ideas to the Competent Authorities in Lisbon it became apparent that there is significant disagreement between member states on this issue, with some taking a similar view to us and others taking the view that the Directive only requires data on analytic validity. Disagreement on such a fundamental point is a serious cause for concern. Neither public health nor industry are well served by such a lack of clarity.

Regarding the socio-economic impact of the changes we propose, we believe that requiring as a bare minimum that a company be able to cite the existing scientific literature that supports their intended use for a test, is not an unreasonable burden; it does not require significant investment in clinical trials and it allows rapid entry to the market but it would constrain companies from making unsubstantiated and overblown claims for the value of their tests.

Regarding timing, we would refer again to the urgency of this matter in the light of both its fundamental nature and the rapid pace of innovation in molecular diagnostics. As with the issue

of the revision of risk classification, the essential requirements can be revised through comitology since they appear in an annexe to the directive.

3 Evaluation procedures Item 7 'harmonised specific requirements'
On page 14 of the briefing our discussion of the issues surrounding analytic and clinical validity concludes with the recommendation that: "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." To date there have been no guidance documents or other kinds of standards developed for genomic tests in Europe, an issue which some industry stakeholders have suggested to us was a problem for them and which offers little protection for public health. Amongst medical device regulators, the FDA is the most advanced in its development of guidance on the evaluation of genetic tests. It is not unusual for regulators from other countries to adapt FDA guidance documents 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. Whether this absence of standards is dealt with through harmonised specific requirements or another harmonised European standards system is less important than the need to address this gap.

3 Evaluation procedures Item 9/10 A new role for EMEA
Given the well-documented weaknesses of the Notified Bodies system it would be very beneficial for the role of EMEA to be enhanced. EMEA has a particular interest in pharmacogenetics, but its current lack of authority over diagnostic tests means that whilst it can authorise a new medicine whose prescription requires the use of a pharmacogenetic test, it cannot authorise the diagnostic (Hogarth et al, 2006). We believe that the development of pharmacogenetics is hampered by this lack of authority and giving EMEA authority over pharmacogenetic tests (most probably Class III devices in a four-class risk system) and at least some other Class III IVD devices would address this shortcoming. Regarding the options for the respective roles of EMEA and Notified Bodies, it would be essential to avoid the position where a manufacturer meets the requirements set out by a Notified Body only for EMEA then to express dissatisfaction and set out new requirements. To avoid such a position it might be best that EMEA carry out evaluations directly for those categories of devices it has greatest interest in. Regarding option 4, we can see merit in EMEA acting as a meta-regulator, helping to establish clear standards which Notified Bodies work to but with the authority to step in and review cases where there is cause for concern.

Issue 8 Imports, Exports and Counterfeiting Item 17 un-equal checking and control of imported versus domestic medical devices
See above: Issue 1 Scope, Item 3 Medical devices currently not regulated at an EU level
a. LDTs outside EU

The introduction to the consultation suggests that "New and emerging technologies have challenged the current framework, highlighting gaps or pointing to potential loopholes". We would agree with this view and the briefing outlines the complex nature of many new genomic tests (pages 5-6). However, it not just new technologies which highlight limitations in the current framework, it is also new business models. One new business model which is causing serious concern is companies offering tests direct-to-consumer (DTC) over the internet. We are now seeing a development model where new biomarkers are first introduced into clinical use as DTC tests before any adoption by clinicians. This business model is unique to genetic testing, it has no parallel in other areas of clinical lab testing, and it has been the subject of considerable criticism by scientists and clinicians (Jannsens et al, 2008, and van Ommen, G and Cornel, M, 2008). In

general these tests are offered as LDTs. Whilst the Directive has a specific conformity assessment route for self-testing kits, whether this applies to DTC tests offered as LDTs is unclear, and we do not believe it has been enforced as such. In the UK the Human Genetics Commission has suggested that companies who wish to offer genetic tests direct-to-consumer should need to convince a regulator that this is appropriate. An alternative policy is being promoted by the Council of Europe who suggest that genetic tests should only be offered in the context of a medical consultation. We would suggest that it might be appropriate to extend EMEA's new public health role in relation to IVD devices to assessment of whether new tests might be offered direct-to-consumer. Alternatively, the DTC issue might be subsumed within risk classification with a general rule that, for instance, Class 3 and Class 4 tests should not be made available as self-testing kits or DTC LDTs.

References

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