Comments from EASAC and FEAM on the *In vitro* diagnostic medical devices Regulation

Introduction

The proposed Regulations on medical devices represent an important initiative to strengthen the characterisation of benefit-risk for a wide range of products and services, capitalising on the rapid pace of innovation in the health sector and, potentially, contributing to improved health and quality of life in the EU.

We focus here on the Regulation on *in vitro* diagnostic medical devices (to replace Directive 98/79/EC) with particular reference to the newly emerging field of Direct-To-Consumer Genetic Testing (DTC GT). Until recently, human genetic testing was mainly confined to specialist medical genetic services, traditionally focussing on the relatively rare inherited disorders. However, the rapid pace of advance in DNA analysis has led to growing interest in the development of genetic tests for determining susceptibility to the more common, complex disorders. Such tests are increasingly being offered by companies through the internet but provision of these services raises scientific, regulatory and ethical questions.

EASAC-FEAM report

In a report published in 2012[1], the academies of science (European Academies Science Advisory Council, EASAC) and medicine (Federation of European Academies of Medicine, FEAM) reviewed the evidence and ascertained the principles that should underpin the regulatory options for managing DTC GT as part of the broader assessment of *in vitro* diagnostic medical devices.

EASAC-FEAM concluded that DTC GT had little clinical value at present and expressed especial caution in several specific respects, for example relating to testing for high penetrance, serious medical disorders, prenatal screening, nutrigenomic and pharmacogenetic testing, while also noting that regulatory frameworks must be sufficiently flexible to cope with future scientific advances and to enable innovation. In developing general principles for the management of consumer genetic services in the EU, EASAC-FEAM emphasised:

- Susceptibility testing for complex disorders should be regulated on the basis that claims about the link between genetic marker and disease are scientifically valid.
- Test quality assurance must cover not only laboratory analytical quality but also the professional interpretation of results and the provision of counselling that is appropriate to the disease risk and burden.

[1] "Direct-to-consumer genetic testing for health-related purposes in the European Union", report available from www.easac.eu and www.feam.eu.com. This analysis is discussed further in a publication in the European Journal of Human Genetics (November 2012, doi: 10.1038/ejhg.2012.238) and in a short report summarising a joint EASAC-FEAM-STOA discussion meeting in the European Parliament in December 2012.

- Information supplied by DTC GT companies should be controlled by the enforcement of advertising standards and must emphasise who is advised not to use DTC GT services.
- Implications for the established health services and others need to be assessed, for example in terms of the potential waste of scarce resources in unnecessary follow-up to test results.
- Companies should include proper, additional, consent-seeking (specifying the handling of samples and information) when desiring to use data for research.

EASAC-FEAM recommendations and European Commission proposed Regulation

EASAC-FEAM published the report at a time when DG Sanco was actively considering the scope of the proposed Regulations. EASAC-FEAM advised that specific points needed to be taken into account in the European Commission's reform of the legislation covering *in vitro* diagnostic medical devices. The main points are listed in the Table, corresponding to the European Commission's subsequent introduction of an essential feature in the proposed Regulation.

EASAC-FEAM recommendations July 2012	**Key feature of European Commission's proposed Regulation October 2012**
Scope The scope of the Regulation should be clarified to cover all genetic information used to make medical claims. The standards set should also apply to products and services obtained from abroad through the internet.	The definition of *in vitro* diagnostic medical devices covers genetic testing and includes predisposition to medical conditions and disease. The Regulation applies to distance sales and services offered through the internet.
Independent review Options must be explored for introducing robust and independent review of claims made (technical and clinical) for a test, based on some form of risk stratification	There is an enforced requirement for test scientific validity and clinical performance. Assessment will be proportional to class of risk.
Availability of the data base The evidence base for all information provided on the availability, validity and usefulness of a test must be accessible and verifiable, to help physicians and consumers judge for themselves whether to avail of a particular test or service.	An EU database on manufacturers and marketed tests will be established with public access to summaries of test safety and performance, to enable the consumer to make better informed decisions.
Nature of clinical evidence A test with clinical validity might be permitted even if its use has not yet been shown to result in improved outcomes, because considerable	Clinical utility will not be covered by the Regulation as this is perceived as a matter for Member States.

further time may be required to demonstrate clinical utility. Moreover, clinical utility has a subjective dimension – the view of the consumer may differ from that of the physician. There must be transparent and meaningful information provision to the consumer before testing (as well as during and after testing).	 Instructions for test use must include information on test limitations and advise that the consumer should not take medical decisions without consulting a medical professional.
Professional competence and governance Demonstration of scientific validity of claims must be accompanied by appropriate safeguards for ensuring professional and clinical good governance according to standard procedures. Data should also be collected through post-marketing surveillance. Each DTC GT company should have a named professional who takes responsibility for the advice and service provided to the consumer.	All manufacturers will be required to have a quality management system and post-market surveillance plan in place. The Regulation requires a qualified person within the company to be responsible for regulatory compliance.
Notified Bodies These should be strengthened and their consistency across the EU improved, taking account of current good practice in evaluation, for example as developed by EuroGenTest.	The position of Notified Bodies will be enhanced to strengthen their independence and quality of pre-market assessment.
Self-certification in rare diseases It is important to retain self-certification for laboratory-developed testing for uncommon diseases within the established genetic services, because scientific expertise is often limited to the centre offering the test.	In-house (laboratory-developed) tests are exempted from the Regulation if the health institute is accredited and providing that any safety issue is reported.

In summary, there is much in the proposed Regulation that is to be welcomed but there are still some inconsistencies and some of the new steps recommended in the Regulation are controversial.

Remaining issues and controversies

- Nature of genetic data The new risk classification in the Regulation assigns all genetic tests to the same Class (C). However, as discussed in the EASAC-FEAM

report, there is no reason to assume that all nucleic acid-based (genetic) tests should be in the same risk category. Moreover, we have observed that there is controversy about whether using a nucleic acid-based test is fundamentally different to using other types of biomarker as the predictor of risk, and whether concerns expressed about genetic testing are primarily related to the use of nucleic acids as the analyte or to the more general use of predictive risk information. It is important to take a consistent and coherent view of all medical testing as experience is gained in applying the scientific advances.

- Strengthening pre-market approval The Regulation recognises that the activities of some Notified Bodies must be improved but there is still uncertainty and lack of consensus about how the weaker Notified Bodies should be strengthened and how a system of uniform quality of technology assessment can be delivered across all the Member States of the EU. EASAC-FEAM recommended that there is an important role for the established Health Technology Assessment network in the EU in advising on what is required to assemble and use high quality research evidence on gene-disease associations.
- Alternative regulatory approaches While the European Commission in its impact assessment document suggests that the new Regulation will achieve an effect equivalent to the US FDA's proposed enhanced control of DTC GT, and that low quality genetic tests pursuing a medical purpose will disappear, this has yet to be proven. The recent application by at least one DTC GT company in the USA, to the FDA to grant marketing authorisation, will have implications in the EU, perhaps particularly for the EMA. Some have advised that, in due course, the EU should move to a certified, pre-authorisation system analogous to the FDA, rather than relying on the delegation of activity to the Notified Bodies. This alternative approach merits further discussion. There is, of course, a key challenge for any regulatory authority in governing regional provision of products and services in a global, internet-based market. There is growing need for improved coordination of strategy and practices between the regulatory authorities in this respect.
- Impact on public health systems In addition to formalising legislation, the EU should consider what else needs to be done collectively to increase the use of responsible testing and protect against unsound testing. In particular, as discussed in the EASAC-FEAM report, there are priorities for professional bodies, the broader research community, and public health services. Legislative reform to regulatory systems takes time and will only be successful if it is accompanied by, for example: shared commitment to clinical governance; development of evidence-based public health services to translate research advances into clinical practice; improved professional and public education about genetics; provision of accurate and relevant information with greater transparency; and support for public sector research. EASAC-FEAM concluded that these complementary, early, actions would be particularly valuable if resulting in international, standardised repositories of test information, accreditation of DTC GT companies, and faster progress in assessing the validity of tests.
- Sharing information Among critical issues remaining – how will the quality of information on gene-disease associations and its implications be validated in the genetic testing database (registry)? Can EU effort in this regard be integrated with

other international database initiatives? And how will accurate and meaningful genetic information be made accessible to empower the consumer to make informed choices? How should the general public be engaged now in debating these issues?