

The Academy of Medical Sciences and the Royal Academy of Engineering joint response to the Medicine and Healthcare products Regulatory Agency's public consultation on the revision of European legislation on medical devices

Summary

Current European legislation on medical devices requires modernisation, due to technological advances and changes to the European landscape. Legislation should aim to ensure patient safety and timely access to high-quality medical technologies through streamlined and proportionate regulation that reduces administrative burden and facilitates innovation.

- There should be further discussions on the type, methodology of collection and quantity of clinical evaluation data required under the revised legislation, with input from clinicians and manufacturers.
- The new databases proposed in the regulations to support additional clinical evaluation data requirements and improvements in traceability and post-market surveillance must be properly resourced, learn from best practice, and ensure harmonisation with existing databases to ensure that they are fit-for-purpose.
- The definition of companion diagnostic should be flexible enough to respond to ongoing scientific discoveries and technological developments and the resulting emergence of new diagnostic approaches.
- The following revisions to the legislation support the proposals put forward at a recent Academy of Medical Sciences symposium with the aim to facilitate stratified medicines research and development, and the implementation of these approaches in healthcare services:
 - Introduction of a risk-based classification system for diagnostics and greater scrutiny of companion diagnostics, which could guide life changing treatment decision, by notified bodies.
 - Requirement for notified bodies to consult with the medicines competent authority or European Medicines Agency as a part of conformity assessment of companion diagnostics, although further discussion is required on exactly what this would entail.
 - Requirement for health institutions developing and using 'in-house' diagnostics to be accredited, and to report serious incidents and field safety corrective actions. There should be further discussions amongst key stakeholders to develop a robust accreditation framework.
- To ensure the continued development of devices and diagnostics, it is essential to maintain effective incentives for manufacturers by avoiding unnecessary administrative burden, cost and delays in market access. We ask for clarity on some provisions in the regulation that may have unnecessarily negative impacts, especially on smaller manufacturers.

Introduction

The Academy of Medical Sciences and the Royal Academy of Engineering welcome the opportunity to respond to the Medicines and Healthcare products Regulatory Agency's (MHRA's) consultation on the revision of European legislation on medical devices and *in vitro* diagnostics.

The need to modernise current European legislation on medical devices is widely recognised in light of advances in technology and changes to the European landscape. The aim should be for legislation that ensures patient safety and timely access to high-quality medical technologies. It is also imperative that the revisions lead to the introduction of streamlined and proportionate regulations that reduce administrative burden and facilitate innovation.

We therefore support the broad intent of the current proposals to:

- increase transparency;
- improve traceability;
- enhance safety - in part through improved performance of notified bodies and additional pre-market scrutiny of higher risk devices;
- improve vigilance and surveillance; and
- introduce greater co-ordination and harmonisation.

This response focuses on the following issues that we believe require further deliberation.

- The clinical evidence requirements for devices and *in vitro* diagnostics.
- Harmonisation with existing databases.
- Definition and assessment of companion diagnostics.
- Classification of *in vitro* diagnostics.
- Exemption of 'in house' *in vitro* diagnostics.

The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are translated into healthcare benefits for society. Fellows of the Academy of Medical Sciences are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service.

Engineering is at the heart of society, underpinning and continually improving the quality of our lives. The Royal Academy of Engineering brings together the country's most eminent engineers from all disciplines to promote excellence and support the engineering performance of the UK. Biomedical engineering creates new medical technologies and systems that can greatly improve patient care and quality of life. The Panel for Biomedical Engineering is the Royal Academy of Engineering's forum for this increasingly important area of engineering in which the UK is taking a lead.

This response has been informed by consultation with Fellows of both Academies and with external stakeholders, and by two recent events undertaken by the Academies:

- Royal Academy of Engineering and Academy of Medical Sciences roundtable titled: *How can high-level evidence be established for the safety and efficacy of medical devices* (16 January 2013). The meeting brought together regulators, and clinicians and engineers from academia and industry, to discuss current challenges and explore future options for generating safety and efficacy/effectiveness data for medical devices.

- The Academy of Medical Sciences symposium on stratified medicine (10-11 October 2012). The meeting brought together experts from the pharmaceutical and diagnostic industries, health economists, medicines regulators, health service providers, clinical researchers and policy makers with the aim to progress stratified medicines research and development, and the implementation of these approaches in healthcare services. Regulation of companion diagnostics and 'in-house' *in vitro* diagnostics was one of the key topics of discussion at this meeting.

We will be pleased to provide the reports of both of these events upon publication and would welcome ongoing dialogue with the MHRA during the revision and implementation of the legislation.

Clinical evidence requirements for medical devices and *in vitro* diagnostics

There is an ongoing debate about what the clinical evidence requirements should be for medical devices and *in vitro* diagnostics. In order to ensure patient safety and to meet the challenges of increasing healthcare costs, the importance of generating clinical utility evidence is increasingly recognised, not only during the pre-market phase but over the lifetime of the product.

Comparisons are drawn between the requirements for pre-market evidence of clinical utility for pharmaceuticals, typically through randomised controlled trials (RCTs), and the current lack of similar requirements of evidence for the approval of devices and diagnostics. However, there is also a general acknowledgment that the fields of devices and diagnostics are fundamentally different from pharmaceuticals, meaning that the same methods for generating clinical utility evidence are not always feasible or desirable.

Although the proposed regulations require the generation of more clinical data than was previously the case, there is currently insufficient information on what methodology should be used to generate the data, or the quantity of data required, for either approval or post-market follow up. Therefore these details will need to be developed over time, with input from clinicians and manufacturers who will be challenged by these requirements. We will be pleased to submit the report of our joint round table about the evidence base for devices upon publication, which explored these issues in some detail.

Harmonisation with existing databases

The proposed regulations would lead to the creation of new databases for traceability, post-market surveillance and clinical evaluation data of devices and diagnostics. We believe that to ensure any new databases are fit-for-purpose and to avoid any duplication of efforts, care must be taken to learn from best practice and ensure harmonisation with existing databases. It is also important not to underestimate the resources and strong leadership required in setting up and administering effective central databases.

Definition and assessment of *companion diagnostics*

We consider that further discussion is required on the proposed definition of companion diagnostics: *a device intended to select patients with a previously diagnosed condition or predisposition for eligibility of treatment with a specific medicinal product.*

The rapid pace of scientific discoveries and technological development mean that the current model of a single companion diagnostic test directing the use of a single drug (or a small group of similar drugs) will soon become outmoded. There are already diagnostics that enable the identification of multiple biomarkers that can guide decision making to a number of different treatments. This trend is set to continue, particularly as the cost of whole genome sequencing will decrease with next generation sequencing technologies. It is important that the definition of companion diagnostic in the legislation takes account of this changing landscape.

It should also be noted that tests may direct treatment with medical devices, not just therapeutics, and this point should be considered in finalising the definition of companion diagnostics.

At the Academy of Medical Sciences symposium on stratified medicine, participants commented that currently there is no platform for aligning regulatory inputs for developing diagnostics and therapeutics at the EU level. As a result, in Europe, developments of these products often take place independently with little early cross fertilisation. It was noted that more co-ordinated guidance at an early stage will ensure that appropriate development strategies are adopted at the outset to allow effective development of stratified medicines.

Decreasing the separation between drug and diagnostic regulators is likely to help address this issue. The proposed requirement for Notified Bodies to consult with the medicines competent authority or European Medicines Agency as a part of conformity assessment of companion diagnostics is one possibility for achieving this goal, although it is not clear exactly what this might entail. We urge further discussion involving all key stakeholders to discuss all possibilities and clearly define a proportionate solution.

Classification of *in vitro* diagnostics

The current European legislation classifies *in vitro* diagnostics (IVDs) as high risk only if the sample collection itself, such as invasive biopsy or blood testing, poses a high risk to the tester or the patient. The risk to patients receiving the wrong treatment due to incorrect diagnosis is not recognised.

Attendees of the Academy of Medical Sciences' symposium on stratified medicine highlighted that, with IVDs being used to guide life-changing treatment decisions, there is a strong argument to classify these devices as moderate or high risk, so that they receive greater scrutiny from regulatory authorities. The current proposals to move the classification of IVDs from a list-based to a risk-based system, and the inclusion of companion diagnostics in a class that is subject to review by a Notified Body, are therefore in line with the recommendations made at the symposium.

The symposium attendees also called for further efforts to ensure global convergence for the classification and assessment of IVDs.

Exemption of 'in-house' *in vitro* diagnostics

At the Academy of Medical Sciences' stratified medicine symposium, participants noted that diagnostic tests manufactured and used 'in-house' by a health institution (IHTs) are not required to follow quality assurance measures under the current European legislation and obtain CE marking. This raises two issues: safety concerns arising from variation in standards between sites and countries; and reduced incentives for manufacturers to develop diagnostics.

Participants highlighted that whilst IHTs allow hospitals and laboratories to diagnose and stratify patients with diseases where there are no commercially available tests (e.g. rare diseases), the lack of any standardised performance and safety review can pose a serious risk to patients. IHTs may also duplicate and or replace tests that are fully validated and already commercially available. Participants noted that accreditation of laboratories performing predictive and prognostic diagnostic tests to defined criteria will facilitate standardisation and improve quality.

The current proposal, which places an obligation on health institutions developing and using 'in-house' diagnostic tests that are classified as A, B and C based on risk, to be accredited according to the ISO 15189 standard and to report serious incidents and field safety corrective actions, therefore aligns with the suggestions made at the Academy's symposium. We urge that there are further discussions amongst key stakeholders to define what accreditation of these institutions should look like.

Proportionality

To ensure the continued development of devices and diagnostics, it is essential to maintain effective incentives for manufacturers by avoiding unnecessary administrative burden, cost and delays in market access. In addition to the points raised above, we believe that the proposed regulations do not give sufficient clarity around the following issues, all of which could have significant impact on the manufacturers, particularly small and medium sized enterprises:

- introduction of EU reference laboratories;
- requirement for a qualified person within each manufacturer; and
- additional pre-market scrutiny of higher risk devices by the Medical Device Coordination Group (MDCG).

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