Regulatory Developments in the EU, USA and Australia

By John Worroll and Mary C Getz, PhD

Introduction

This article examines some of the major regulatory developments in the last six months in the EU, the USA and Australia.

The major topic in the EU is the ongoing debate on the Commission proposal for two new regulations to cover medical devices (including active implantables) and in vitro diagnostic medical devices which were published on 26 September 2012. The medical devices proposal is currently the subject of a vigorous and wide-ranging debate among the various stakeholders and there is considerable uncertainty about its eventual implementation date. However, the IVD proposal is much less contentious and it may well be possible to reach agreement in time for it to come into full force by 2018.

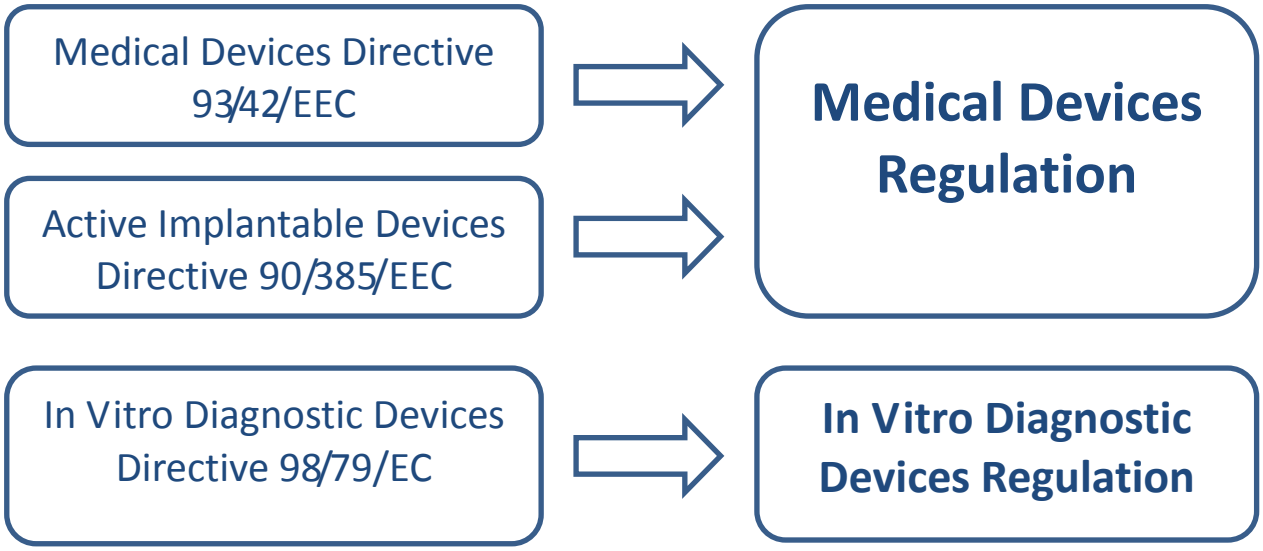
Meanwhile in the USA, the International Medical Device Regulators Forum (IMDRF) has been focusing on several areas: developing the Medical Device Single Audit Program (MDSAP) and establishing a single audit program by of 2013. The group is led by Kim Trautman, FDA – CDRH division.

In Australia, many high-risk medical devices (Class III devices, implantable intra-ocular lenses, intra-ocular visco-elastic fluids and barrier contraceptives) were excluded from the EU-Australia mutual recognition agreement from 1 January 2013.

EU Developments

1. Revision of the medical devices directives

The Commission proposals were published on 26 September 2012. The two proposed regulations, when agreed, will eventually replace the three existing medical devices directives as shown by the diagram.



The proposals are the result of long discussions between the Commission and stakeholders in the 27 member states and aim to address the perceived weaknesses of the previous regimes. Some of those weaknesses were highlighted by the PIP breast implant scandal and the orthopaedic implant metal on metal failures which led to much discussion and debate, including in the lay press.

The initial timetable provided for publication of the regulations in the Official Journal of the European Union by 2015 with full compliance by 2018, to allow stakeholders time to adopt and implement the new requirements. However, there is also the possibility that the debate will be extended, thus delaying the implementation date.

Unlike the directives, the regulations will apply directly to member states without needing to be transposed into local legal systems. This aims to reduce inconsistencies stemming from varying transpositions, but does not address any differences in the ways the member states translate, interpret or implement the regulation.

1.1 The proposed regulation for medical devices

The most obvious difference between the draft medical devices regulation and the two directives it replaces is that the draft runs to 194 pages, as opposed to 60 for the Medical Devices Directive (MDD) and 35 for the Active Implantable Medical Devices Directive (AIMDD).

Overall, the new regulation follows the principles behind the directives under the New Approach (recently re-branded as New Legislative Framework), although the new regulation has much more detail and rigour. For example, it makes compulsory much of the guidance (e.g. concerning vigilance and clinical data) in MEDDEVs[1] and GHTF[2] documents, and includes 50 definitions instead of the original 14.

[1] Meddevs are official guidance documents agreed by member states and issued by the EU Commission: http://ec.europa.eu/health/medical-devices/documents/guidelines/index_en.htm

The new regulation appears to cover the whole life cycle of a medical device, from design through clinical trials to post-market issues. The main changes and features of the proposed new regulation are that it:

- **Puts more emphasis on clinical data,** including more closely defining the conduct of clinical investigations by inclusion of parts of ISO 14155
- **Mandates manufacturers to employ a Qualified Person** who possesses expert knowledge in the field of medical devices and has a relevant degree or equivalent plus five years' professional experience
- **Provides much more detail on the obligations of economic operators,** e.g. authorised representatives, importers and distributors
- **Gives more detail on requirements for notified body (NB) audits,** e.g. by increasing the sampling regime for Class IIa technical documentation, which will probably result in more audit time and hence greater costs
- **Provides for member state scrutiny of Class III devices** (via the Medical Device Coordination Group (MDCG)) of which NBs will have to notify all applications and provide summary data on request. The practicalities are unclear, although the Commission has said it would scrutinise only 10 percent of such products and that the process would not take more than 90 days.
- **Requires much more information to be made public** via Eudamed, the central EU database for medical devices
- **Makes much greater demands for product traceability** throughout the product life cycle, including by means of a unique Medical device identification. I think this should be capitalised.
- **Provides for better coordination of the vigilance system**, including investigation and subsequent action
- **Sets much more detailed and rigorous requirements for NBs**, especially their competency and expertise. It also requires complete re-evaluation and designation of all NBs which could result in significantly fewer NBs.
- **Mandates NBs to carry out unannounced audits** of manufacturers and to take sample products for examination
- **Provides for better coordinated and enhanced market surveillance** by member states

However, many areas are largely unchanged. For example, although the **conformity assessment routes** are described in much more detail, they are basically similar to the originals except that the final inspection only option I think this should be capitalised.(Annex VI in the current directive) appears to have been removed.

[2] GHTF is the Global Harmonisation Task Force which issued guidance documents agreed by its stakeholders (USA, EU, Australia, Japan and Canada) plus industry and conformity assessment body representatives to foster harmonisation of medical device regulation: http://www.imdrf.org/documents/documents.asp

Classification rules, although basically similar, contain three extra rules making apheresis devices, nano materials and substances inhaled, ingested or administered rectally or vaginally Class III. The details of these proposals are still subject to debate.

General safety and performance requirements are basically similar to the old essential requirements I think this should be capitalised, but with a GHTF influence. Labelling requirements are much more detailed.

The role of **harmonised standards** as a method of showing compliance appears unchanged, although the concept of a common technical specification (CTS) is introduced from the IVD world.

The requirements for **systems and procedure packs** are largely unchanged and there is still provision for **custom-made devices** which remain exempt from some of the requirements.

Own-brand labelling is not explicitly mentioned, as was the case in the directives. However, this may yet come under scrutiny because of pressure from member states to increase the NBs' activity in this area.

1.2 The proposed regulation for in vitro diagnostic medical devices

Background

The IVD Directive was developed in the 1990s against the background of problems with the use of IVDs in the characterisation of blood donations and in the screening for diseases such as HIV. These and similar issues took the IVDD away from the form of the other medical devices directives in three important respects:

- Device risk classification is in the form of two lists, known as "List A" and "List B".A and B. The obvious disadvantage of the list approach is that it makes it very difficult to keep up with subsequent developments, e.g. the emergence of CJD and Alzheimer's diseases.
- Instead of using harmonised standards for these high-risk products, it was felt that common technical specifications I think this should be capitalised (CTS) would be easier and quicker to produce.
- The IVD Directive had a much more comprehensive product registration provision than the MDD or the AIMDD.

The proposed regulation moves away from the list-based approach to a rule-based system of classification similar to that used in the medical devices regulation and based on GHTF philosophy. For IVDs, this has a major impact on the number of products which will be subject to conformity assessment by NBs (see below for more details).

On the other hand, the comprehensive product registration is retained, as is the CTS as an alternative to harmonised standards.

Classification and conformity assessment

The major change introduced by the proposed regulation is that it replaces the list-based system found in the current directive with a rule-based classification system based on the Global Harmonisation Task Force (GHTF) classification rules. It divides IVDs into four risk classes: A (lowest risk), B, C and D (highest risk). This change is summarised in the table below, and will impact nearly all IVD manufacturers as the majority of IVDs currently self-certified will now require the involvement of a notified body in the conformity assessment process.

Class	Risk level	Examples	Conformity assessment route
A	Low individual and low public health risk	Clinical chemistry analyser, specimen receptacle	Manufacturer self-certification, except for devices intended for near-patient testing, having a measuring function or sold sterile
B	Moderate individual risk and/or low public health risk	Vitamin B12, pregnancy self-test	Quality management system assessment
C	High individual risk and/or moderate public health risk	Blood glucose self-test, rubella tests, genetic tests, companion diagnostics	Quality management system assessment plus assessment of representative samples of technical documentation
D	High individual risk and high public health risk (Equivalent to current List A devices)	HIV blood donor screening, HIV blood diagnostic	Design and the quality management system assessment plus batch verification

Other significant changes

Other significant changes include clarifying and extending the scope of the IVD Directive, relative to:

- High-risk devices manufactured and used within a single health institution
- Tests providing information about the predisposition to a medical condition or a disease (e.g. genetic tests) and tests providing information to predict treatment response or reactions (e.g. companion diagnostics)
- Medical software, which is explicitly mentioned in the definition of IVDs

- Increased requirements for informed consent, especially for tests where patient knowledge of the result could be potentially life-changing, for example in genetic tests some people capitalise the first letters of a list such as the above, some don't. However, if you add semi-colons, then it emphasises that each item isn't a sentence and therefore shouldn't be capitalised.

Finally, the IVD proposal introduces several changes which parallel those of the medical devices regulation in that it:

- Puts more emphasis on clinical data, in the form of making performance studies mandatory unless duly justified to rely on other sources of clinical performance data
- Makes more detailed requirements for NB audits
- Requires manufacturers to employ a Qualified Person
- Provides much more detail on the obligations of economic operators
- Requires much more information to be made public via Eudamed
- Makes much greater demands for product traceability via the Medical
- Provides for better coordination of the vigilance system
- Sets much more detailed and rigorous requirements for Notified Bodies
- Mandates NBs to carry out unannounced audits
- Provides for better coordinated and enhanced market surveillance by member states

1.3 The current debate and possible outcomes

It would appear that the Commission proposal for IVDs has a reasonable prospect of meeting the original timetable for full implementation by 2018. Areas of ongoing discussion include informed consent for potentially life-changing genetic tests, and availability of self-tests for diseases where patient support and counselling might be needed dependant on the result.

However, the situation on the Commission proposal for medical devices is much less clear in that it has been criticised by organisations representing medical insurers and patients for providing insufficient protection against unsafe high-risk devices. In particular, the European Parliament's Environment, Public Health and Food Safety (ENVI) Committee has made several highly controversial and, according to the medical devices industry, potentially impractical and innovation-damaging counterproposals. These include a provision for central pre-market authorisation for high-risk devices and a requirement that all devices are deemed to be re-usable unless the manufacturer can produce positive evidence that it is unsafe to do so.
The debate is heated and it is very hard to predict either the outcome or the timescale by which agreement might be reached. However, in this author's opinion a central pre-market authorisation agency is unlikely because of the potential costs.

The other major, but less controversial, issue to be addressed by both regulations is the competency of notified bodies (NBs) where Team-NB, the NBs' trade association, has been proactive in producing a draft Code of Conduct which addresses most of the criticisms made of NBs. Among other matters, the Code of Conduct attempts to set out a practical method of implementing the controversial provision for NBs to make unannounced inspections.

The next step for both regulations is for the Council of Ministers to negotiate with the European Parliament to agree on the final proposals. Two significant dates are the vote in the ENVI Committee on the medical device regulation on 10 July and the EU plenary vote scheduled for September 2013.

If the whole process goes on too long, it might preclude any action until well after the European elections, due to be held in 2014, and the debate might not re-start until 2015. However, the European trade associations would prefer the debates to be concluded sooner rather than later, and so current speculation is that there appear to be three possible outcomes:

- New regulations agreed on in total before elections – unlikely given the widely differing positions of the various stakeholders on the medical devices Regulation
- The IVD regulation plus the less controversial parts of the medical devices regulation (e.g. improved control of NBs, improved market surveillance by member states, etc.), agreed on before the elections, leaving the more contentious issues such as pre-market approval for high-risk products until afterwards
- Everything delayed until after the elections

Consequence for manufacturers and recommended action

The revision will have a significant effect on all aspects of CE-marking pre- and post-market, especially with regard to high-risk or novel devices which are likely to become more difficult to bring to market and to have enhanced post-market surveillance requirements.

Many more IVDs will need the intervention of a NB before they can be CE marked and placed on the market and so IVD manufacturers are advised to begin developing their relationships with NBs.

For medical devices, the situation is unpredictable and so manufacturers are recommended to keep in touch with developments of interest via journals, the Commission website, trade associations, MHRA and their NB. They should also plan for longer approval times and increased scope and costs of NB audits.

2. European Medicines Agency expects more marketing authorisations for ATMPs

The European Medicines Agency (EMA) has carried out a survey to find out why its advanced-therapy medicinal product (ATMP) certification procedure is not more widely used by small- and medium-sized enterprises (SMEs). They found that the SMEs did not clearly understand how the certification procedure fitted in relative to CE marking (for medical devices) and product licensing (for drugs). Specifically, the link between their ATMP certification procedure and marketing authorization was seen to be unclear.

Consequence for manufacturers and recommended action

Potential manufacturers of ATMPs should consult EMA early in their product development in order to gain the best possible understanding of the regulatory process.

For more information about how NSF Health Sciences Medical Devices can support your regulatory strategy for drug device combinations, contact EUdevices@nsf.org.

USA Developments

International Medical Device Regulators Forum (IMDRF)

The International Medical Device Regulators Forum (IMDRF) was created in February 2011 as a forum to discuss future directions in medical device regulatory harmonisation. It is composed of a group of medical device regulators from around the world, which includes the FDA, TGA, Japan MoH, Health Canada, ANVISA and European Commission along with MHRA. These regulators have come together to build on the strong foundational work of the Global Harmonisation Task Force (GHTF) on Medical Devices. The mission of the IMDRF is to strategically fast track international medical device regulatory meetings that promote an efficient and effective regulatory model for medical devices. Their goal is to be responsive to emerging challenges in the sector while protecting and maximizing public health and safety. Since their inception, several working groups have been formed.

The update is on the working group convened to address the Medical Device Single Audit Program (MDSAP). Their goal is to establish a program along with criteria for the recognition and re-recognition of third-party auditing organisations.

Medical Device Single Audit Program (MDSAP)

The IMDRF working group developed a standard set of requirements for auditing organisations performing regulatory audits of medical device manufacturers' quality management systems. These documents will be applicable to competent authority auditing groups/inspectors, as well as third-party organisations that conduct such audits.
Two documents have been drafted, approved and posted for comment until 14 June 14, 2013:

- **WG (PD2)/N3R5 – Recognition and Monitoring of Organizations undertaking Audits of Medical Device Manufacturers**. This document explains the criteria on how regulatory authorities shall assess the auditing organisation.
- **WG (PD1)/N4R2 - Auditor Competency and Training Requirements for Organizations undertaking Audits of Medical Device Manufacturers.** This document specifies competency requirements for personnel involved in medical device regulatory audits and decision making in recognized auditing organisations.

There was a recent meeting in Nice, France, where the working group began work on several additional documents. These included: **Assessor Competency and Training Requirements for Regulatory Authorities undertaking Assessments of Auditing Organizations** and the

Assessment Program and Auditing Strategy of Medical Device Recognized Auditing Organization.

The goal for the working group is to submit final documents to the IMDRF Management Committee by October 2013 and to have a suite of the about four documents on the MDSAP by end of 2013.

Australian developments

1. Many high-risk medical devices are excluded from the EU-Australia MRA as from 1 January 2013

This development removed a relatively easy method of getting device approval for Australia, based on its CE marking for all Class III devices, implantable intra-ocular lenses, intra-ocular visco-elastic fluids and barrier contraceptives. It appears to echo the lack of confidence in the CE certification shown by some EU stakeholders. These devices may be reinstated in the mutual recognition agreement (MRA) after a confidence building period. Transition arrangements are being put in place in the meantime.

Consequence for manufacturers and recommended action

Manufacturers of high-risk products sold in Australia via the MRA are advised to consult their NBs (certification bodies) on next steps.

About the authors:

John Worroll is a senior consultant with NSF Medical Devices, part of NSF International's Health Sciences Division. Before that, he worked for MHRA for 27 years in a variety of regulatory roles, followed by eight years at the BSI Notified Body for medical devices where he was responsible for their regulatory compliance worldwide. He can be reached at EUdevices@nsf.org.

Mary C Getz, PhD, is the Director of Quality Systems, Medical Devices with Becker & Associates Consulting, part of NSF International's Health Sciences Division. Prior to joining Becker, she had over 25 years of experience within the pharmaceutical and medical device industries. She held various roles within Fortune 500 companies in quality, compliance and regulatory affairs organizations and had a proven track record of success as VP and SVP of quality and compliance. Mary has a PhD in microbiology and molecular genetics from Rutgers, as well as Black Belt Certification in Six Sigma, which she uses along with her considerable experience to help build strong quality and compliance programs. She can be reached at mary.getz@nsf.org.

Cite as: NSF Regulatory Developments in the EU, USA and Australia
NSF: Ann Arbor, MI