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Cover story : The EU IVD Regulation: The Practical Challenges Ahead For Manufacturers: Interview With Sue Spencer

By A Wenzel adapted from an article of in scrip regulatory

Discussions concerning new requirements for medical devices usually seem to dominate debate on the future EU regulations, which are currently under negotiation. But it is likely to be the IVD sector that experiences the biggest upheaval when they are adopted. Amanda Maxwell spoke with Sue Spencer, head of IVDs at BSI notified body, about the practical challenges ahead for the IVD sector

IVDs are high up on the European agenda at present[1]. The European Parliament, the Council of the European Union and the European Commission are trying to thrash out a new regulatory way forward for diagnostic products, and are due to meeting on Nov. 10, to try and find agreement on Europe's new IVD Regulation.

The hope is that the the IVDR – along with the Medical Device Regulation with which it is partnered – will be adopted within the next six months at the latest, and implemented within five years.

In the Q&A below, Sue Spencer, head of IVDs at **notified body** BSI describes the practical hurdles that lie ahead for notified bodies and manufacturers, which mean that all players should already be engaging with and preparing to meet the likely new requirements now.

Q: How long do you think the transition period should be for IVDs and why? In reality, how long is it likely to be?

Sue Spencer: The IVD sector is about to undergo a quantum leap change in the depth of regulatory oversight. The medical device sector has effectively had a series of five revisions with an associated increase in expectations and requirements; whereas the IVD sector will undergo all these changes at once with the adoption and then implementation of the In Vitro Diagnostics Regulation (IVDR). We understand that the regulators realize the magnitude of this change and as a result the IVD sector will have a five-year transition period. Whilst the negotiations are still on-going it is generally accepted that this will not change.

Practical experience from the implementation of the Australian regulations suggests that an implementation period of three years is not feasible**.** It is widely recognized that even with a five-year transition period manufacturers should not delay their preparations if they wish to avoid resource limitations – whether this be in-house resource to make the necessary changes to documentation and the quality management system, or to ensure there is sufficient capacity in the notified bodies.

Q: The proposed changes in classification in the proposed IVDR are going to mean that considerably more IVD products will need to be assessed by notified bodies than in the

past. Some people are talking about 80% of IVDs needing to be reviewed by notified bodies in the future in the EU compared to some 20% now. Staffing is already becoming an issue. How do you perceive the challenges and solutions?

SS: Initial estimates were that under the IVDR 80% of IVD manufacturers would require an IVD notified body. Following recent proposed changes this figure may be now closer to 90%. The latest draft of the IVDR requires in-depth technical file reviews for classes B, C and D devices by a notified body; this means that notified bodies require in-house technical experts to cover their scope of designation. At BSI it takes 18 months to train a technical expert, as they have to receive in-depth classroom training and supervised on-the-job training in all aspects of the job and different certificate types. In addition notified bodies will require additional quality management system staff, who are experts in IVD manufacturing processes and technology. in order to be designated under the IVDR (and, indeed, for medical devices too), notified bodies need to have the required staff; this means that if a notified body wishes to be designated in 2016/17 it really should already have established its in-house team of experts to cover the desired scope.

Technical experts need to have direct experience of the design and manufacturing process; we can teach the regulatory requirements but there is no substitute for genuine experience. The notified body code of conduct from Team-NB [ie the European association of notified bodies] requires four years' experience, which must include practical experience – not just academic knowledge – in the appropriate sector. Quality management system assessors are also required to have four years' experience in the relevant production technology; at BSI most experts have a PhD or MSc and over seven years' experience.

Q: Among products that do not need to be reviewed under the current IVD Directive, but which will need to be reviewed by a notified body under the IVDR are companion diagnostics. How do you see the future regulation of these products?

SS: The requirements for the assessment and designation for notified bodies who conduct companion diagnostic assessments has not yet been defined and agreed. This is one of the areas where notified bodies and industry have been asking for further guidance to be prepared.

The consultation process will be different to a drug/device consultation. The consultation will have to be with the medicinal product competent authority that approved the original drug (rather than any other competent authority). This is important because the authority that approved the drug will understand and have access to data to determine what specification and performance is required by the diagnostic or for the medicinal product to perform as intended.

The commission's IVD notified body working group is currently discussing this subject with the aim of proposing a list of topics that should be reviewed by the notified body, by the medicinal product competent authority and, in some cases, both.

Many companion diagnostics are not co-developed with the pharmaceutical – they can be paired at a late stage of development, and there could be many technologies involved. The key challenges here will include the approval of subsequent "me too" diagnostics, where the subsequent diagnostic manufacturer does not have access to the original medicinal product clinical trial data or samples, and therefore the design of bridging studies will be important.

These issues also pose a challenge under the IVDD and are being hotly debated internally by several competent authorities; however, at present these IVDs are self-declared and there is no notified body involvement.

References

1. EU Medtech Reform Trilogues Take Off Amid Turbulence and Late Landing Fears, Scrip Regulatory Affairs, Oct. 16, 2015

Amanda Maxwell is the medtech regulatory affairs editor for *Clinica Medtech Intelligence*, a sister publication of *Scrip Regulatory Affairs*.

No. 1

1. AHWP Seeks Feedback On Common Format For Medical Device Applications

By A Wenzel adapted from an article in scrip regulatory

The Asian Harmonization Working Party has issued a draft guidance document on how to prepare a medical device marketing application in a format that would be acceptable to all AHWP member economies[1].

The draft guidance describes the format for a common submission dossier template (CSDT), which the AHWP expects will harmonize the differences in documentation formats that presently exist in the different AHWP member jurisdictions. Once finalized, it will apply to all products that fall within the definition of a medical device, except for *in vitro* diagnostic medical devices.

Adoption of the guidance document by the AHWP member economies would "eliminate the preparation of multiple dossiers, arranged in different formats but with essentially the same contents, for regulatory submission to different regulatory authorities," the draft document says. "The format of the CSDT recommended… is based upon the goal of both regulators and manufacturers to strive for the least burdensome means" to demonstrate conformity to the "essential principles" of safety and performance for all classes of medical devices, the AHWP says.Essentially, the CSDT contains elements of the summary technical documentation (STED) that the Global Harmonisation Task Force (now the International Medical Device Regulators Forum) developed for demonstrating conformity to the essential principles.

The draft guidance lists the specific sections that a CSDT should include (eg, executive summary, device description, summary of design verification and validation documents) and explains what kind of information is needed to complete them. Where there are sections not

applicable to the medical device, the reason for the non-applicability should be provided under the section heading.

The draft guidance points out that the CSDT must be prepared in accordance with the requirements specified in the local regulation. For example, countries or jurisdictions may set the requirement for having the label of a medical device in their national languages.The guidance provides an example of what an essential principles conformity checklist should look like. The checklist, it says, should be prepared based on the list of essential principles as defined by the country or jurisdiction regulatory authority.

The AHWP has released the draft guidance for consultation. The deadline for submitting comments on the document is Sept. 30.

The 24 AHWP member economies are Abu Dhabi, Brunei Darussalam, Cambodia, Chile, Taiwan, Hong Kong, India, Indonesia, Jordan, Saudi Arabia, Laos PDR, Malaysia, Myanmar, Pakistan, China, Philippines, South Korea, Singapore, South Africa, Kuwait, Tanzania, Thailand, Vietnam and Yemen.

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Source: Neena Brizmohun , Scrip Regulatory

No. 2

2. EMAUK Awaits MHRA Medical Device Fee Consultation While Regulatory Costs Mount

The UK Medicines and Healthcare Products Regulatory Agency's widely anticipated consultation on medical device fees is being delayed as official processes of scrutiny are still being finalized[1,2].

The target start date for the device fee levy was April 2016. However, Wilkinson sees that as challenging, given the likely timing of the consultation. But ideally it would come into being during the 2016-17 UK fiscal year, he told delegates at the ABHI conference, mindful that the notice is not long and could present certain budgeting challenges.

MHRA device funding has slipped in real cash terms to below £9m ($13.6m) annually in 2015-16 from around £11.5 million in 2009-10. Some of this reduction is justified, and has come about through different ways of working and less wastage etc. But the workload is mounting all the time and the agency needs the additional resources to be able to meet its obligations and the demands that, say, 15,000 adverse incidents annually place on it.

Another potential challenge might come in UK Chancellor of the Exchequer George Osborne's 2015 spending review, announced in July, in which he asked government departments to model two scenarios of 25% and 40% of savings in real terms by 2019-20. This could mean a squeeze on the MHRA's already relatively small government allocation for device work of just over £8m. This would happen at the same time as the MHRA's regulatory footprint is increasing. The problem is who to charge. Market surveillance accounts for a vast proportion of MHRA spending on the devices side, and this is all state-funded activity so far. The MHRA's medicines side already has fees for this activity, but it's not a popular theme among industry, to say the least. "No one likes it," is Wilkinson's frank assertion.

Clinical Inspections Spared From Fee Hikes

The MHRA is also looking at its existing device charges, which are out of date and have not been revised since 2009. Some fees associated with notified body activity are set to rise. These include the initial designation of notified bodies (currently £3,840), and audits (£3,840-£7,670). There will be new fees for re-designation applications. Elsewhere, the Class I product registration fee (£70) will also increase.

But the MHRA considers that the charges for the inspection of clinical investigations can be managed mainly at their current levels (eg £3,820 for a Class I, IIa or IIb). Clinical investigation activity has been flat in the UK in recent years, and the MHRA wants to encourage more of that activity.

Not A Tax Or Registration Scheme

Several other EU member states already apply sales-related levies to their device activities, although their rules, bands, percentages and cut-offs vary significantly. Ireland is currently planning cost recovery. France charges a tax, and product registration schemes have begun to become more popular around the EU, with Latvia and Estonia latterly setting schemes. "The UK position is that this is Eudamed's [the medical device database] job," said Wilkinson. "We don't want to burden the industry with unnecessary costs, and ideally we seek an equitable pan-European solution that avoids double counting." Talking with stakeholders, including the ABHI, is a key element in the UK's plan.

The aim would be to recover from industry the £8m – a "tiny amount", in the words of ABHI guest speaker Professor Chis Hodges, Oxford University law professor – that the government allocates for devices ,"and a bit more". Wilkinson said: "This is about performing our market surveillance function, so we need to charge for market surveillance. But we also want somehow to add value." By comparison, the pharma side of the MHRA has a £30m income for pharmacovigilance activity.

References

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2. UK MHRA to float device cost coverage plans for 2016, *Scrip Regulatory Affairs*, Dec. 2, 2014

Source: Ashley Yeo, Scrip Regulatory

No. 3

3. WHO Malaysia Consults On Reducing Info Needed In GDP Certificates For Medical Devices

By A Wenzel adapted from an article in scrip regulatory

Malaysia's Medical Device Authority is inviting feedback on its proposal to reduce the amount of information that conformity assessment bodies need to include in the good distribution practice certificates they issue to various entities[1,2]. Among other things, the MDA has proposed doing away with the need to include the Global Medical Device Nomenclature code and the medical device registration number in the certificates for good distribution practice for medical devices (GDPMD).

GDPMD certificates are needed by all parties involved in supplying medtech products in Malaysia, including the authorized representatives of foreign manufacturers, importers and distributors[3]. The certificates confirm that the concerned devices are consistently stored, transported and handled under suitable condition as required by the marketing authorization or product specification.The MDA is proposing that the section in the GDPMD certificate that lists various devices dealt with by an establishment (ie table5 in Annex 1) should only include information on: the product's GMDN category and description; name of the device manufacturer; details of the brand/model; grouping information (eg single/family/system/test kit/cluster); and device classification (eg Class A, B, C or D).

Currently, the MDA requires this section to also include: the name of the medical device; manufacturer's product number/code; the GMDN code; and the medical device registration number.Stakeholders have until Oct. 1 to comment on the MDA's proposal. The changes, when finalized, will be incorporated into the MDA's 2013 regulation specifying GDPMD requirements.

References

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2. Amendment to table (5) in Annex 1, Sept. 18, 2015, www.mdb.gov.my/mdb/index2.php?option=com_docman&task=doc_view&gid=249&Itemid=59

3. Malaysian device system targets total life cycle regulation, *Scrip Regulatory Affairs*, July 4, 2014

Source: *Vibha Sharma* , Scrip Regulatory

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4. IMDRF Offers QMS Map For Standalone Medical Device Software In Key Jurisdictions

By A Wenzel adapted from an article in scrip regulatory

How should medical device manufacturers go about applying quality management systems (QMS) to standalone medical device software in a manner that would be equally acceptable to different key jurisdictions of the world?

This information can now be found in a guidance document that has now been finalized by the International Medical Device Regulators Forum's management committee[1]. The document, IMDRF/SaMD WG/N23,.applies to software as a medical device (SaMD) irrespective of technology and/or platform on which it is used (mobile app, cloud, server etc).

Who is helped and how?

The 34-page-long IMDRF/SaMD WG/N23 guidance document, officially finalized at the IMDRF Sept 15-17 meeting in Kyoto, Japan, is aimed at:

- groups and/or individuals who are or want to become SaMD developers;
- software developments organizations (large or small) that apply good software quality and engineering practices but may not be familiar with medical device QMS requirements; and
- organizations working within established medical device quality systems that intend to communicate the link between medical device quality system practice and software development practices.

The document provides diagrams and fictitious company examples to help readers grasp the concepts and explains how and where the concepts presented in the document relate to clauses in ISO 13485, the international medical device quality system standard. It also deals with outsourcing and procuring parts, as well as the importance of usability engineering principles. It contains sections on design and development, and maintenance and decommissioning, among many others.

The document was issued for stakeholder consultation in April[2].

Another Key IMDRF Software Document

IMDRF/SaMD WG/N23 is a companion document to the IMDRF/SaMD WG/N10 and N12 documents, further enabling convergence in vocabulary, approach, and a common thinking for regulators and industry.

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For all medical devices, QMS requirements are defined by regulatory agencies in their regulations and in ISO 13485—Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes.

QMS requirements are equally applicable to software. And IMDRF notes that good software quality and engineering practices may readily align with the general principles of medical device QMS requirements when the patient safety perspective is included.This latest document, IMDRF/SaMD WG/N23, it explains "highlights elements of good software quality and engineering practices and reinforces medical device quality principles that should be appropriately incorporated for an effective SaMD QMS."

The IMDRF makes it clear that the document is not intended to provide guidance on how to undertake good software quality and engineering practices or how to implement QMSs; and nor how to rewrite, repeat, or contradict QMS principles that are articulated in medical device regulations or standards.

Other Key Developments

Also at the Tokyo meeting, the IMDRF management committee agreed to start work on a new project on clinical evaluation of medical device software.In addition, it agreed to publish information documenting relation to: IEC 62304:2006: Medical device software – Software life cycle processes. This is one of a handful of core international standards that the IMDRF is aiming to harmonize at international level.

References

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2. IMDRF consults on QMS requirements for medical device software, *Scrip Regulatory Affairs*, April 8 2015

3. Software as a Medical Device (SaMD): Key Definitions (IMDRF/SaMD WG/N10FINAL:2013), Dec. 9 2013, www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf

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This article has also been published in Clinica Medtech Intelligence. *Scrip Regulatory Affairs brings selected complementary coverage from our sister publications to our subscribers*.

Source: Amanda Maxwell , Scrip Regulatory

5. EU Guideline On Validating, Assessing Device Trials Overhauled

By A Wenzel adapted from an article in scrip regulatory

The European Commission has made substantial changes to its guideline on how national competent authorities should go about validating and assessing clinical investigation applications and what they should require of manufacturers under the EU directives on medical devices (93/42/EEC) and active implantable devices (90/385/EEC)[1].

Among other things, the updated guideline (Meddev 2.7/2, revision 2) includes nine new appendices to support the validation and assessment processes. The appendices aim to standardize specific procedures and provide stakeholders with helpful checklists. The 68-page revised guideline will replace the 2010 version of the guideline, which is 10 pages in length[2].

A commission spokesperson has previously told *Scrip Regulatory Affairs* that the revision would result in the 2010 guideline being "completely restructured" to align it with the structure of the relevant international standards[3,4]. The updated guideline states that clinical investigations should generally be "designed, conducted and reported" either in accordance with the harmonized standard EN ISO 14155 (on good clinical practice requirements for medical device clinical trials) or to comparable standards, and in compliance with the Declaration of Helsinki and other national regulations.

In addition, the revised guideline provides "some basic criteria" to support harmonization among EU member states on the assessment of clinical investigation applications. In the guideline, the commission acknowledges that the roles of national competent authorities in the assessment of clinical investigation applications may vary among different member states due to differences in national legislation (for example, in some cases ethics committees may be involved in this process). The commission recommends that competent authorities should encourage the use of the revised guideline by all national bodies involved in the assessment of such applications.

The changes to the guideline also aim to promote further understanding of the requirements of the EU directives on medical devices and active implantable devices. Specifically, the updated guideline:

- Contains several new terms for which clear definitions have been provided. Some of these definitions will be adjusted later on when the commission finalizes changes to its existing guidance for manufacturers and notified bodies on the clinical evaluation of devices (Meddev 2.7.1).
- Outlines procedures/documents/information that are of primary, but not exclusive, importance for validation and decision-making with regard to ethical considerations of a device trial.
- Outlines the steps to be followed for the assessment of clinical investigation applications to ensure, among other things, that the essential requirements applicable to the investigational

medical device, apart from those which are to be examined in the clinical investigation, are correctly identified and fulfilled (eg use of relevant harmonized standards).

- Explains the types decisions that a national competent authority might issue based on the outcome of the validation and/or assessment process. In cases where an objection letter is issued, the guideline states that it should contain, among other things, specific information required of the manufacturer in a resubmission in order to address the grounds for objection.
- Describes the types of actions that national competent authorities can take while a clinical investigation is ongoing (eg suspension) and the types of action that sponsors should take when they terminate or temporary halt a trial.

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4. Not quite there: EU medtech guidelines revision sign-off delayed, *Scrip Regulatory Affairs*, June 4, 2015

Source: *Vibha Sharma* , Scrip Regulatory

6. About us:

By L. Wenzel

P.SS.T is primarily specialized in the area of Medical Devices and new drug development, beginning with licensing and subsequent planning of pre- and clinical development phases and the respective project management up to marketing authorization applications and pre-marketing activities. Monitoring of clinical studies is as well included in our own services. Additionally we offer resources from our co-operation partners worldwide. We provide scientific services for all sections of healthcare, medicine, medical devise, cosmetics and pharmaceutical industry.

We provide you with regulatory affairs know-how, a specialized clinical research background and close contacts to opinion leaders in the following medical and scientific areas: cardiovascular, respiratory, metabolic and gastro-intestinal diseases, dermatology, immunology / transplantation, infectiology including AIDS, oncology, ophthalmology, osteoporosis, urology (BPH / prostate cancer).

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