TOPRA Annual Medical Devices Symposium 2017

Regulatory challenges today and tomorrow

SESSION 1: Optimising the implementation of the new MDR

Reported by **Tiffany Powell,** *Senior Regulatory Affairs Manager Medical Devices, GlaxoSmithKline Consumer Healthcare, UK.*

Margareth Jorvid, Methra Uppsala AB, LSM Group, Sweden, introduced the first session and speakers with an excellent background on the development of the new regulations in 2012, through to adoption in 2017. It was a clear reminder that industry and regulators must not lose sight of the patient. Focus must now be with the implementation. We all have a huge task to make this work.

Erik Hansson, Deputy Head of Unit, Directorate General for Internal Market, Industry, Entrepreneurship and SMEs, Health Technology and Cosmetics, European Commission, gave a presentation on the new EU Regulation on devices and first steps of their implementation. He offered an overview of the new Regulation, what is being done and what still needs to be done. Key aspects of the Regulation were summarised, including stricter market control of certain high-risk devices; inclusion of certain aesthetic devices; reprocessing of single-use devices; reinforced designation and oversight of notified bodies (NBs); greater detail on clinical investigations and clinical evaluations.

Mr Hansson outlined key dates from November 2017 for the new NB application for designation under the Medical Device Regulation (MDR) and establishment of the Medical Device Coordination Group (MDCG), through to the coordinated procedure for multicentre clinical investigations in 2027. He focused on 18 urgent top priority implementing acts to be adopted via a procedure to include an impact assessment and an online four-week period for public feedback. NB codes for the Regulation, common specifications for aesthetic devices, unique device identification (UDI) and Eudamed are on the priority list.

Céline Bourguignon, Director Global Regulatory Policy, Johnson and Johnson, Belgium, then spoke on the implementation of the MDR and possible consequences for industry. Dr Bourguignon opened her presentation with a clear message that non-compliance will result in a loss of business. Capacity and resource issues for NBs are likely to create a queue for registration/submissions due to greater focus on clinical evidence and vigilance, expert reviews on new technologies and labelling obligations which will have a significant impact on industry (from supply chain to distribution).

One question that arises is "what is sufficient clinical evidence"? There are cost implications for conducting clinical evidence on simple devices where such studies would be too expensive for industry to support. A pragmatic approach is needed by the NB and industry.

A further question is "how will manufacturers and NBs maintain two quality systems?" And what will the periodic safety update reports (PSURs) look like for devices? There are so many unknowns which still need to be clarified. Dr Bourguignon finished with a key message that there will be a huge impact on cost, resources and planning and to monitor implementation.

In the panel discussion which followed, the session speakers

Acronyms and abbreviations

- **CA –** Competent Authority
- **CAMD –** Competent Authorities for Medical Devices
- **CRO –** Contract Research Organisation
- **EMA –** European Medicines Agency
- **HMA –** Heads of Medicines Agencies
- **IMDRF –** International Medical Device Regulatory Forum
- **IVDR –** In Vitro Diagnostic Regulation
- **MAA –** Marketing Authorisation Application
- **MDCG –** Medical Device Coordination Group
- **MDR –** Medical Device Regulation
- **MHRA –** Medicines and Healthcare products Regulatory Agency
- **NB –** Notified Body
- **NBOG –** Notified Body Operations Group
- **OCP –** Office of Combination Products
- **UDI –** Unique Device Identification

were joined by **Giovanni Di Rienzo, Global Director, TÜV SÜD Product Service GmbH, Germany,** and **John Wilkinson, Director of Devices, MHRA, UK.**

Mr Wilkinson commented that the presentations eloquently outlined the mammoth tasks ahead. The consistency of implementation is key, and challenges must be identified as soon as possible. A realistic understanding of the concepts that add little value with high costs should be identified, and pragmatism is vital.

The panel then took several questions from the floor. The first query was whether the Commission wanted the UK to maintain such a key presence in the competent authorities for medical devices (CAMD). Mr Hansson explained that the UK would maintain a key role. The UK is home to a significant number of NBs, authorised representatives and legal manufacturers. Some of the existing non-EU models such as mutual recognition could be the basis of EU/UK cooperation – it depends on political openness and willingness.

Mika Reinikainen, Abnovo Authorised Representative, asked how non-government institutions will have access to consultations. Mr Hansson responded that he foresees stakeholder representatives as observers to participate in discussions with the MDCG; however, the Commission and EU member states are still discussing how this will work.

Neil Armstrong, MeddiQuest Regulatory Affairs Limited, Ireland, then asked if there are any safeguards in place to ensure innovation isn't stifled by the stricter requirements of the Regulations. Mr Hansson clarified that negotiations achieved a good balance to include new features to help ensure the safety of devices. He agreed with Mr Wilkinson that a pragmatic approach is required.

Erik Hansson, Deputy Head of Unit, Directorate General for Internal Market, Industry, Entrepreneurship and SMEs, Health Technology and Cosmetics, European Commission

Mr Di Rienzo concluded with a concern from an NB viewpoint, saying that he believed the Regulation may force more businesses to innovate in the US.

Mark Corbett, Inceptua Medicines Access, asked how far we can go with a pilot project, given so many unknowns. Dr Bourguignon responded that we should map our expectations to that of the NB. A further question raised was how the MEDDEVs will be managed post-implementation of the Regulation. Mr Hansson explained that most of the MEDDEVs will become implementing acts and will be dealt with by the MDCG, although this may not be in time for 2020.

SESSION 2: Implications of new regulatory oversight requirements

Reported by **Beata Wilkinson,** *Head of Regulatory Services, CROMSOURCE CRO, UK.*

This session was chaired by **Sabina Hoekstra, Lead for European Regulation, Philips, the Netherlands,** who outlined the recent developments which continue to raise the bar for regulatory oversight by competent authorities (CAs) and NBs. These developments include the 2016 publication of MEDDEV 2.7/1 rev 4 guidance on clinical evaluation. Under the new MDR, regulators will need to ensure permanent availability of competent personnel. The speakers in this session were asked to describe how they manage the burden of increased oversight and what they expect from the parties they oversee.

The first speaker, **Giovanni Di Rienzo, Global Director – Cardiovascular Focus Team, TÜV SÜD Product Service, UK,** discussed the impact of new regulatory oversight requirements on his NB. He said that "the storm is coming for everyone, and TÜV SÜD has been preparing for it." The company set up an MDR impact assessment working group in 2014 and has been hiring personnel (doubling its resources in 2014), training them, updating relevant processes and informing manufacturers.

New duties or requirements have been identified as applying to: devices without a medical purpose (which may be viewed as an opportunity, not just an extra task); re-certification of all devices (a one-off requirement); class 1 reusable surgical instruments; class IIb implantable devices; post-market surveillance oversight; stricter clinical evaluation requirements; and clinical evaluation consultations. In addition, TÜV SÜD has to meet generally stricter requirements and cope with transfers from other NBs.

Despite the date of application of the MDR (26 May 2020) and the date when NB designation can begin (26 November 2017) being fixed, the date when the first MDR certificates are expected to be issued, originally thought to be sometime in 2018, is now more likely to be sometime in 2019. This means a best-case scenario of one to two years for transition to implement the MDR, which will be a huge challenge. A forecast of the workload shows a large peak around the first half of 2020, and it is important to find a way to deal with such a peak. While, some people believe there will be an extension of transition period, Mr Di Rienzo said that TÜV SÜD does not think this is the case. The company therefore plans to prepare by carrying out more work ahead

Valerie Field, Head of Devices Software/Apps, Devices, MHRA

of the anticipated peak, such as pilot projects, mock simulated quality system (QS) audits, and mock technical file audits.

The MEDDEV 2.7/1 Rev 4 guidance on clinical evaluation represents a useful first step towards compliance with the MDR's more stringent clinical data requirements. Although it is not entirely aligned with the MDR and is not legally binding, it presents a uniform, state-of-the-art, scientific method to conduct a clinical evaluation.

The presentation ended with a discussion on the areas of concern. One is the very short transition period for NBs to implement the MDR. Another one is the overall lack of resources such as regulatory staff, contract research organisations (CROs), NBs and consultants to implement the change smoothly. On top of that are uncertainties regarding the NB designation process and timelines, and unclear MDR text requiring common interpretation. There is also the added challenge of other regulatory changes to be implemented at the same time as the MDR, such as the Medical Device Single Audit Program (MDSAP) and MEDDEV 2.7/1 rev 4.

The second speaker, **John Wilkinson, Director of Devices, MHRA, UK,** discussed the impact of new regulatory oversight requirements on the MHRA. The revision of the MDD has been timely and important but open questions remain as to how CAs should manage new responsibilities. The three main areas are: (1) regulation of non-medical devices listed in Annex XVI of the MDR that carry much of the same risks as medical devices; (2) supervision of the supply chain (importers and distributors) that CAs are not used to supervising; (3) drug-device combination products; although this area is fraught with challenges, the MHRA has been working with stakeholders with some fruitful and interesting outcomes. The regulation of software as a medical device is an additional major concern. This footprint is very large – for example, in the US 1,000 health apps are released onto the market every month.

In terms of expansion of current responsibilities, the importance of the UDI was stressed for identifying products and improving surveillance. In the UK this is about safety, linking to patient records, and demonstration of effectiveness in patients.

The MDR legislation has been evolving since 2008 and the direction of travel was firmly laid down in 2012. The MHRA has prepared a detailed operational plan and will be able to meet the MDR implementation timetable. NBs are being urged to "get their act together". NBs are partners, sub-contractors, and the more they can work with CAs, the better (rather than being audited into shape).

The MHRA sees several constraints to MDR implementation. The dual regulatory system will be difficult. EU legislation will be "cut and pasted" into UK law, but for the evolving medical device legislation this will be overwhelmingly more difficult than for most other areas. The Eudamed database is of great concern to all stakeholders. If delays occur to its implementation there will be a need for a pragmatic and dynamic approach. The MDR will be directly applicable, but there are cultural diversities to consider. Organisations dealing with some of these constraints are the Implementation Task Force, set up in the UK (which is stepping down from leadership) and the Transition Subgroup with lawyers on board.

European governance will change, transitioning from the CAMD) to the MDCG. The MDCG is the main body supporting the European Commission in implementing the future regulations. Although the future role of CAMD is uncertain, there are several reasons why it should continue post-CAMD, but it should not duplicate the MDCG's role. The greatest challenge for the MHRA will be how to support these groups. One aspect that will not change is the requirement for goodwill and collaborations between CAs.

SESSION 3: Embracing the digital healthcare revolution

Reported by **Janine Jamieson,** *JCombinations AB, Sweden.*

Recognising that regulators are trying to adapt in a rapidly changing technological environment of apps, connected devices and other digital support services, the aim of this session was to consider where regulators and industry could collaborate further to realise digital health benefits in a timely but safe and controlled manner.

Opening the session, **Valerie Field, Head of Devices Software/Apps, Devices, MHRA,** outlined the challenges for regulators with the pace of development of new technology, the changes being brought in by the new MDR and the guidance and help available to maintain patient safety.

Risks relating to possible negative interaction with other IT systems and cybersecurity were discussed both in the presentation and further in the panel discussion, reflecting the concerns of both clinicians and patients. It was stressed that the software incorporated into medical devices should be developed and manufactured in accordance with the state of the art, taking into account the principles of development lifecycle and risk management, including information security, verification and validation.

The new software classification Rule 11 was covered – with most medical device software being used to support clinical decision-making in class IIa, except if such decisions have an impact that may directly or indirectly cause deterioration of health or death, in which case a higher classification will apply.

Traceability and transparency were also mentioned, with the new requirement for UDI and eventual recording of information on the Eudamed database.

Challenges for the MHRA are to work with the EU on agreeing interpretation and implementation of the changes, also looking to international approaches via the International Medical Device Regulatory Forum (IMDRF), the US FDA and others; working with NBs on being ready for the changes and engaging with the major app stores, such as Google to make them aware of their responsibilities as importers and distributors.

The next presentation was an industry perspective from a large pharma company, given by **Kirsten Paulson, Global CMC-Medical Device Lead, Pfizer, US.** Noting that software is becoming increasingly popular with pharma, Ms Paulson described some of the top industry challenges with software as a medical device (SaMD), explaining the impact of MDR on software from an industry perspective. She also

Kirsten Paulson, Global CMC-Medical Device Lead, Pfizer, US

discussed the FDA regulation of clinical decision support software and recent US legislation and initiatives, including the FDA pre-certification pilot programme with nine selected companies with proven quality systems that may potentially be able to bypass FDA review. Ms Paulson finished with a plea for global harmonisation of requirements to enable global access to innovative products using SaMD. Explaining that there are different definitions, development costs, change control expectations and timelines across countries which complicate development plans and increases time/cost, Ms Paulson emphasised the need to apply the correct designation early in project development.

The final presentation of the session was a perspective from a rapidly expanding digital health development company, with **David Hubanks, VP Operations, Propeller Health, US,** sharing his company's experiences of releasing software in a regulated environment – every week. Mr Hubanks explained that Propeller Health made the early decision to start as a medical device company and recruited a Quality regulatory person as first hire to work in the development team, alongside the product design and engineering members. To be successful in such a fast-paced environment, he described how they have implemented lean principles with Kanban agile techniques to visualise flow of work; focusing on continuous improvement as the company culture. Some things they had learned were to be smart and take on smaller, more frequent changes, allowing greater concentration, efficiency and higher quality.

Other learnings shared included allowing more time for testing "like a user" and trying to break things, as well as utilising automation where possible – also that celebrating a release with a box of doughnuts is not good for health when you release each week!

In the panel discussion that followed, one challenging question from MedTech SPIN member Neil Armstrong queried regulator expectations for validation of learning algorithms bordering on artificial intelligence. Ms Field acknowledged this was an unknown but that a way to approach it would be to consider if the algorithm was one where the logic could be followed – that was fairly straightforward. However, if it was a black-box neural AI one where there was no comprehension of the logic, it was very difficult. She suggested that was a case where greater engagement with clinical colleagues would be helpful, to consider the outcomes – if the outcome is reproducible and meets a need, then, being "quite revolutionary", the end outcome could be considered the important factor – there may not be another way to do it. It would then be for the developing manufacturer to prove that the outcome is indeed reproducible.

SESSION 4: Personalised medicine: In vitro diagnostics and companion diagnostics

Reported by **Neil Adams,** *Associate Director Regulatory Affairs, Illumina Inc.*

Wednesday at the symposium was a full day of joint sessions which looked at issues of common concern in the new IVD Regulation for Human Medicines and Medical Devices. To start the day **Nick Baker, Technical Manager, LRQA,** began with an overview of classification under the In Vitro Diagnostic Regulation (IVDR) and how it relates to companion diagnostics. Companion diagnostics are defined in EU law for the first time in IVDR Article 2(6) as: "A device which is essential for the safe and effective use of a corresponding medicinal product to: identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product." This definition does not cover "complementary diagnostics" – diagnostic products that are not directly necessary for the use of a medicinal product, but provide guidance in the use of a medicinal product.

Under the new classification and conformity assessment rules, most IVD assays will be reviewed by an NB. Companion diagnostics also have their own conformity assessment requirements requiring NBs to consult either with the European Medicines Agency (EMA) or CAs. The session focused on how this will work in practice for pharmaceutical and diagnostics manufacturers.

The IVD device classification system is risk-based, and companion diagnostics will fall into Class C, ie, products that could have a high personal risk and a moderate to low public health risk.

Questions for Mr Baker focused on resource concerns in NBs and their ability to undertake the work. He explained that NBs can start the certification reviews now before designation, so that they are in a position to certify the products promptly when they are designated under the IVDR. Therefore, it behoves manufacturers to get to it as soon as possible.

Daryl Colombage, Senior Medical Device Specialist, MHRA, gave a CA perspective on the IVDR and companion diagnostics. Ms Colombage considered the clinical evidence requirements in the IVDR, pointing out that, generally, compliance is based on clinical evidence from clinical performance studies. She reminded everyone that "interventional studies" require CA approval and CAs should be notified about "non-interventional" studies, and ran through the procedure, with key timelines and requirements relating to application, verification, assessment, running the trial and the performance study report. There are key obligations and time constraints on sponsors for the all the steps in the process that will come as a shock to some manufacturers not used to working with regulated products. The key message is that you should speak as early as possible to regulators and make sure you have procedures in place to cover foreseen problems that can arise with a study.

Peter Martin, Senior Director Global Regulatory Affairs, Roche Diagnostics, Germany, reflected on the challenges for industry in bringing companion diagnostics to market under the IVDR. He pointed out that though companion diagnostics are explicitly mentioned in Rule 3 as being in risk class C, they could also fall in the highest risk class D. When could a companion diagnostic fall in

Peter Martin, Senior Director Global Regulatory Affairs, Roche Diagnostics, Germany

risk class D? When it is used to determine the infectious load of a life-threatening disease where its monitoring is critical in the process of patient management.

There was a focus on a number of areas of concern for manufacturers, particularly issues relating to the transition of existing companion diagnostics. Products CE marked under Annex III of the IVDD do not require NB or EMA review to bring them to the market; retrospective review by an NB and the EMA will be necessary. What happens if the EMA finds data insufficient? Access to samples cannot be guaranteed for additional data, and the drug already on the market depends on the companion diagnostic. There could be ethical concerns on collecting new samples.

In the panel discussion, the EMA agreed that if pharmacovigilance for existing products is clean, there should be no need to generate new data, but we need to sort out detail of procedures to make sure data are of sufficient quality to meet requirements of the IVDR. Questions suggested that the process for new products is relatively clear, but there is work to do understand the processes for current products moving from self-declaration under the IVDD where the medicinal product has been regulated by member states rather than the EMA.

SESSION 5: Medicinal products incorporating device components – significant change ahead

Reported by **Tim Chesworth,** *Senior Director – Medical Devices & Combination Products, Regulatory Affairs, AstraZeneca, UK.*

Janine Jamieson, JCombinations AB, Sweden, opened the session highlighting some of the many changes and challenges in the area of combination products. These were explored in more detail by the subsequent presenters. **Theresa Jeary, Head of Notified Body – Medical Devices, LRQA, UK,** provided an NB perspective on Article 117 in the MDR and the significant change that it represents, in particular the requirement for NB review of the device component of single integral drug-device combination products. While NBs are involved to a limited degree in this kind of activity, it is currently done on a discretionary basis and on request from a pharmaceutical company. However in the future this will become a regulatory expectation in the EU and will be part of the evidence used to evaluate a marketing authorisation application (MAA) for this type of product. Ms Jeary encouraged all those impacted, or potentially impacted, by this change to engage with an NB to begin a dialogue. However finding a suitable NB may be difficult as the number of NBs has reduced and is expected to decrease further. It is also unclear which NBs will be in a position to provide the required review. Currently there remain many areas of ambiguity in relation to Article 117 that require clarification: what the CAs will be looking for in future MAAs; what level of information will be required and in what format; what will need to be in place for the NB to issue an opinion. Consequently, more detailed guidance needs to be provided to answer these questions. Groups such as the Notified Body Operations Group (NBOG) and Team-NB are well placed to work with CAs and the European Commission to help draft this guidance.

Armin Ritzhaupt, Regulatory Affairs Officer, EMA, provided an overview of how the EMA currently reviews drug-device combination products and how this will change under the MDR. There has been a significant increase in these types of products being submitted for approval. Since 2010, of 360 MAAs submitted; 48 (13%) were in combination with a device. Of these 48 applications, two-thirds have been filed since 2015 and this rate is expected to increase. This change has, in part, driven the inclusion of Article 117 in the MDR as there is recognition that as these products become an important part of the EU healthcare system, the level of oversight and scrutiny needs to increase. Earlier in 2017, the EMA published a concept paper on quality requirements for drug-device combination products. Many comments were provided on the concept paper from a broad range of stakeholders and the EMA is working through this input with the aim of publishing a guideline. This guideline will cover key topics such as: dossier requirements for integral and non-integral combination products; information in the summary of product characteristics (SmPC), labelling and leaflet; usability study requirements; product lifecycle management.

John (Barr) Weiner, Associate Director, Office of Combination Products (OCP), FDA, presented the latest situation in relation to combination products which has been an area of high activity within the FDA. This has been across a wide range of subjects from classification of products as drugs or devices to post-market safety reporting and human factors to the inter-centre consultation process. Similarly to the EU, there are an increasing number and complexity of combination product applications, so the FDA has created the Combination Products Council, which is a senior level forum to address combination product issues. It is chaired by the Deputy Commissioner for Medical Products and includes the Centre Directors for CBER, CDER, and CDRH and the Office Director for OCP. This group now plays a key role is improving and ensuring more consistency in the review of combination products. Mr Weiner highlighted the value of gaining input from and collaboration with industry, particularly via industry groups. This is particularly important to ensure that the FDA is aware of and can then begin to address these issues. In conclusion, Mr Weiner gave some key messages from the OCP: focus on efficiency, consistency and coordination; commitment to a risk-based approach; commitment to speaking with one voice; desire to hear from and collaborate with industry and work together; look to OCP as a resource.

Liz Baker, Group Manager Licensing Division, MHRA, concluded the presentations by describing some of the challenges from a CA perspective (eg, around 30% of 500 scientific advice enquiries involve devices/combination products/drug-device borderline.) Ms Baker also discussed a new initiative between the Heads of Medicines Agencies (HMA) and CAMD to address the increasingly complex regulatory environment for combination products.

During the panel discussion, a key theme from an EU perspective was the urgent need for more guidance on Article 117 of the MDR, as industry needs to start taking action now.