ENGAGING WITH THE NEW EUROPEAN REGULATORY LANDSCAPE FOR MEDICAL DEVICES – CHALLENGES AND OPPORTUNITIES

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Summary Report

Overview and round-up

On 21 March, the European Society of Cardiology (ESC) invited leading scientists representing some twenty medical associations in Europe to discuss the safety and performance of the medical devices they use to diagnose and treat their patients, how the new European regulatory landscape impacts that, and what opportunities lie ahead for the involvement of experts in the regulatory process. They were joined in Brussels by EU and national regulators currently involved in preparing to implement the landmark regulation.

In 2017, the European Union (EU) adopted two new pieces of legislation aimed at regulating the life cycle of medical devices and in vitro diagnostic (IVD) medical devices[1]. These include more stringent safeguards before new technology is allowed to market, as well as strengthened surveillance after market approval. Importantly, the new laws also foresee the increased involvement of scientists and physicians alongside regulators, for the provision of expert advice.

Opinions during the high-level meeting were fairly evenly divided on whether the regulation presents more 'challenges' than 'opportunities', but all agreed that a deep understanding by healthcare professionals and academia of the implications on clinical practice is necessary to guarantee the best patient outcomes. Attendees welcomed the ESC's demonstrated leadership both during the regulation's gestation and now as it starts to gain momentum across Europe ahead of full implementation in May 2020.

According to Alan Fraser, who is chair of ESC's EU Regulatory Affairs Committee on Medical Devices and the driving force behind the 21 March event: "Experts from all medical specialties and a broad base of healthcare professionals should similarly engage in the implementation of the new regulations, to guarantee timely access to safe and effective devices for European patients."

"It is a long journey and outside our comfort zone," stressed ESC's President Jeroen Bax, "but we need to do it, and to do it right in order to further improve patient care."

[1] Regulation (EU) 2017/745 of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
Regulation (EU) 2017/746 of 5 April 2017 on in vitro diagnostic (IVD) medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

A day of contrasts … with a closing dose of optimism

In the morning, the wider political picture was painted before talks drilled down to specific provisions, acts, timescales and tools for the regulations, their clinical impacts, and the role of notified bodies, and treatment of clinical evidence. Quick-fire presentations and probing questions in the afternoon delved into evidence-based practices (priorities, transparency, clinical requirements, registration, examples, etc.), health technology assessments, and standards for medical devices. A final session on how to engage experts and the governance issues, including interventions from US delegates, provided valuable take-home messages for everyone.

The meeting kicked off with a rousing introduction by ESC's President Jeroen Bax and the European Commission's Salvatore D'Acunto, who is responsible for health technology and cosmetics at DG GROW (the Directorate- General for internal market, industry, entrepreneurship and SMEs).

People are healthier for longer but many medical conditions, including cardiovascular disease, are still big challenges that call for new medical devices, suggested Prof. Bax, which makes the new EU regulations so important for patients and for medical associations including the ESC.

Mr D'Acunto – providing a welcome legal perspective – echoed the "massive" importance of implementing the new regulations effectively with as "little bureaucracy as possible", to avoid stifling European jobs and growth generated on the back of medical device innovations. "Every 50 minutes, a new medical device patent is introduced," he said, "higher than for pharmaceuticals."

Dr Paul Piscoi also from DG GROW explained to the delegates the background of EU law-making in general, the actors involved – i.e. European Commission proposals debated and voted into law by the Parliament and Council – and the role of various Commission teams in the medical devices regulation. He summarised the provisions of the new regulations and the opportunities for expert engagement.

KU Leuven's Karin Sipido, chair of the Scientific Panel for Health at the research directorate of the Commission reviewed the role of research and innovation, the EU's remit in health and healthcare research, and the main advisory mechanisms, which give opportunities for experts to be involved alongside policymakers. For instance, the Commission's DG Research and the lesser-known Joint Research Centre (JRC) provide valuable 'in-house' expertise, supported by individual ad-hoc research projects, permanent advisory groups and others, such as the Scientific Panel for Health, a science-led expert group that advises on the provisions of the Horizon 2020 Programme.

Peter Liese, MEP and rapporteur for the IVD medical device regulation, said anyone who thinks the EU has no competence in health is talking "complete rubbish". European Union legal provisions are "not just for cars and toys but also for medical devices". It is important to have strict EU regulation, he stressed, because responsibility to protect health across borders is specified in the EU Treaties. It was clear from the implant scandals and other evidence that the previous medical device directives were out of touch. He and many others joined the efforts to improve them, and he was pleased to have worked together with Mr D'Acunto and his colleagues during the trialogue that revised the legislation.

Sufficient resources and clarity?

Resources and capacities were running themes during the event. Prof. Fraser pointed out the challenges that the Commission's dedicated medical device team face, and the thinly-spread competences across multiple agencies, directorates and activities. There have been as few as seven full-time equivalent (FTE) employees managing medical devices for the European Commission, and although there is approval for the total to expand to more than 30, recruits have to be found mainly by transfers since there is a moratorium on new expenditure. The dearth of expert physicians in the Commission to cover diverse medical devices compares poorly to the US Food and Drug Administration (FDA), which counts some 1700 FTE, including 117 medical officers and 75 statisticians, for a country with a population less than the EU total.

"There are more software engineers working on the EUDAMED database than actual staff working on the main actions," he lamented, calling for assurances that more resources be made available. This will be critical to match the pace of innovation with corresponding expertise, and secure the right balance between legislation, early access, more choice and safety. "In 2011, we published a paper[2] proposing a single agency for the regulatory governance of medical devices, and we maintain the need for it. Although we see in hindsight why it wasn't taken up, adequate system capacity remains paramount," he said.

He explained the complex role of notified bodies (NBs), which as independent organisations are not governed by EU legislation on open access to documents, but they conduct the reviews of individual high-risk devices and they are where most expert staff within the EU system are located.

Unknown risks of new medical devices should be shared internationally, he said, and the ESC has been a strong advocate (e.g. at the International Medical Device Regulators Forum) for global convergence of standards and access to better data as part of more robust scrutiny. Physicians need to contribute to registries and post-market surveillance to ensure that risks are detected.

Bassil Akra, who is head of the cardiovascular, orthopaedic and clinical section of TÜV SÜD, Europe's biggest notified body, was more hawkish about the abilities of Europe's 59 NBs ("bigger than the FDA") to meet the challenges presented by the new regulations, including his own organisation where some 700 staff work on medical devices. "We waited eagerly for the new law and now it is time to apply it."

While appreciative of the regulation's compact structure, which "helps to find what you're looking for", he called for more definition and clarity on several terms like 'sufficient clinical data' and 'relevant clinical expertise', and the use of 'internal versus external' experts. Some standards bodies may still interpret these their own way, he stressed, especially with the addition to the regulation of cosmetic devices like contact lenses.

"The primary challenge is to regulate a disparate area of hundreds of thousands of devices … a system that works for a wheelchair or a heart valve, [so they're] safe for the intended purpose," said Tom Melvin of Ireland's Health Products Regulatory Authority (HPRA), who is co-chairman with Paul Piscoi of the EU regulators' committee on clinical investigation

[2] Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform: Report of a policy conference of the European Society of Cardiology (European Heart Journal - May 2011) https://academic.oup.com/eurheartj/article/32/13/1673/507544

and evaluation of medical devices. There are a number of important developments with respect to clinical evidence in the MDR, such as the ability to create technology-specific guidance (i.e. 'common specifications') or the scrutiny procedure for high-risk devices. The summary of safety and clinical performance (SSCP) will also improve transparency with respect to the evidence to support high-risk medical devices.

According to Lund University's David Erlinge, who chairs Sweden's SCAAR PCI registry – one of Swedeheart's component registries – their system is able to produce fine-grained, longitudinal (1982-present) data covering many dozens of variables ranging from drug regimes to implants to patient follow-ups. A unique programme of national ID numbers, he said, offers full traceability across the whole system, which only costs around €700,000 a year to maintain, as data input costs are borne by individual hospitals who employ, for example, just one FTE to do it. Informed consent is on an opt-out basis, he suggested.

Swedeheart's overall approach was benchmarked on several occasions during the meeting, and the subject of data registries – how to manage them effectively especially in different national settings (legal, financial, data protection, etc.) – came up in several questions from the audience. Attendees were interested in how companies used Swedeheart's detailed longitudinal datasets for post-market studies and follow-up, the validity of endpoints for limited datasets delivering specific conclusions, and prospects for a European non-commercial registry and avenue for prospective randomised trials that offers the necessary scientific, logistical, and financial guarantees. Prof. Marian Zembala, the President of the European Association for Cardio-Thoracic Surgery, asked the ESC and all participants to be clear on a "common message" and pragmatic response to this need.

The ESC had advocated that clinical follow-up of new devices after CE marking should include registries that are run independently by medical associations and academic bodies, according to Alan Fraser, but this was left out of the final version of the legislation. He added that he was aware of interest in the Commission to support the development of independently-run registries providing safety signals to the regulators. "We've been looking for ways to fund that," he said.

Transparency, clinical impact … and everything in between

The Brussels event also encouraged efforts to boost transparency on clinical evidence concerning medical devices and IVDs, in particular to address gaps identified in post-market clinical follow-up, to define 'equivalency' data for high-risk devices, and to provide more communication covering their use, efficacy and any device alerts or recalls. Discussions also highlighted requirements for and methods of developing device-specific guidance and common technical specifications.

Repeated questions from delegates touched on the lack of specificity in the wording of some parts of the regulations, as well as shortage of mechanisms to deal with special cases such as orthopaedics or paediatrics, and the practical, logistical, legal, educational and administrative systems needed.

Calling from the USA, Ileana Piña of the Montefiore Medical Center in New York, who is a clinical academic and part-time FDA employee, explained how the FDA recruits and trains experts and how it develops networks with different medical societies. Feedback and constant improvement are key, she said.

Experiential training – including on clinical trial design, statistics and practical considerations – are part and parcel of the FDA's approach to developing expertise and matching it to the regulatory landscape in a particular field, she suggested. Field trips to individual manufacturers and R&D labs are not uncommon, which means when the expert then comes across a file, they can actually see in their mind how that device is made. "So, a lot goes on in the background before I get a file," said Dr Piña, and that file is often worked on by a team of experts, from biomedical engineers to clinicians, who bring something different to the table.

Training in regulatory science for healthcare professionals and academia is likely needed in Europe as well, if it wants to ensure that experts are in the position to contribute effectively to the system set up by the new laws, participants noted during question time.

Data quality, a recurring theme

One theme of note was the fear that poor-quality data are being used for approvals of high-risk medical devices. *JAMA Internal Medicine* editor and medical device specialist at the University of California, San Francisco, Dr Rita Redberg, elaborated on the continuing risk of "watered-down" data where even "anecdotal evidence" has been allowed as support for device approval, and her concern that traditional US-EU rivalry – to be first to market – may "subject millions to unsafe or untested devices". The innovation-first argument, she said via video-conference, is that speed is needed for patients. "But how do we know it is innovative? Faster can mean dangerous devices not innovative devices!" she challenged.

Dr Redberg proposed a wish list to ensure progress on both sides of the Atlantic:

1. Apply data-driven approaches with unique device identification (or UDI) for retrace and recall
2. Use higher-quality data and effective post-market evaluation planning with clear consequences if not followed
3. Perform double-blind randomised trials with 'sham' interventions in control subjects
4. Set significant end-points and larger, more representative samples
5. Make data publically available
6. Release data faster (real time) by subgroup
7. Find a realistic balance between innovation and safety

Data quality, it was shown, is also critical for health technology assessment (HTA). Julia Schmitz from the Commission's DG SANTE elaborated on a Commission legislative proposal for strengthening EU cooperation on HTA, explaining the added value of the proposed regulation[3] and its main provisions. HTAs are used to inform decision-making at national level by providing a scientific basis for decisions on the pricing and reimbursement of health technologies. The Commission

[3] Proposal for a regulation of the European Parliament and of the council on health technology assessment and amending directive 2011/24EU https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/com2018_51final_en.pdf

proposal focuses on joint work on common scientific and clinical aspects in HTA, leaving the assessment of more context-specific aspects (e.g. economic, ethical) and decision-making at Member State level. Participants also learned about the important ongoing work of EUnetHTA in boosting cooperation on HTA Europe-wide, including the piloting of joint clinical assessments and the development of tools and templates.

Self-declared "undercover agent" and evidence-based medicine expert at Oxford University, Carl Heneghan, said the drug-approval approach and success of the European Medical Agency is a clear benchmark for medical devices. As a founder member of the AllTrials campaign, which calls for "all past and present clinical trials to be registered and their full methods and summary results reported", Prof. Heneghan has the distinct impression that the device world is not talking enough to the pharmaceutical world, and vice-versa.

Speaking during the 'Transparency of evidence for medical devices – clinical requirements' session, he said the onus to publish clinical trial data within a year is key to tackling concerns raised by Prof. Redberg and others. He showed a series of articles highlighting systemic failures in reporting, due diligence, consenting processes, and generally slow responses to problem cases.

Prof. Heneghan's activism uncovered evidence of major, undeclared complications arising from metal-on-metal hip replacements, which set in motion investigations (see *The BMJ*). Most of the litigation problems, he pointed out, are based on people "not being adequately consented", which is a huge issue that the new regulations have yet to resolve.

Ever the optimist

As head of the medical device division of HPRA, Niall MacAleenan countered that the engagement of medical experts throughout the life cycle of a new medical technology is critical to fulfilling the potential of the new medical device regulations, and to overcoming any hurdles.

The 2012 storm created by the PIP breast implant scandal and by the complications of metal-on-metal hip replacements were the impetus for much more active oversight of the European system, which was a significant step forward. The new regulations offer more legal tools and specific mechanisms for investigation, transparency, and sharing data, and for addressing many other challenges and concerns that were raised during the meeting. "I'm optimistic about it," he concluded.

The European Society of Cardiology and the Alliance for BioMedical Research in Europe (Biomed Alliance) will now coordinate joint efforts by specialist medical associations in the European Union to support the implementation of the new Regulations.