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A compelling strategic role for Medical Affairs in the context of the new EU MedTech regulations

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ABSTRACT:

This article provides an overview of the new MedTech European regulatory environment and opportunities for the Medical Affairs function to evolve and bring value to the respective organizations. The European Regulations ask for an increased effort from manufacturers to generate and communicate clinical evidence on the safety and performance of their Medical devices, In vitro-diagnostics and Drug Device Combinations. In conjunction with increased quality standards they make a compelling case for Medical & Scientific Governance with a prominent role for Medical Affairs in many pre- and post-market processes. A transformation of Medical Affairs into a strategic business function makes the medical device industry an exciting place to be for Medical Affairs professionals.

INTRODUCTION:

For over two decades, Medical devices and In-vitro Diagnostics have been regulated in Europe by Directives for MEDICAL DEVICES (MDD) and IN VITRO DIAGNOSTICS (IVDD)[1, 2, 3] that were published in 1993 and 1998 respectively. A separate Directive for Active Implantable Medical Devices (AIMD) was published in 1990 with a last revision in 2009. According to these Directives, devices are approved for the European Single Market only after having obtained CE Mark for which manufacturers need to demonstrate conformity to essential requirements relating to the device's performance and safety for patients and users. After public consultation by the European Commission in 2008 it became clear that an update of the Directives was needed, one reason being the simple fact that new technologies such as companion diagnostic devices were not yet covered. The need for revision gained traction after incidents with breast implants, transvaginal meshes around 2009 and metal-on-metal hip prostheses a couple of years later. Eventually, the revision process that started in 2012 resulted in the Medical Device Regulation (MDR) in which MDD and AIMD were combined and the In Vitro Diagnostics Regulation (IVDR)[4, 5]. The new Regulations were published in 2017, with May 25, 2017 as the official date of entering into force. A transition period to full implementation of the MDR and IVDR was allowed for three and five years respectively, which means the MDR applies from May 26, 2020 and IVDR from May 26, 2022.

So far so good… and then the COVID-19 crisis struck Europe, right at the moment when the medical device industry and notified bodies are transitioning to the new Regulations. Therefore, in order to "take the pressure off national authorities, notified bodies, manufacturers and other actors so they can focus fully on urgent priorities related to the coronavirus," the European Commission has decided to move back the date on which the new MDR would fully apply by one year, to 26 May 2021. MedTech Europe, the European trade organization of medical device manufacturers, has advocated for a similar delay for the IVDR.

Since the early days of the global COVID-19 crisis the medical industry has made a so far unseen effort in finding (bio-)pharmaceutical solutions, developing vaccines and reliable test kits. Simultaneously, in an attempt to address the relative shortage of masks and intensive care equipment such as ventilators, traditional medical device manufacturers ramped up production. Although regulators accommodate the surge of new devices by fast tracks and exemption rules, new devices are subject to meticulous assessments of performance and safety. And rightly so, since national policies to curb transmission of the virus rely on the quality of diagnostics and personal protection equipment. Especially important is the scrutiny in assessing new medical devices which are intended to be used in the management of the most vulnerable and severely ill COVID-19 patients who end up in hospitals and ICUs.

MEDICAL DEVICE REGULATION (MDR)

In general the new Regulations devices, improve traceability and transparency and define stricter requirements to clinical evidence and post-market surveillance. The MDR now also regulates devices for cosmetic purposes such as colored contact lenses and cosmetic implant devices. The introduction of Unique Device Identification should improve traceability, and transparency is created by the European Databank of Medical Devices (EUDAMED) where all mandatory regulatory documentation on each device is kept and updated. Manufacturers must re-certify devices in accordance with the new regulations and update their technical documentation accordingly with special attention to higher clinical requirements for class III and implantable devices. A shift of focus from a mere pre-market perspective towards a life-cycle approach also includes stricter requirements regarding post-market surveillance, post-market clinical follow-up and vigilance.

This brings us to the Clinical Evaluation, which lies at the basis of CE mark approval and the life-cycle approach. It is defined as "a systematic and planned process to continuously generate, collect, analyze and assess the clinical data pertaining to a device in order to verify the safety performance, clinical benefits of the device when used as intended by the manufacturer." The Clinical Evaluation process is described in a MEDDEV (MEDical DEVices) guidance document. MEDDEVs promote a common approach to be followed by manufacturers and notified bodies that are involved in conformity assessment procedures. Although these MEDDEVs are not legally binding, it is expected that their guidance be followed, ensuring the uniform application of the various elements of the directives/regulations. MEDDEV 2.7/1 rev. 4[6] is the guidance document with regards to Clinical Evaluation and is prescriptive on the process, the required qualification of the evaluators and the contents of a Clinical Evaluation Report (CER).

The CER should "describe the intended clinical benefit and provide evidence of safety and performance" where performance is defined as "the ability of a device to achieve its intended purpose as stated by the manufacturer." This report describes the risk profile of the device based on the technical documentation and provides an appraisal of all available clinical data related to safety and performance. Any evidence gaps and residual risk need to be addressed in Post-Market Clinical Follow Up (PMCF) studies to demonstrate long-term performance safety. The results from the intensified surveillance are laid down in the Periodic Safety Update Report (PSUR, mandatory for Class IIa/b and III) and Summary of Safety and Clinical Performance (SSCP, for implantables and Class III). These documents must be uploaded in EUDAMED, which allows public access to the SSCP.

Although European market approval of new devices can still be obtained by referring to clinical data of predicate equivalent devices, the MDR explicitly lists criteria by which equivalence can be claimed from a technical, biological and clinical perspective. The equivalence under the MDD was less well defined. Under the MDR, the predicate device must have a similar design, use the same materials and come in contact with the same tissues and body fluids, and be used for the same clinical indications. If a device does not meet these criteria, manufacturers need to generate their own clinical evidence with appropriate clinical investigations.

CE Marking requires Notified Body involvement for most medical device classes and is related to implementation of a Quality Management System, which must include plans pertaining to Clinical Evaluation, Post-Market Surveillance (PMS) and Post Market Clinical Follow-up (PMCF). For non-sterile Class I devices, manufacturers can conduct the conformity assessment themselves and basically self-certify. For Class I devices that are sterile, measuring or reusable surgical instruments as well as for all higher device classes, oversight of a Notified Body is required. In the end, it is the Notified Body that issues a CE Marking Certificate and ISO 13485 Certification. Only with these certificates in place the manufacturer can prepare a Declaration of Conformity and put the CE Mark sign on their products and labelling.

IN VITRO DIAGNOSTICS REGULATION (IVDR)

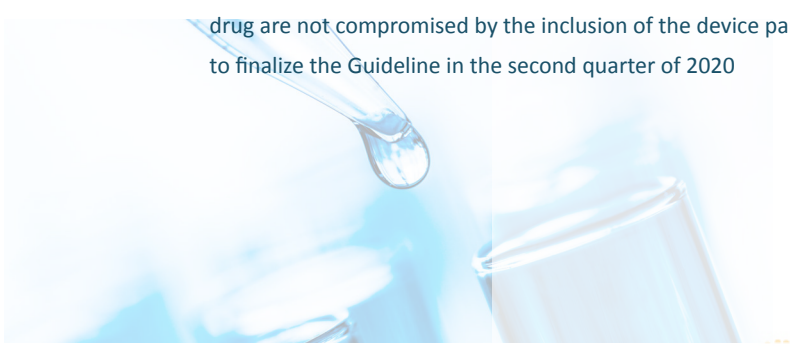
In Vitro diagnostics (IVDs) are medical devices with which tests are performed using human specimens such as urine or blood. Familiar examples of such devices are pregnancy tests and tests for determining the level of glucose or cholesterol in the blood. The current directives distinguish between medium risk and high-risk lists of IVDs. Those IVDs not captured in these lists are automatically classified as low risk. Obviously more stringent market authorization procedures with Notified Body oversight apply to high risk IVDs. Whereas in the past only a minority of IVDs required involvement of a Notified Body, under the new classification an estimated 90% will now require it. The IVDD had some gaps and this binary system was thought to be no longer sufficient. Hence, like for the MDR, a risk-based approach classification was introduced based on the severity of the disorder tested for and possible consequences of an incorrect test result. Instead of two lists, the new IVDR now distinguishes four categories, Class A (lowest risk), Class B, Class C, and Class D (highest risk) and dictates that Class B and above IVDs will require oversight from a Notified Body as part of their conformity assessment.

Aside from the risk-based classification, it will not surprise you that the new IVDR has more features in common with the MDR. As is the case for medical devices, the IVDR requires clinical evidence and post-market performance follow-up. This will require a Performance Evaluation plan and report for all IVD Classes, which will describe how to demonstrate scientific validity, analytic performance, and clinical performance.

COMBINATION PRODUCTS/DRUG DEVICE COMBINATIONS

Some medicines are used in combination with a medical device, usually to enable the delivery of the medicine. In the European Medicines Agency (EMA) view, if the principle intended action of the combination product is achieved by the medicine, the entire product is regulated as a medicinal product under Directive 2001/83/EC[7] or Regulation (EC) No 726/2004.[8] However, MDR's Article 117 brought some relevant additions. First, two categories were defined: (a) Integral, where the medicinal product and the device form a single integrated product (e.g. pre-filled syringes and pens) and (b) Co-packaged, where the medicinal product and the device are separate items contained in the same pack (e.g. reusable pen for insulin cartridges). Next, Article 117 also incorporated some relevant amendments to Directive 2001/83/EC to ensure combination products comply with the medical device legislation. Per MDR's Article 117, the marketing authorization application should include a CE certificate for the device or an opinion from a Notified Body on the conformity of the device (except for non-sterile, non-measuring and non-reusable surgical Class I devices).

Probably as a reaction to the rapid growth of combination products in recent years and the need to bring further clarity in this area, in June 2019 EMA released for public consultation a draft Guideline on Quality Requirements for Regulatory Submissions for Drug-Device Combinations.[9] The aim of this Guideline is to clarify expectations laid down in Directive 2001/83/EC and address the new obligations in the MDR. EMA makes it clear that the Notified Body assessment and marketing authorization review would not result in duplicate assessments. The former will review the device alone, while the latter will ensure the safety and efficacy of the drug are not compromised by the inclusion of the device part. The consultation period ended in August 2019 and EMA is now due to finalize the Guideline in the second quarter of 2020



It is also worthwhile making a reference to medical devices which may contain an ancillary medicinal substance to support the proper functioning of the device (e.g. drug-eluting stents). These products should comply with the medical device legislation. Yet, the manufacturer should also seek a scientific opinion from EMA on the quality and safety of the ancillary substance if it is derived from human blood or human plasma, or if it is within the scope of the centralized procedure for the authorization of medicines. For other substances, the Notified Body can seek the opinion from EMA or a national competent authority. Of note, EMA has recently issued a Consultation Procedure for Ancillary Medicinal Substances in Medical Devices.

Companion diagnostics are seen by EMA as in vitro diagnostic tests that support the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment. Applicable regulations were discussed above. Yet, before the Notified Body can issue CE Marking, it must seek a scientific opinion on the suitability of the companion diagnostic to the medicinal product concerned from EMA or a national competent authority, as appropriate. Similarly, a scientific opinion would also be needed for some other medical devices made of substances that are absorbed by the human body to achieve their intended purpose. These devices are normally introduced into the human body via an orifice or applied to the skin. Last, we should not forget the so called “borderline products”. These are complex healthcare products for which there is uncertainty over which regulatory framework applies. Common borderlines are between medicinal products, medical devices, cosmetics, biocidal products, herbal medicines and food supplements. The European Commission publishes the ‘Manual on borderline and classification in the Community regulatory framework for medical devices’ which provides examples and recommendations for determination of classifications. National competent authorities classify borderline products either as medicinal products or, for example, as medical devices on a case-by-case basis based on the product's composition and constituents, its mode of action and its intended purpose. This determines the applicable regulatory framework.

THE OPPORTUNITIES FOR MEDICAL AFFAIRS: MEDICAL & SCIENTIFIC GOVERNANCE

The new European regulatory environment (MDR, IVDR and EMA guidance on Drug Device Combinations) in conjunction with expanded quality standards for MedTech products and a rapidly changing reimbursement landscape are intensifying the need for a Medical Affairs role in the product lifecycle management. Furthermore, the increased trade organization’s guidelines as well as a more complex competitive environment in which the direct comparator might not be another MedTech product but instead a Drug or a Drug Device Combinations, all work favorably for Medical Affairs to step up its game and demonstrate its value in many regards.

The traditional competencies of Medical Affairs are still required to produce the new mandatory regulatory deliverables (Clinical/Performance Evaluation Report, Periodic Safety Update Report, Summary of Safety and Clinical Performance). However, more than ever Medical Affairs involvement needs to be formalized for various other key processes ranging from product development to device application. In order to give real meaning to patient and customer centricity, the inclusion of Medical Affairs contribution is indispensable with regard to, for instance, risk analyses, claims development and identifying user training needs.

In addition, medical and clinical research functions must lead in the development of coherent and affordable clinical research programs that serve regulatory compliance, reimbursement and commercial adoption purposes. The increased effort the companies must make to generate clinical evidence will undoubtedly put strain on human and financial resources. The careful planning and design of studies should avoid waste in time and money while providing the evidence the business needs in a timely fashion. Therefore, as non-inferiority assessments are giving space to superiority assessments, an increased is expected in reliance for regulatory purposes on less conventional evidence generation strategies such as registries, collaborative research and investigator lead studies.

Furthermore, ensuring the safe application of current devices, medical communication and interactions with healthcare stakeholders and health authorities, collecting and weighing medical intelligence on future directions in healthcare all require medical scientific oversight. The medical scientific oversight will be fundamental in the advancement of the company's innovation agenda as the bar is higher than ever, as are the associated entry and maintenance costs.

CONCLUSION

The new environment makes a compelling case for installing a structure for Medical and Scientific Governance and a proactive strategic role for Medical Affairs. This in turn opens the discussion on how to develop and organize competencies around organizational capabilities that relate to the development of innovative and relevant devices, the substantiation of medical-clinical and health economic claims and ultimately oversight to ensure safe and appropriate use. Thus, we argue that now is the time to engage in captivating thought exercises about whether a company's fabric with a prominent role of Medical Affairs adds to the organizational capability and resilience to handle current and future challenges.

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