ROPES & GRAY

TRANSCRIPT

September 6, 2021

Scientific Technological Challenges and EU Medical Devices Regulatory Framework

Chinese language transcript begins on page four

Ladies and Gentlemen, it is a great pleasure to be invited to speak at this conference and to share with you some thoughts on regulatory developments in the European Union.

To set the scene and to provide the context, I will first discuss the practical challenges to the medical technology sector as a result of the continuing changes to the external environment as well as the need for the sector to respond to the technological changes.

Then I will discuss the evolving regulatory landscape seeking to respond to those practical challenges.

In particular, I will focus on the need for the regulatory system to take a balanced approach by: on one hand creating a regulatory ecosystem that promotes innovation and on the other hand, ensuring that a robust and responsive regulatory framework is established to protect public health.

But, these two competing interests are not mutually exclusive as they are highly relevant to advancing patient interests.

The medical technology sector has undergone significant transformations in the recent years. And the sector will continue to evolve. In order to ensure its sustainability, the regulatory framework should be sufficiently enabling to respond to those challenges. Those challenges arise from the external environment. For example:

- **The public health systems** will need to respond to new and emerging needs to overcome inequalities to medical treatment and interventions as well as changing demographics, particularly the aging population who are living longer thanks to mdical advances. This will require a renewed and shared understanding of healthcare objectives.
- **Access to healthcare** can be costly, both to the patients and to the national health systems. Policy makers have to ensure that patients get better access to new innovative technology to improve health and optimise patient care as well as at affordable prices.
- Accordingly, the framework will need to be **responsive and adaptive** to sustain innovation to fully embrace emerging scientific and technological advances. The regulatory framework is part of the ecosystem of stimulating such research and development efforts.

The broader medical technology sector has a fundamental role in saving lives by providing innovative healthcare solutions for the diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease.

Europe has a competitive and innovative sector, characterised by the active role of small and medium-sized enterprises. It is supported by a regulatory framework that aims to ensure the proper functioning of the internal market to achieve a high level of protection of health for patients and users.

In the EU, there are over 500,000 different types of marketed devices and diagnostics. The sector continues to research and develop a broad range of healthcare products with varying degree of complexity and characteristics designed for the intended purpose of use on or in various parts of the human body: from simple sticking plasters for covering the skin to implantable devices.

In vitro diagnostic medical devices have also evolved from those tests used for detecting pathogens to tests that are used for identifying the genotypic and phenotypic characteristics of patients who are more predisposed to a particular clinical condition. And such diagnostic tests are increasingly being applied in combination with drug treatment in the area of precision or personalised medicine so that patients who are more likely to respond to treatment with the specific genetic predisposition will receive the drug.

The sector's research and development efforts in innovations benefit the global citizens.

In common with many established regulatory systems around the globe, approval process is based on an evaluation of three inter-locking parameters relevant to assessing the safety and performance characteristics of a device. They are:

- The proper design and manufacture that should take account of (a) the quality system being applied, (b) a thorough evaluation of the potential hazards that may arise from the choice of the materials used and product design, (c) the construction of the device and (d) the intended use.
- An appropriate evaluation of the totality of data relating to the design and manufacture, the available non-clinical testing where relevant and the clinical evaluation in order to inform a view of whether the benefits outweigh the risks. Where such risks exist in the evaluation, the question is whether those risks are manageable in order to define the circumstances in which the device can be used safely and effectively.
- We also need to recognise that pre-approval dataset is generally limited in size and may not necessarily represent completely how the product will be used in the real world. The benefit/risk balance should be the subject of ongoing market surveillance and where necessary through incremental research to generate relevant data to optimise the safe and effective conditions of use of the device.

These underlying regulatory and scientific principles are universally applied, irrespective of where the device is approved, as already acknowledged by the International Medical Devices Regulatory Forum (replacing the previous Global Harmonization Task Force) which was established to enhance international harmonisation amongst the participating countries in the technical evaluation of medical technology products.

The design and construction of a device in relation to the proposed clinical mode of use is a central part of the overall benefit/risk evaluation of a medical device. This is because the design must be done is such as way that the device exhibits the desired characteristics to treat the underlying conditions. Some devices are intended to be implanted in or near to the anatomically vital organs and can have diverse applications.

For example, inferior vena cava filters are commonly indicated for treating deep venous thrombosis or pulmonary thromboembolism. Cerebral stent is used to treat brain aneurysm resulting from a weak or thin spot on a blood vessel wall in the brain; and intracranial stenosis which is narrowing of brain blood vessels due to atherosclerosis as a result of build-up of fat and plaques in the blood vessels.

Certain devices can be used in combination with drugs to enhance the treatment effects.

Therefore, it is critically important in the evaluation to take account of the anatomical sites and physiological functions. The information generated from the initial appraisal will form the basis of informing the proper safe and effective conditions of use to support the label claims. The initial assessment will also determine whether there is a need for post-market studies to be carried out to address the gaps in the knowledge base or otherwise missing information.

Advances in science and technology will revolutionise the way we will treat clinical conditions. Greater interest in material science for certain polymers to be used in combination with drugs or biological substances has underpinned the development of regenerative medicine to restore or rejuvenate injured or damaged organs or tissue; to produce neo-

organs. New materials are being developed to provide site-specific targeted drug delivery to optimise treatment effects while minimising unwanted side effects.

Finally, in addition, value based drivers and pressures for change in market access have a material effect in overhauling the research and development landscape to focus on speedier diagnostics and patient stratification to optimise patient care and disease management. Conventional diagnostics to identify infectious agents could be multiplexed. Identification of new biomarkers could enhance earlier diagnosis of chronic diseases, particularly those age-related conditions such as dementia affecting the older population.

Diagnostics in monitoring treatment adherence and clinical monitoring of disease progression following treatment could be coupled with mobile or electronic applications.

Ladies and Gentlemen, these research and development efforts to benefit public health and patient interests will challenge the regulations in terms how they should be regulated in a proportionate way without imposing unnecessary regulatory burdens that may impede innovations.

Striking this right balance is critical in any proposed legislative or regulatory policy changes.

In the EU, similar to the approach taken in other regulatory systems, regulation of devices is risk-based. The risks associated with the product characteristics, the duration of use, the mode of use will determine the level of evidence required to support the so-called conformity assessment which is to determine whether the device is safe and possesses the desired performance characteristics for the intended use.

The regulatory framework has evolved since the first set of directives was adopted in the 1990s in response to two key elements:

- Increasing globalisation and global harmonisation
- Significant advances in science and technology

The legislative framework should therefore be upgraded to ensure that it is fit for the purpose and most fundamentally to maintain public health interest and confidence.

The latest changes were made in 2017 through the adoption of the Medical Devices Regulation and In Vitro Diagnostic Medical Devices Regulation. These Regulations preserve the over-arching public health protection objective.

But they sought to address specific regulatory uncertainties for certain product classes in relation to their classification, regulatory status and the level of evidence required to support an assessment to establish their safety and performance characteristics.

The aim is to ensure a regulatory framework that is robust, transparent, predictable and sustainable to achieve a high level of public health protection. At the same, a balanced approach is taken to support innovation. Most importantly, the legislation seeks to ensure a uniform interpretation in the legal requirements across the single internal market.

Greater focus is placed on:

- Verification of designation of the conformity with the requirements
- Reinforcement of market surveillance by imposing specific obligations on the identified economic operators
- Improvement of vigilance oversight

- Development of tools through specific device identifiers to ensure device traceability.

One of the key changes is related to clinical evaluation, an integral part of the process to demonstrate conformity with the requirements. The regulatory expectation is not didactic. Rather, the requirement sets out a set of guiding principles for manufacturers to consider in the clinical evaluation.

Clinical evaluation is not limited to data generated from the manufacturer's own clinical investigations. The concept enables manufacturers to rely upon other data sources including relevant literatures relating to safety, performance, design and intended purpose of the device.

It is incumbent upon manufacturers to determine (a) relevance; (b) validity and (c) weighting of the evidence in the overall clinical evaluation. Comparative assessment could be considered to establish the therapeutic position by contextualising the treatment effects. Manufacturers may choose to consider alternative methodological approaches to data analysis.

Greater scrutiny is placed on the high risk devices.

Similarly, in vitro diagnostic devices include now "companion diagnostics" which are expected to be used with drugs for identifying the genotypes and phenotypes for stratifying treatment. The performance characteristics will include not only the need to establish accuracy, precision, reproducibility but the clinical correlate for the purpose of establishing the claimed clinical application.

Put it simply, the framework for clinical evaluation is an iterative process which can be divided into five stages: planning to define the scope of the clinical evaluation; identification of relevant and valid data; evaluation of the relevant data as to whether they are supportive of and adequate for the clinical claims; the data analysis; and finally to generate the report to inform benefit/risk evaluation and to determine what post-market activities ought to be considered.

I hope that in the course of my short presentation I have given you a flavour of the key issues to stimulate further discussion at this conference. Thank you for your attention.

* * *

科学技术挑战与欧盟医疗器械监管框架

各位女士、先生，十分荣幸受邀在本次大会发言，并与大家分享有关欧盟监管动态方面的观点。

首先，我将介绍整体背景环境，讨论医疗技术行业因外部环境持续变化以及为应对技术变革需要而导致其所面临的实际挑战。

随后，我将讨论为应对这些实际挑战而不断变化的监管环境。

我将特别关注监管体系采取方法，一方面创建促进创新的监管生态，另一方面确保建立健全有力、反应迅速的监管框架，以保护公众健康，并达到平衡的必要性。

然而，这两种相互竞争的利益并非互斥关系，均与推进患者利益高度相关。

医疗技术行业近年来发生了重大转变。且这一行业将不断发展演进。为确保其发展的可持续性，监管框架应足以应对这些挑战。这些挑战源自外部环境。例如：

- **公共卫生系统**需要应对各种新兴需求，来克服医学治疗及干预方面的各种不平等，以及人口结构的不断变化，特别是由于医疗进步而延长寿命的老年人群。这将需要对医疗目标达成新的共识。
- 对于患者及国家卫生系统而言，**获得医疗服务**均成本高昂。政策制定者必须确保，患者能够以可承受的价格更好地获得能够改善健康及优化患者护理的创新技术。
- 因此，这一框架需要具有**响应性及适应性**，以维持创新，充分接受新兴科学技术的进步。该监管框架是促进此类研发工作的生态系统的组成部分。

整个医疗技术行业通过为疾病诊断、预防、监测、预测、预后、治疗或缓解提供创新医疗解决方案，在拯救生命方面发挥根本性作用。

在欧洲，医疗技术行业充满竞争与创新，以中小型企业发挥积极作用为特点。该行业受到监管框架的支持，这一监管框架旨在确保内部市场正常运作，实现对患者与用户健康的高水平保护。

在欧盟，市场上存在超过 50 万种不同类型的医疗器械及诊断产品。医疗技术行业持续研发各种医疗产品，这些产品具有不同复杂程度与特性，其设计的预期目的为用于人体各个部位：从简单的覆皮粘性胶布到可植入装置。

体外诊断医疗器械也已从用于检测病原体测试发展为用于识别更易患某种特定临床病症患者的基因型及表型特征测试。并且此类诊断测试日益与精准或个性化医疗领域的药物治疗结合使用，以便那些更有可能对特定基因倾向治疗产生反应的患者接受该等药物治疗。

医疗技术行业在创新方面的研发工作造福全球民众。

与全球诸多成熟监管体系一样，审批流程是基于对与评估某一医疗器械安全与性能特征有关的三项关联参数的评价。这三项关联参数分别是：

- 恰当的设计与制造应考虑：(a)所适用的质量体系，(b)对因所用材料选择及产品设计而可能产生的潜在危险的全面评估，(c)医疗器械的构造，以及(d)预期使用目的

- 对有关于设计及制造、相关的可用非临床测试以及临床评价的全部数据进行适当评估，以便了解效益是否大于风险。若在该评估中存在此类风险，那么问题在于该等风险是否可控，目的是确定能够安全有效使用该医疗器械的情形。

- 我们还需要认识到，预先批准数据集规模通常有限，未必能够完全体现产品在真实世界中的使用情况。效益/风险平衡始终应是市场监督的目标，必要时可通过增量研究生成的相关数据以优化医疗器械安全有效使用的条件。

正如国际医疗器械监管机构论坛（取代此前的全球协调工作组）所确认，无论医疗器械在何处被批准，该等基本监管与科学原则均普遍适用。国际医疗器械监管机构论坛的建立旨在加强参与国之间在医疗技术产品技术评估方面的国际协调工作。

与拟临床使用模式相关的医疗器械设计及构造是医疗器械整体效益/风险评估的核心部分。这是因为，医疗器械治疗相关病症所需特征特点必须在其设计中得以展现。某些医疗器械将被植入重要的生理器官当中或附近，并可能有多种功能。

例如，下腔静脉滤器通常用于治疗深静脉血栓形成或肺血栓栓塞。脑内支架用于治疗由大脑血管壁上的薄弱点引起的脑动脉瘤；以及颅内狭窄，即由于血管中脂肪及血小板积聚导致动脉粥样硬化从而引起的脑血管变窄。

某些医疗器械可与药物结合使用，来增强治疗效果。

因此，在医疗器械整体效益/风险评估中将生理结构部位及生理功能考虑其中至关重要。基于初步评估产生的信息，医疗器械正确安全且有效使用的条件将得以了解，继而产品标签声明的内容能得到支持。初步评估还将确定是否需要进行上市后研究以解决知识库中的空白或其他信息缺失的问题。

科技的进步将彻底改变我们治疗临床疾病的方式。对将某些聚合物与药物或生物物质结合使用这一材料科学的极大热忱，支持了再生医学的发展，再生医学旨在恢复或复原受到损伤的器官或组织，以及生成新的器官。目前，提供特定部位靶向药物输送的新材料正在开发，在优化治疗的效果同时最大限度地减少有害的副作用。

此外，基于价值的驱动因素以及市场准入变革的压力对彻底改变研发格局具有重大影响，使其专注于更快速的诊断与患者分层，从而优化患者护理与疾病管理。识别传染源的传统诊断方法可以被多路复用。新生物标志物的鉴定可以加强对慢性病的早期诊断，特别是与年龄相关的疾病，如影响老年人群的痴呆症。

监测治疗依从性的诊断及治疗后疾病进展的临床监测可与移动或电子应用产品相结合。

各位女士、先生，这些有益于公共卫生与患者利益的研发工作将对监管法规提出挑战，即应如何以适当的方式对其进行监管，避免施加不必要的监管负担，以免阻碍创新。

对于任何拟议立法或监管政策的变化而言，取得这种适当的平衡至关重要。

在欧盟，与其他监管体系采取的方法类似，医疗器械监管系以风险为基础。与产品特性、使用期限、使用模式相关的风险将决定支持所谓的“合格评定”所需的证据水平。“合格评定”旨在确定该医疗器械是否安全并具有预期使用目的所需的性能特征。

自 20 世纪 90 年代通过第一套指令以来，监管框架为应对两项关键因素，已经发生了变化，这两项关键因素为：

- 日益全球化及全球协调
- 科技的重大进步

因此，立法框架应当更新以确保其符合立法目的，且最根本主旨是维护公众健康利益及信心。

最新变化是 2017 年通过的《医疗器械条例》及《体外诊断医疗器械条例》。这些条例保留了保护公共卫生这一首要目标。

但同时试图解决某些产品类别特殊的监管不确定因素，涉及其分类、监管状态以及足以支持其安全性与性能特征评定所需的证据水平。

这些条例目的是确保建立健全、透明、可预见、可持续的监管框架，以实现高水平的公共卫生保障。同时，采取平衡方法以支持创新。最重要的是，该等立法寻求去确保在欧盟这个单一内部市场中对法律要求有统一的解释。

其更加聚焦于：

- 验证型号是否符合要求
- 通过对确定的经营者施加特定义务加强市场监督
- 提高监督警惕性
- 通过开发特定器械标识工具来确保医疗器械可追溯性。

其中一项关键变化与临床评价有关，临床评价是证明符合要求过程中的一个重要组成部分。监管期望并非说教式。相反，该要求规定了一套供制造商在临床评价中考虑的指导原则。

临床评价并不限于从制造商自身临床研究中产生的数据。基于这一理念，制造商能够依赖其他数据源，包括与医疗器械安全、性能、设计及预期使用目的有关的相关文献。

制造商有责任去确定该等文献的：(a)相关性；(b)有效性及(c)在整体临床评价中的证据权重。可考虑通过采用对治疗效果进行背景分析的比较评估方式来确定治疗定位。制造商可选择考虑其他替代方法来进行数据分析。

对高风险医疗器械实施更严格的审查。

同样，体外诊断器械目前包括“伴随式诊断”，其将与药物一起被用于分层治疗中的基因型及表型识别。为确立所宣称的临床应用目的，性能特征将不仅需要包括确立准确度、精密度、重复性，还需包括临床相关性。

简而言之，临床评价框架是一个迭代过程，可分为五个阶段：临床评价范畴的界定计划；相关有效数据的识别；相关数据是否足以支持所宣称的临床目的的评价；数据分析；以及最终生成报告为效益/风险评价及确定应考虑哪些上市后活动提供信息。

希望我的简短演示能就关键问题向大家提供一些浅见，并为本次会议的进一步讨论抛砖引玉。感谢大家的关注。