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Medical Products Law: Introduction

Policymakers around the world have long recognized the need to regulate medical products, meaning interventions intended to prevent, diagnose, treat, or cure diseases and other health-related conditions. Generally speaking, these interventions can be subdivided into medicinal products (sometimes known as drugs or medicines, and hereafter ‘medicines’) and medical devices, although the distinctions between these categories can be blurred and some commercialized products comprise both. In most of the world, the rules for these two broad categories differ somewhat, although many of the basic principles are the same. Further, these basic principles inform medical products law throughout the developed and developing world. At the same time, the regulation of medical products can present a variety of ethical, legal, and social issues that countries will choose to resolve differently. As a result, even in the developed world, regulation of medical products can differ in important ways from one country to the next.

The four chapters that follow explore medical products regulation in the United States and the European Union. We consider several broad themes, including the challenges of approving products with inherent risks, some of which are unknown and possibly unknowable; the challenges of ensuring that the regulation of medical products encourages the discovery and development of treatments that address pressing public health needs; the need to find an appropriate level of regulation that does not impose more burdens or barriers on innovation or access to the market than necessary; and the desire to ensure robust competition on the basis of price as well as (where applicable) accurate information about differing product features. With respect to each jurisdiction, we consider recent controversies and ongoing debates as well as product categories that have presented special difficulties for policymakers. These include human cell and tissue-based products, gene therapy products, genetic testing and 3D printing of medical devices.

Over the last century, regulators in the United States and in the European Union have developed complex frameworks for regulation of medicines and medical devices marketed within their borders. In both jurisdictions, these frameworks have evolved in response to public health crises, such as discoveries that marketed products were not nearly as safe and effective as previously assumed, as well as genuine scandals — that is, serious situations in which a product’s manufacturer bears fault. To give a well-known example, the primary U.S. law governing medical products dates to 1938 — one year after an antibiotic mixed with a sweet but toxic solvent (without any malicious intent) killed over 100 people in the United States. Major medicines legislation in the United States in 1962 and in the European Union in 1965 followed on the heels of the thalidomide tragedy — after widespread use of this treatment for morning sickness led to severe birth defects in roughly 10,000 babies, mostly in the European Union, Australia, and Japan. And the discovery of a French company illegally manufacturing and selling breast implants made of industrial, rather than medical, grade silicone, which were associated with increased risks of rupture, prompted changes in European rules governing medical devices. Other scandals, which have similarly informed the development of medical products law in both

jurisdictions, have involved the claims made by companies about their products. Some have involved fraudulent or otherwise unsupported claims of cure — such as drugs marketed in the United States in the early twentieth century as effective in curing cancer, even though the companies knew the claims were false.

In light of this history, medical products regulation in both jurisdictions rightly focuses on protection of the public health. Generally speaking, both jurisdictions seek assurance that medicines — drugs and biologics in the United States, medicinal products in the European Union — are safe and effective for their intended purposes. Both require medical devices to be safe, and the United States also requires an assurance of medical device effectiveness. Moreover, in both jurisdictions the requirement to establish safety (and where applicable, effectiveness) applies *before* product launch. Thus many medical products must be the subjects of extensive applications presenting the results of studies performed and asking permission to launch from regulatory agencies (mainly the European Medicines Agency (EMA) and national medicines agencies in the European Union and the U.S Food and Drug Administration (FDA) in the US). For other medical products (medical devices in the European Union), the conformity to essential legal requirements has to be established by the manufacturers, sometimes via the competent authorities' authorizations. To ensure product safety, both jurisdictions also impose “quality” requirements, a prerequisite which generally mean that the manufacturer must tightly control the manufacturing process in order to prevent errors and ensure consistency in product characteristics: ensuring product quality means, in part, ensuring its conformity to the claimed formula or design. In addition to protecting the public health, European Union law also aims to create a single European market for both medicines and medical devices through generally prohibiting certain barriers to trade, and promoting the free movement of goods, capital, services, and persons across Member States' boundaries.

Where both safety and effectiveness must be assessed prior to marketing, a medical product may be launched only if its benefits outweigh its risks, based on the information available at the time. This broad principle reflects two facts: first, that no medical product is perfectly safe or perfectly effective, and second, that a product's safety and effectiveness cannot be fully understood on the basis of any reasonable sized premarket research program. Risks may be inherent in a product, or they could result from external factors such as misuse (or use in a way that was not studied or intended). The risks acceptable in a particular medical product — and the level of uncertainty about risk that is acceptable — will often depend on the expected benefits of the product. It may also differ over time or, indeed, depend on the jurisdiction. And while it might be possible to generate additional information about a medical product's safety (and, where relevant, effectiveness) prior to launch, requiring additional study imposes costs of its own, in the form of delay in treatment and expenses which must be borne by the payer in the end. In both jurisdictions the medical products regulatory framework at any given time reflects the then-acceptable level of uncertainty about the safety and effectiveness of particular interventions, given the cost and delay that would be involved in generating additional evidence. Further reflecting the challenge of striking the right balance between ensuring further study, on the one hand, and providing patients with access even with incomplete information, on the other, each jurisdiction has adopted programs to expedite the availability of medical products for patients with serious or terminal illnesses who lack satisfactory treatment options. Nor do the risks end with product approval; a medical product may trigger adverse events (anticipated, or even unanticipated) even when used properly, just as it might trigger adverse events when used

incorrectly. The laws of both jurisdictions also seek to manage the risks of medical products after approval, through regulatory requirements and (where applicable) liability rules.

The necessary premarket research and development required in both jurisdictions not only delays patient access to new medical treatments, it also imposes costs and risk on innovators. These costs must be recovered during the marketing of the resulting product. High cost and risk can also discourage innovation, particularly if there are questions about the recovery of research and development costs. In some cases, cost and risk might steer researchers towards less risky projects or projects that are more likely to produce commercially successful products. Policymakers in both jurisdictions therefore seek to ensure that regulatory requirements applicable to medical products do not impose undue barriers that might operate as an unnecessary disincentive to innovate. This requires striking a balance between ensuring quality and robust premarket testing, on the one hand, and ensuring manageable costs and time investment, on the other hand. Similar considerations apply to post-market regulation, which can discourage post-market innovation (such as the development of newer manufacturing techniques) if unduly burdensome. The laws of both jurisdictions also provide incentives for innovation — patents for new and useful inventions, temporary protection of testing data, and special regulatory incentives intended to encourage specific types of research (such as exclusivity for development of treatments for rare diseases) — although the data protection and regulatory exclusivity rules differ. At a high level the principles of patent law are harmonized between the two jurisdictions. Although the chapters that follow do not discuss patent law in any detail, we briefly touch on the special relationship between patents and U.S. and European drug regulatory requirements.

Policymakers in both jurisdictions, as elsewhere in the world, must also strike a balance between encouraging innovation and ensuring a steady supply of newer medical treatments, on the one hand, and ensuring that available medical treatments are in fact affordable for payers and patients, on the other hand. With respect to medicinal products, regulators in the United States and Europe facilitate the affordability of medical treatments by approving copies (generic drugs and biosimilar biologics, known as “similar biological medicinal products” in Europe) on the basis of smaller applications that are less expensive and time-consuming to prepare. Patents, data protection, and targeted incentives encourage innovation by providing a period of exclusivity in the market — before these copies can be approved. For instance, a patent protecting the active ingredient of a new medicinal product and protection of the testing data that supported approval of the medicinal product can work together to preclude copies of the product until both the patents and data protection expire. As a result, although robust incentives ensure a steady stream of new medical products, they inherently delay the introduction of lower cost alternatives. Of course, pricing and reimbursement rules also play a role in patients’ access to medical treatments and may address affordability concerns, including during the exclusivity period for medicines. Patients’ access to a medicine or device is a function both of whether the relevant requirements for regulatory authorization have been met and whether patients can afford the treatment. But pricing and reimbursement rules are complex and differ substantially between the United States and Europe, as well as between the Member States of the European Union (which implement their own heterogenous health care systems), and are outside the scope of these chapters.

Although innovators may recover their research and development costs during the exclusivity term through higher prices than are available after generics and biosimilars reach the market, medical products may experience some competition from other innovative medical

products during exclusivity periods. The medical products laws of both jurisdictions address the functioning of this competitive marketplace, focusing on protection of consumers from economic harm and protection of the marketplace from unfair competition, although other regulators may also play a role. We will focus mainly on U.S. law, which requires, for instance, that manufacturers provide truthful and non-misleading information about their medical products, whether marketing to health care providers or directly to patients. European law prohibits direct-to-consumer advertising of prescription drugs, to protect the public health. Competition (antitrust) authorities also play a role in both jurisdictions, and those laws are beyond the scope of these chapters.

Continuing innovation in medical products — particularly significant innovations that fundamentally change the mode of intervention — can challenge existing regulatory programs. Over the last century, the medical products laws of both jurisdictions have evolved and adapted to new medical knowledge and new scientific capabilities. For instance, after the biotechnology revolution of the 1970s and 1980s, regulators in the European Union and the United States adapted their approval processes to the special issues presented by recombinant protein products. The sequencing of the human genome in 2001 has made it possible for researchers to develop pharmacogenetic medicines and, recently, gene therapies. Introduction of the personal computer in the 1980s began an electronic and engineering technology revolution that has given rise to mobile health “apps” (“e-health”) as well as 3D printing, among other things. Advances in microbiology have led to cellular-based therapies and may also lead to microbiome-based therapies. These newer treatment modalities — which could also be called “medical technologies” — may not fit neatly within existing medical products law. Policymakers and regulators must determine whether existing laws and programs can be adapted to oversee novel technologies, or whether new laws and regulatory approaches are needed.

In the four chapters that follow, we explore the principles that guide medical products law in the European Union and the United States as well as the approaches taken by regulators in the European Union and the United States to reconcile these differing goals of medical products oversight. We devote two chapters to each jurisdiction — one for medicines and one for medical devices. Although many of the overarching principles for regulation are the same, there are significant differences between the medical device law of the two jurisdictions, and each jurisdiction treats medicines and medical devices somewhat differently. Within each chapter, we explain the threshold concepts and principles governing regulation, the legal rules governing access to the market, the rules relating to innovation and competition, and the regulatory approach to risk management. As a general rule, we focus on the work of the European Medicines Agency (EMA) for medicines and the U.S Food and Drug Administration (FDA) for both medicines and medical devices. Because, unlike the FDA, the EMA has no role in the regulation of medical devices, we focus on the European Union’s reliance on balancing the roles of private and public actors in regulated medical devices. Additionally, further differences between the European and U.S. chapters result from the diverging political structure of the jurisdictions. Where relevant, therefore, we note the role of *state* law in the United States or the law of individual *Member states* in the European Union. Each chapter concludes with a discussion of innovative medical treatments — such as 3D printing, or cell and tissue therapies (known with gene therapies as Advanced Therapy Medicinal Products in the European Union) — that challenge the current paradigm. We use these examples to explore what the regulatory approach to recent and emerging breakthrough innovations suggests about the future of medical products law.

