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## Regulating Medicines in the European Union

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This chapter describes the framework for regulation of medicines in the European Union (EU). The overall goal of this framework is to ensure that medicines are of good quality, safe and effective. This is accomplished through extensive regulation of medicines throughout their lifecycle, from early research and development through to marketing authorization. In European contexts, medicines regulation interfaces in important ways with authorization for reimbursement within national health systems. In practice, without such reimbursement authorization, patients will not be able to access medicines, even if they have formal marketing authorization for the EU. Reimbursement decisions consider *relative* therapeutic benefits, whereas marketing authorizations consider only quality, safety and efficacy.<sup>1</sup>

Although the overall goals of the European and U.S. medicines' frameworks are the same, the structure of the EU framework is complicated by the fact that both EU-level and Member-State-level authorities have responsibility for regulation of medicines. For instance, some marketing applications must be reviewed centrally by the European Medicines Agency (EMA) (and, if they are approvable, will be approved by the European Commission). Overall, EU law is dominant from research to marketing authorization while national law is dominant for healthcare services and reimbursement issues.<sup>2</sup> At the EU level, the EMA is the European counterpart to the U.S. Food and Drug Administration (FDA) although, unlike the FDA, the EMA is not competent for medical devices. Each Member State also has its own medicines regulatory authority, known as a "national competent authority." For example, the French government includes *L'agence nationale de sécurité du médicament et des produits de santé* (ANSM), and the Italian government includes *Agenzia italiana del farmaco* (AIFA). As this chapter illustrates, responsibility for some aspects of the broader medicines regulatory framework falls to these national authorities.

### I- Defining Medicines

As a threshold matter, the regulatory framework described in this chapter applies to medicinal products — here, "medicines" — intended for human use. The scope of the term "medicines" has evolved over time, through both jurisprudence (judicial decisions) and revisions of the key European legislation — Directive 2001/83/EC.<sup>3</sup> These changes have taken into account the emergence of new therapies as well as the challenges presented by "borderline products" — those that have characteristics of both medicines and other regulated products. For instance, a

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<sup>1</sup> Space precludes a full discussion of reimbursement laws, which are nationally determined in Europe.

<sup>2</sup> Reimbursement issues are discussed in [chapter](#). [Syrett and den Exter]

<sup>3</sup> Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 311/67-128. This chapter will discuss different parts of the Directive throughout.

product with the claim “promoting hair growth” is usually considered as a medicine, especially when it contains a substance that is prohibited as a cosmetic ingredient such as minoxidil. However, a product with the claim “reducing hair loss” is usually considered as a cosmetic product. Another example could be dental pastes, some are considered as medicines while other are medical devices, depending on their mode of action.

Under EU law, a product will be classified as a medicine by virtue of either its presentation *or* its function. Both national and EU authorities can make this determination. First, a medicine is “any substance or combination of substances presented as having properties for treating or preventing disease in human beings.” This generally entails considering the looks of the product, including the claims made about the product. The claims may be explicit or implicit, including, for example, testimonials from medical practitioners commending the qualities of the product or even simply references to research by pharmaceutical laboratories or to methods or substances developed by medical practitioners. Other evidence, including the product’s form and packaging could give rise to classification as a medicine.<sup>4</sup> For instance in France, the French medicines agency (ANSM) has considered injectable skin lightening products are medicines by presentation as their presentation online for selling (high risk administration presented online: “injection into a vein or muscle or under the skin”) can lead to the averagely aware consumer thinking it is a medicine. Second, a medicine includes substances used to restore, correct or modify physiological functions or to make a medical diagnosis. This entails considering the product’s function, including its use. Thus, the national competent authority considers all of the characteristics of the product — including its composition, its pharmacological properties, the manner in which it is used, the extent of its distribution, its familiarity to consumers, and the risks associated with its use. For instance, in France, the French medicines agency (ANSM) has considered two massage oils (HL2 oléokinum and TRH5) not as cosmetics but medicines by function as they are very concentrated in essential oils which give them pharmacological properties.

Within the broad category of medicines, EU law also defines various specific types of medicine — such as biological medicines,<sup>5</sup> blood or plasma-derived medicinal products,<sup>6</sup> immunological medicinal products,<sup>7</sup> radiopharmaceuticals,<sup>8</sup> homeopathic medicinal products,<sup>9</sup> and herbal medicinal products.<sup>10</sup> Some specially defined categories are subject to their own regulatory frameworks: orphan medicines (discussed in section IV. B, below),<sup>11</sup> medicines for paediatric use (discussed in section IV. B below), and advanced therapy medicinal products<sup>12</sup>

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<sup>4</sup> See ECJ, 21 March 1991, Delattre, aff. C-369/88, ECR I-1487, ¶ 41.

<sup>5</sup> A biological medicinal product has an active “biological substance,” which in turn is “produced by or extracted from a biological source.” Immunological medicines and medicines derived from human blood and human plasma are also considered biological medicinal products.

<sup>6</sup> These products include albumin, coagulating factors and immunoglobulins of human origin.

<sup>7</sup> An immunological medicinal product is one consisting of vaccines, toxins, serums or allergen products.

<sup>8</sup> A radiopharmaceutical is a medicinal product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

<sup>9</sup> A homeopathic medicinal product is one prepared from a substance known as a “homeopathic stock” in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or a pharmacopoeia used officially in the Member States.

<sup>10</sup> An herbal medicinal product is one containing, as active ingredients, only herbal substances, herbal preparations, or a combination of the two.

<sup>11</sup> These are medicines that are intended to treat rare diseases or which are not otherwise expected to generate sufficient return in the marketplace to justify their development.

<sup>12</sup> These medicines are based on genes, cells or tissues of human or animal origin.

(discussed in section V, below). But all of these are “medicines” in the first instance, either because of their presentation or because of their function.

In some cases, a product may have features of both a medicinal product and another type of regulated product — such as a food, novel food,<sup>13</sup> cosmetic, medical device, *in vitro* diagnostic medical device,<sup>14</sup> or biocidal products.<sup>15</sup> EU law refers to this as a “borderline product.” In the first instance, national authorities or European agencies determine the appropriate categorization in borderline cases, applying the definitions of the different product categories, subject to supervision by the courts (national and European). The European Commission has published several guidance documents to facilitate this determination and to help manufacturers determine which rules will apply. It can also be helpful for companies to have early contact with regulators, especially the European Medicines Agency (EMA). EU law also specifies that in cases of doubt, the rules governing medicinal products should apply. In that context, the broad interpretation of the “medicine by presentation” protects consumers from products which do not have the effectiveness which they are entitled to expect. On the other hand, the definition of “medicine by function” covers products “the pharmacological properties of which have been scientifically observed and which are genuinely designed to make a medical diagnosis or to restore, correct or modify physiological functions”.<sup>16</sup> Consequently, this “rule of doubt” does not apply if it is merely *possible* that the product could be classified as a medicinal product, if it has not been “scientifically established” that the product is a medicinal product by function — in other words, if it has not been established that the product is *capable* of restoring, correcting, or modifying physiological functions or *can* be used to make a medicinal diagnosis.<sup>17</sup>

Nevertheless, the appropriate classification of some borderline products remains unresolved. For instance, it is not yet clear how microbiome-based products should be classified. These products contain live bacteria and include fecal microbiota, currently used to treat recurrent *C difficile* infections. Although the U.S. FDA has concluded that microbiota are biological products and drugs when intended to treat illness, there is no consensus yet in the European Union. They might be classified as medicinal products, but they might also be classified as medical devices or food supplements, depending on their mechanism of action, characteristics, or claimed intended treatment.<sup>18</sup>

## II- Bringing Medicines to the Market

### A- Standard Approval Process

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<sup>13</sup> “Novel food” is food not very used for human consumption in the EU before 15/05/1997. A wide range of products is covered, such as food with a new or modified molecular structure, food using a new food production process (bread treated with UV-light to increase vitamin D content) or produced from microorganisms, fungi or algae. Regulation (EU) 2015/2283 on novel foods OJ L 327/1–22.

<sup>14</sup> They are devices used *in vitro* for the examination of human biological elements such as blood or tissue, or for providing information, such as on a physiological or pathological process or state or on a congenital physical or mental impairment. This covers a wide range of devices such as self-tests for pregnancy or tests for highly transmissible substances using specimens taken from the human body.

<sup>15</sup> These products such as household disinfectants, insecticides and other chemicals, are used to protect materials or to suppress pests (such as parasites, fungi, or bacteria).

<sup>16</sup> See Case C-319/05 Commission v Germany [2007] ECR I-9811, ¶ 61.

<sup>17</sup> See Case C-140/07 Hecht-Pharma GmbH v Staatliches Gewerbeaufsichtsamt Luneburg [2009] ECR I-00041, ¶ 29.

<sup>18</sup> Nino Mihokovic, EMA Experience and Perspective, Regulatory challenges in the drug-food continuum, IMI Stakeholder Forum 2017, Microbiome forum 2017 (powerpoint slides) ([here](#)).

No medicine may be lawfully marketed in the European Union without marketing authorization from either the national competent authority or the European Commission. There are four possible procedures. One is national: authorization only at the individual Member State level. Three are European: authorization that directly operates Europe-wide (the ‘centralized’ authorization procedure which is mandatory for some medicines), and two types of authorization that involve Member States relying on each other’s assessments (the ‘decentralized’ procedure and the ‘mutual recognition’ procedure).

First, certain products must — and others may — be reviewed under the centralized authorization procedure, governed by Regulation 726/2004.<sup>19</sup> Under this procedure, a company submits a single market authorization application to the EMA. The application is reviewed by the relevant scientific committee within the EMA, typically the Committee for Medicinal Products for Human Use (CHMP). The CHMP may consult one of its Scientific Advisory Groups (SAG), groups of external experts comparable to FDA advisory committees in the United States, to provide advice.<sup>20</sup> The EMA’s evaluation should ordinarily take 210 days, following which it provides a recommendation (or “opinion”) on the approval decision.<sup>21</sup> The European Commission makes the final decision generally following the opinion of the EMA, and its decision is binding throughout Europe. In other words, medicinal products authorised under the centralized procedure may be marketed in all EU Member States as well as European Economic Area (EEA) and European Free Trade Association (EFTA) States — thus also Iceland, Liechtenstein, Norway, and Switzerland.

The centralized procedure is mandatory for some medicines: medicines derived from biotechnology (including notably medicines based on recombinant DNA technology), orphan medicines, Advanced Therapy Medicinal Products, and biosimilar medicines. It is also mandatory for any medicine that contains a new chemical, biological or radiopharmaceutical active substance and that is intended for the treatment of AIDS, cancer,<sup>22</sup> a neurodegenerative disorder,<sup>23</sup> diabetes,<sup>24</sup> an auto-immune disease or other immune dysfunction,<sup>25</sup> or a viral disease.<sup>26</sup> The centralized procedure is optional for medicines containing a new active substance for a different indication,

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<sup>19</sup> OJ L 136/1–33.

<sup>20</sup> As in the United States, these expert consulting groups are classified by therapeutic area: cardiovascular issues, anti-infectives, diabetes and endocrinology, HIV and viral diseases, neurology, oncology, psychiatry, and vaccines.

<sup>21</sup> In 2018, EMA’s recommendations for marketing authorisations included 84 positive opinions, and 5 negative opinions. EMA, Human medicines highlights 2018 ([here](#)).

<sup>22</sup> For instance, Xermelo® has been authorised on 17/09/2017 in the EU. It contains the active substance telotristat. It is used to treat adults with severe diarrhoea associated with a carcinoid syndrome occurring when certain tumours produce and release too much serotonin into the blood.

<sup>23</sup> For instance, Ongentys® has been authorised on 24/06/2016 in the EU. It contains the active substance Opicapone. It is used to treat adults with Parkinson’s disease, a progressive brain disorder causing shaking and muscle stiffness, and slows movement.

<sup>24</sup> For instance, Xigduo® has been authorised on 16/01/2014 in the EU. It contains the active substances Metformin hydrochloride and Dapagliflozin propanediol monohydrate. It is used together with diet and exercise, to control blood glucose (sugar) levels in adults with type 2 diabetes.

<sup>25</sup> For instance, Lemtrada® has been authorised on 12/09/2013 in the EU. It contains the active substance Alemtuzumab. It is used to treat adults with relapsing-remitting multiple sclerosis, a disease where inflammation destroys the protective sheath surrounding the nerve cells.

<sup>26</sup> For instance, Zepatier® has been authorised on 22/07/2016 in the EU. It contains the active substances elbasvir and grazoprevir. It is used to treat adults with chronic hepatitis C (infectious disease affecting the liver) caused by the hepatitis C virus.

as well as other medicines that constitute a significant therapeutic, scientific or technical innovation, and medicines for which EU-level authorization is in the interests of public health.

The logic behind this distinction between compulsory and optional centralised procedure can be considered multiple. First, biotechnological medicines were accepted and disseminated in Europe, thanks to a legal common approach and a high level of expertise in the EU (legal harmonisation in this field began in the 1990's). Moreover, their cost of development as well as the rarity of the targeted disease for orphan drugs do not allow that they are restricted to few national markets. Thus, specific attention and interest is given to biotechnological medicines. Furthermore, the optional pathway allows, on the one hand, other medicines which are not specifically named and framed, and constitute therapeutic innovation, to benefit from the centralised procedure if their manufacturers consider it to be helpful as for the manufacturers of biotechnological medicines. On the other hand, it exists to give Member States the possibility of authorising at national level the generic form of medicines authorised at the European level, as long as each EU Member State has its own national policy to govern the generics sector, especially their pricing and reimbursement.

Second, the decentralized procedure is available for medicines that have not been authorised in any individual Member States and for which the centralized procedure is not compulsory. The applicant submits identical applications to the competent national authorities in several Member States, seeking access to their markets. It identifies one Member State to act as the “reference Member State” and thus take the lead in the evaluation. The theory, in other words, is that the Member States can rely on the scientific evaluations and judgments of each other's national competent authorities. The other Member States will consider the marketing application, but the reference Member State has the primary responsibility for assessment. If the reference Member State issues a positive assessment and there is disagreement between the Member States, a “Coordination Group for Mutual Recognition and Decentralized Procedures for human medicines” (CMDh) considers the issue.<sup>27</sup> Disagreement must be based on a “potential serious risk to public health.” If the CMDh in turn cannot reach consensus within 60 days, the matter goes to the EMA (specifically, the CHMP) for arbitration.<sup>28</sup> The CHMP adopts an opinion within 60 days, and the European Commission takes the final binding decision.

Third, the mutual recognition procedure is available if a medicinal product has already been authorised in one EU Member State. The theory here is essentially the same; the Member States rely on each other's assessments and judgments. The first Member State to authorise the medicine is considered the “reference Member State” and provides its evaluation of the application to the other Member States selected by the applicant. As is true when an applicant selects the decentralized procedure, if a country refuses to recognize the original national authorization (on the ground of a potential serious risk to public health), the issue is taken to the CMDh.<sup>29</sup> If the CMDh cannot reach consensus, the matter goes to the EMA for arbitration.

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<sup>27</sup> This group is composed of one representative per Member States, plus Norway, Iceland, and Liechtenstein. In 2018, only 5 out of 1023 decentralised procedures (0,5%) were referred to CMDh. CMDh Statistics 2018, *op. cit.*

<sup>28</sup> In 2018, half of the procedures (6/12) referred to the CMDh went to the EMA for CHMP arbitration. However, it is not specified whether they were related to decentralized procedures, mutual recognition procedures, works sharing or repeat use. CMDh Statistics 2018, *op. cit.*

<sup>29</sup> In 2018, only 4 out of 291 mutual recognition procedures (1,4%) were referred to CMDh. CMDh Statistics 2018, *op. cit.*

Finally, it is possible to secure approval simply at the Member State level, by applying to the national competent authority of each Member State. In practice, this really means 28 national procedures for 28 national markets. Medicines manufacturers will use the national procedure when medicines are not in the scope of the centralised procedure. It is particularly used for generics given the impact of their pricing on the national healthcare systems, an area that is regulated at the national level rather than the EU level. The national procedure can be combined with the mutual recognition procedure.<sup>30</sup>

Although the four licensing procedures are different, the substantive requirements for approval are similar. In each case, as in the United States, approval is based on a showing during an open assessment that the medicine meets the three criteria of quality, safety and efficacy; and complies with benchmarks: the Good Manufacturing Practices (GMP)<sup>31</sup> and the pharmacopeia.<sup>32</sup> As in the United States, the marketing application contains preclinical and clinical data, as well as detailed “quality” information — about the chemistry and manufacturing of the medicine. Indeed, the substantive requirements for marketing authorization in Europe are largely harmonized with the drug and biologic approval requirements in the United States. An applicant in Europe organizes its application in accordance with the Common Technical Document (CTD), which was designed to provide a common format for marketing applications in Europe, the United States, and Japan.

Generating the safety and effectiveness data necessary for marketing authorization is a multi-step process that begins with laboratory studies and culminates in large randomized controlled clinical trials (“phase 3 trials”) in patients. The EMA and national competent agencies in the Member States regulate preclinical testing (laboratory and animal testing) through good laboratory practices (GLP).<sup>33</sup> In addition, testing in animals must comply with European law on the protection of animals used for scientific purposes. After preclinical testing indicates that it is safe to proceed with testing in humans, the manufacturer applies for permission to conduct clinical trials.

Clinical trial regulation in Europe is in a state of transition. At the time of writing, clinical trials were governed by the EU Clinical Trial Directive, with national legislation put in place to

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<sup>30</sup> For instance, in France in 2017, the French National agency for medicines (ANSM) has delivered 955 marketing authorisations including 801 for generics, 305 in accordance with national procedures, 606 in accordance with decentralized procedures and 44 in accordance with mutual recognitions procedures. ANSM, Rapport d’activité 2017, p.105 ([here](#)).

<sup>31</sup> GMP are a benchmark of various principles and guidelines to be respected in order to guarantee the highest standards of quality, as a prerequisite of safety and efficacy in any process that involves the manufacture of medicines. They include basic requirements on pharmaceutical quality system, personnel, premise and equipment, documentation, production, quality control, outsourced activities, complaints and product recall, and inspection, as well as specific guidelines on the manufacturing of particular medicines, such as radiopharmaceuticals, biological active substances, sterile medicines, etc...

<sup>32</sup> It provides a legal and scientific reference for the quality control of medicines, including notably a set of appropriate tests to confirm their identity and purity, ascertain the strength of their active substance and their performance characteristics.

<sup>33</sup> GLP are a benchmark of various principles and guidelines to be respected in pre-clinical testing through analytical, toxicological and pharmacological experiments in order to promote the quality and validity of the data generated in the testing of medicines.



implement the directive.<sup>34</sup> A new Clinical Trial Regulation, however, will soon take effect.<sup>35</sup> Once it takes effect, manufacturers will apply for permission to start clinical trials using a single point of entry: an EU clinical trial portal. The new Regulation also introduces an assessment procedure leading to a single decision for the EU Member States, as well as rules on the protection of subjects and informed consent, and transparency requirements. The Regulation will take effect six months after the European Commission publishes confirmation that the portal and the EU associated database on clinical trials are fully functional. Technological challenges relating to this portal, and the relocation of the EMA from London to Amsterdam, have caused some delay, but the EMA has recently predicted that the system could go live in 2020. As a “regulation,” the Clinical Trial Regulation will apply immediately throughout the EU without the need for transposition into national laws.

Even after the Clinical Trial Regulation takes effect, though, the individual Member States will have responsibility for authorizing and overseeing clinical trials within their borders. If a company intends to perform its trial in more than one Member State, it will designate a “reporting Member State.” This country has responsibility for preparing a “Part I” assessment of the clinical trial application, focusing on the scientific and medical aspects of the trial. This assessment considers, for example, the information known about the investigational medicine and the risks to trial subjects. The reporting Member State circulates the “Part I” assessment to the other involved countries for a coordinated review and final consolidation by the reporting Member State. Every clinical trial is also subject to ethical review by an ethics committee in accordance with the law of the Member State in which it will occur. Thus, each involved Member State also conducts its own “Part II” assessment of the ethical aspects of the trial. Following assessment of the clinical trial application, the sponsor is notified by way of a single decision sent through the EU portal. Ordinarily this decision must be made within 60 days of the submission of the application.

As in the United States, clinical trials must be conducted in compliance with good clinical practices (GCP). This means that the trial’s sponsor and investigators must comply with a variety of rules designed to ensure the protection of human subjects and the validity and reliability of the clinical trial data. EU law requires an investigator to obtain informed consent from research participants, for example, and to report adverse events to the sponsor. A national regulatory agency may suspend or terminate a clinical trial if the criteria for proceeding are no longer met — for instance if research participants face unreasonable risks.<sup>36</sup> The Clinical Trial Regulation also created a new category — the “low-intervention clinical trials” — which pose minimal risk to

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<sup>34</sup> Directive 2001/20/EC on good clinical practice in the conduct of clinical trials, OJ L 121/34–44). The Clinical Trial Directive does not apply to non-interventional trials, and the new Clinical Regulation will wider not apply to non-interventional studies. Non-interventional trial is defined as “a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data” (Directive 2001/20/EC, art. 2c). Non interventional study means “a clinical study other than a clinical trial” (Regulation (EU) 536/2014, art. 2(4)).

<sup>35</sup> Regulation (EU) 536/2014 on clinical trials, OJ L 158/ 1–76.

<sup>36</sup> Regulation (EU) 536/2014.



subjects compared to normal clinical trials, and for which modified risk procedures are appropriate.<sup>37</sup>

A new marketing authorization is valid for five years. After the first five-year period, the authorization can be renewed indefinitely or — if appropriate given safety concerns — renewed for another five-year period. Authorization can be suspended or withdrawn at any time if the legal requirements are no longer satisfied.

## **B- Expediting Access**

The standard process for securing marketing authorization is time consuming and expensive, which can significantly delay patient access to new medicines. As a result, several mechanisms to expedite access to the new medicines have been developed. They fall in three categories: formal legal alternatives to the standard marketing authorization procedure, programs sponsored by the EMA to speed the development process, and mechanisms allowing patients access to medicines before marketing authorization.

### 1- Alternative Marketing Authorization Procedures

Regulation (EC) 726/2004 establishes three additional legal procedures to accelerate access to the market for products subject to centralized authorization. Individual Member States also have mechanisms for accelerating the process for national marketing authorizations, which are not described here.

First, in some cases conditional marketing authorization may be available. This procedure is available for medicines intended to treat, prevent, or diagnose seriously debilitating diseases or life-threatening diseases, as well as “orphan medicinal products” — those intended to treat rare disease. In the first ten years after the conditional marketing authorization regulation was adopted, the European Commission granted 30 out of 52 requests for conditional marketing authorization. Of these, 11 were converted into standard authorizations, two were withdrawn for commercial reasons, and 17 are still conditional. In 2018, only one medicine obtained a conditional marketing authorisation: Rubraca® to6 treat relapsed or progressive ovarian cancer.

Conditional marketing authorization is also available in emergency situations and in response to public health threats. Pandemic influenza vaccines have been approved via this pathway. In these cases, although the applicant lacks the comprehensive safety and effectiveness data ordinarily required for marketing authorization, the European Commission will grant authorization for renewable one-year terms. The European Commission will grant this authorization if (1) the medicine’s benefit-risk balance is positive, (2) it is likely the applicant will be able to provide comprehensive clinical data, (3) the medicine will fulfil unmet medical needs, and (4) the benefit to the public health of the medicine’s immediate availability outweighs the risk inherent in the fact that additional data are still required.

A conditional authorization can be converted to a standard authorization once the applicant submits the data that were lacking. Conditional marketing authorization has no equivalent in the

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<sup>37</sup> A low intervention clinical trial studies an already authorised medicine, the use of which follows the terms of the marketing authorizations or published scientific evidence. Any additional procedures must not pose more than minimal additional risk or burden to the safety of the participants compared to normal clinical practice. Regulation (EU) 536/2014, Art. 2.3. In these cases, a risk proportionate approach to clinical trial practice may be warranted. *See* Risk proportionate approaches in clinical trials: Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) 536/2014, 25 April 2017 ([here](#)).

United States, although the U.S. “accelerated approval” pathway plays a similar role for similar drugs.<sup>38</sup> For instance, Adcetris (brentuximab vedotin), a lymphoma drug, was approved under conditional marketing authorisation by the EMA and through the accelerated approval pathway by the FDA.

Second, the European Commission can grant marketing authorization under exceptional circumstances. This procedure — which allows for marketing authorization without comprehensive data and without any expectation of comprehensive data in the future — has no equivalent in U.S. law. An applicant may be eligible for marketing under exceptional circumstances if (1) the intended condition is so rare that gathering the data will not be possible,<sup>39</sup> (2) comprehensive information cannot be provided given the current state of scientific knowledge,<sup>40</sup> or (3) the collection of full information would be unethical.<sup>41</sup> A marketing authorization under exceptional circumstances is valid for five years and can be renewed after five years for an unlimited period, but the medicine’s benefit-risk balance is re-assessed annually. Unlike the conditional marketing authorization, marketing authorization under exceptional circumstances does normally not lead to the completion of a full dossier or become a standard marketing authorization. There were six opinions recommending marketing authorisation under exceptional circumstances between 2015 and 2018.

Third, some marketing authorization applications are eligible for accelerated assessment at the EMA. In these cases, assessment occurs within 150 days instead of the usual 210 days. This accelerated review, which is equivalent to the “priority review” in the U.S.,<sup>42</sup> is available for medicines that are “of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.” Applicants must request accelerated assessment, however. For instance, the CHMP agreed to the applicant’s request for an accelerated assessment of Hemlibra®, a medicine used to prevent or reduce bleeding in patients with haemophilia A, as it was considered to be of major public health interest. Between 2013-2017, 58 requests for accelerated assessment were accepted, and 32 were rejected.

## 2- EMA Regulatory Programs

The EMA has established two regulatory programs intended to expedite access to medicines in Europe by assisting with the research and development process. First, in March 2016, it launched “PRIority MEdines” (PRIME) to provide supplementary support for certain priority medicines. A medicine is eligible for PRIME if early clinical data show its potential to benefit patients with unmet medical needs, which in turn means it might offer a major therapeutic advantage over existing treatments or benefit patients without treatment options. Once a medicine

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<sup>38</sup> [\[Insert cross reference to U.S. medicines chapter\]](#)

<sup>39</sup> For instance, Lamzede® was approved through this path. It is a medicine used for patients with mild to moderate alpha-mannosidosis, a rare, inherited disease with features that include notably learning disability and difficulty controlling movement.

<sup>40</sup> For instance, Mepsevii®, a medicine to treat mucopolysaccharidosis type VII (also known as Sly syndrome), an inherited disease caused by a lack of an enzyme needed to break down complex carbohydrates known as glycosaminoglycans, has been authorized under ‘exceptional circumstances’ both because the disease is rare and because in the present state of scientific knowledge, comprehensive information could not be provided.

<sup>41</sup> For instance, Qarziba®, a cancer medicine used to treat cancer of nerve cells (neuroblastoma), in patients over 1 year of age has been authorized under ‘exceptional circumstances’ because obtaining complete information implied giving placebo to some patients during a trial, which would have been not ethical--the active substance of Qarziba®, Dinutuximab beta, is a recommended treatment for high-risk neuroblastoma.

<sup>42</sup> [\[Insert cross reference to U.S. medicines chapter\]](#) [Zettler and Lietzan]

has been selected for PRIME, the developer benefits from early dialogue and regular exchanges with the EMA. The goal is to help the company optimize its clinical trial designs to speed the development plan and ensure the production of quality data that can be submitted for marketing authorization. The marketing authorization application, in turn, should generally also be eligible for accelerated assessment. By 12 November 2018, the EMA had received 211 requests for PRIME eligibility; of these, it granted 46. More than one quarter of the medicines found eligible are intended for treatment of cancer.

Second, the EMA has developed an “adaptive pathways” approach to medicine development and data generation. This involves iterative development: an applicant may either (1) obtain (conditional) marketing authorisation based on early data using “surrogate endpoints”<sup>43</sup> (or early time points, or a smaller population sample) and expanding later with additional clinical data to reduce uncertainty, or (2) obtain approval in stages, beginning with a narrow patient population and expanding later to a broader patient population. The first option corresponds to “accelerated approval” in the United States as far as surrogate endpoints are concerned, in the sense that it allows patients access to important new medicines before phase 3 trials have confirmed clinical benefit.<sup>44</sup> Both options involve iterative phases of evidence gathering and progressive licensing adaptations, as uncertainties about the medicine’s safety and efficacy are progressively reduced and/or the targeted population is expanded. The adaptive pathways approach also allows an applicant to supplement clinical trial data with evidence gathered through real-life use of the medicine.

Although the adaptive pathways approach responds to patient needs for earlier access to innovative medicines, it necessarily involves a trade-off between early access and certainty about a medicine’s actual risks and benefits. Between March 2014 and August 2016, the EMA ran an adaptive pathways pilot to explore the practical implications of the concept with medicines under development. Among the 62 applications received, 18 proposals were selected for face-to-face meetings. At the end of this pilot project, six of the applicants received parallel advice from EMA and Health Technology Assessment (HTA) bodies and one benefited from EMA scientific advice. The EMA has considered this concept needs to be further explored, and this is being done in the context of parallel scientific advice with HTA bodies, with the inclusion of additional stakeholders, such as patients and payer organisations.

Indeed, patients and HTA bodies are also involved in the discussion of individual product development programs using the adaptive pathways. HTA bodies provide recommendations on new medicines that might be financed or subject to reimbursement by the relevant national or regional healthcare system; in countries where they operate, their assessments are used to determine reimbursement status, among other things. The involvement of HTA bodies in the new adaptive pathways approach is part of new European trend of promoting collaboration between regulators and HTA bodies in order to “narrow the gap” between regulatory and HTA body expectations and to “promote harmonization” among the differing European HTA bodies. This should be in the interests of both patients and companies, by eliminating duplication of work and allowing earlier decisions on pricing and reimbursement, which in turn may allow earlier access to medicines. However, this new approach has been criticised for its defects in evidentiary support. Drugs approved on “early,” and therefore limited, evidence may lead to false conclusions about

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<sup>43</sup> Rather than reflecting an actual improvement in health such as longer survival, surrogate endpoints reflect measures that correlate with improvements in health, such as shrinkage in the size of a cancerous tumor.

<sup>44</sup> [\[Cross reference U.S. medicines chapter.\]](#) [Zettler and Lietzan]

efficacy and safety, thereby harming patients. In addition, realistic management strategies are still needed to obtain reliable real-world data, and post-marketing confirmatory studies are often slow to be completed. As a result, medicines with uncertain benefit-risk ratios may be prescribed to patients for an extended period of time. Moreover, many HTA bodies and payers are afraid to pay for weakly tested yet expensive treatments while manufacturers have to address uncertainty regarding assessment by HTA bodies and payers, as well as possible sustainable price, and managed entry agreements.<sup>45</sup> Although the latter are growing in number, they are neither successful nor available in every EU Member State, or commonly used for products with a conditional marketing authorization or authorized under exceptional circumstances. Ultimately, patient access to medicines is not achieved until products have gone through pricing and reimbursement national systems which are regulated differently in each different EU Member State.

### 3- Named-Patients and Compassionate Use

Like U.S. law, EU law allows patients access to medicines outside of the marketing authorisation pathway, by exception in certain situations. First, EU law contains what is known as a “named patient” exception to the marketing authorization requirement. The primary EU medicines directive authorises individual Member States to exempt medicines from the marketing authorization and other requirements in the directive, in order to fulfil special needs and apart from any clinical trial. Exempted medicines must be supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional, and intended for use by an individual patient under the direct personal responsibility of the prescribing physician.<sup>46</sup>

Second, EU Member States may make certain medicines available for “compassionate use.”<sup>47</sup> This is appropriate for patients with a life-threatening, or chronically or seriously debilitating disease, who cannot be treated satisfactorily by an authorised medicinal product. The medicine in question must be the subject of a pending marketing authorization application or ongoing clinical trials. The Member State must notify the EMA when it permits compassionate use, and the CHMP may adopt opinions on the conditions for use and distribution and on the patients targeted. As long as this is an area of EU medicines law where there is not a single EU

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<sup>45</sup> Managed Entry Agreements are agreements between manufactures and payers to share financial risk due to uncertainty with the provision of new innovative drugs in order to enable and foster access to medicines.

<sup>46</sup> For instance, French law provides for named provisional authorizations (*autorisation temporaires d'utilisation nominatives*). See Article L5121-12 2° of the French Public Health Code (named). Alpelisib, administered plus fluvestrant, to treat a genomic subgroup of breast cancer patients, or Crizotinib for infant and children with lung cancer have obtained named provisional authorisations in France. The United Kingdom permits the supply of unlicensed medicinal products (“specials”) in order to fulfil the special needs of a single patient. Human Medicines Regulations 2012, Reg. 167; MHRA, The supply of unlicensed medicinal products “specials” MHRA guidance note 14, 2014 ([here](#)).

<sup>47</sup> Regulation 726/2004. For instance, French law provides for group provisional authorizations (*autorisation temporaires d'utilisation de cohorte*). See Article L5121-12 1° of the French Public Health Code (group). Larotrectinib for the treatment of glioma, which has obtained a marketing authorisation in the U.S. and for which a marketing authorisation application under the European centralised procedure is ongoing, has obtained a group provisional authorisation in France. The UK also launched an “Early Access to Medicines Scheme” (EAMS) in April 2014; this program gives patients with life threatening or seriously debilitating conditions access to medicines that are not yet authorized. See Implementation of Article 5(1) of directive 2001/83/EC; Office for Life Sciences, Early access to medicines scheme (EAMS): task group and principles, 2016 ([here](#)) and Office for Life Sciences, The Early Access to Medicines Scheme (EAMS): Operational Guidance, 2016 ([here](#)).

approach, the individual Member States take differing approaches to named patient access and compassionate use. Consequently, many but not all EU countries benefit from a compassionate use programme, and patients can access them at different times depending on where they live in the EU.

### **C- Other Routes to Market**

Specific medicines may also reach the market in Europe without approval of full marketing authorization applications containing data from safety and effectiveness testing.

First, like U.S. law, European law allows the authorisation of abbreviated applications for generic medicines. A generic application is exempt from the requirement to contain data showing safety and effectiveness. Instead it makes a comparative showing to an earlier authorised medicine and relies on the research performed to support that medicine's market entry. A generic medicine must have the same qualitative and quantitative composition in active substances as the reference medicine, as well as the same pharmaceutical form, and it must be bioequivalent to the reference medicine. It can be prepared more quickly and cheaply than a full application. The resulting medicine is therefore less expensive than the original ("reference") medicine, which provides savings for patients and healthcare providers and contributes to the sustainability of healthcare financing in Europe.

Approval of a generic medicine means that the manufacturer of the original reference medicine will lose its exclusive position in the market and, typically, its market share and price will drop dramatically. This means it must recover its research and development costs *before* generic market entry, and it is generally assumed that continued development of innovative medicines depends on those medicines having a sufficient period of exclusivity in the market. EU law aims to balance the need for a continuing supply of innovative medicines, on the one hand, and the need for prompt access to inexpensive generic medicines, on the other hand.

Like U.S. law, EU law therefore specifies a period of time *before* generic applications may be submitted and authorised. For medicines authorised through the central procedure *and* those approved at the Member State level, generic applications cannot be accepted until eight years after approval of the reference product and the generic drug cannot be marketed until ten years after this approval. This ten-year period of marketing exclusivity is extended to eleven years if, in the first eight years, the marketing authorization holder of the reference medicine obtains approval of a new indication that brings a "significant clinical benefit in comparison with existing therapies." EU law permits a generic company to conduct the studies and trials needed for a generic application during these periods, notwithstanding any patent protection on the reference medicine.

Second, in some cases, approval of an abbreviated application is not possible — because the strict legal definition of "generic medicinal product" is not satisfied, bioequivalence cannot be demonstrated through bioavailability studies, or changes have been made to the active substance, therapeutic indication, strength, pharmaceutical form, or route of administration. Such medicine is so-called "Hybrid medicine". For instance, Kigabeq®, for treating epilepsy in children between 1 month and 7 years of age, is similar to a 'reference medicine' (Sabril® 500mg granules) containing the same active substance (vigabatrin) but Kigabeq® is available in a different form and strengths. In this case, the applicant must submit the results of appropriate pre-clinical tests or clinical trials. This application relies in part on the research that supported the reference medicine and in part on new research. It is to be prepared more quickly and cheaply than a full application, and it can be

expected to produce cost savings for patients and healthcare systems. The same eight, ten, and eleven years exclusivity rules apply.

Third, EU law permits the approval of “similar biological medicinal products,” also known as “biosimilars.” Like generic medicines, biosimilars are authorised on the basis of abbreviated marketing applications, but they are copies of biological medicines, and the marketing applications are therefore different. Biological medicines include recombinant proteins, monoclonal antibodies, medicinal products derived from human blood and human plasma, immunological medicinal products, and advanced therapy medicinal products. If a biological medicine cannot satisfy the conditions for generic approval — due to differences in raw materials or manufacturing processes from its reference product — the applicant must submit results from preclinical tests or clinical trials. As in the United States, the applicant must illustrate similarity in terms of quality characteristics, biological activity, safety, and effectiveness, based on a comprehensive comparability exercise. The EMA has issued detailed guidelines on the type and quantity of supplementary data needed, including numerous guidelines tailored to specific product classes. Use of this centralized procedure is mandatory for copies of biotechnology-derived medicines and certain other biological medicines, but (as is true of reference biologics as well) other biosimilars may be authorised at the national level.

Fourth, the EU medicines regulatory framework does not apply to certain medicines prepared by pharmacies for patients. There are two possibilities. A pharmacy might prepare a medicine for an individual patient in accordance with a medical prescription for that patient, for instance because the patient is allergic to an ingredient in the commercial preparation. This medicine is known as a “magistral formula” and corresponds to a “compounded medicine” in the United States. Individual Member State laws governing compounding vary as there is no single EU-wide regulatory approach here. For example, some Member States permit third parties to compound medicines *for* pharmacies, and others do not. In the alternative, a pharmacy may prepare medicines in accordance with a pharmacopeia and supply those medicines directly to its patients. This medicine is known as an “officinal formula” and has no equivalent in the United States. The specific entity of a formally recognized pharmacist is a key element of the European regulatory landscape. Hence, we have these kinds of approaches regarding the “officinal formula” but also “behind the counter medicines” (see below) where the pharmacist has a central role.

### **III- Risk Management**

All medicines have both desirable beneficial effects and undesirable adverse effects. Indeed, the dual nature of medicines is embodied in the etymology of the words “medicine” and “pharmaceutical.” They derive from the Latin *medicamentum* and the Greek *pharmakon*, both of which mean both remedy and poison. Because medicines have this dual nature, regulators must consider both when assessing marketing applications, and authorization is granted only if a medicine’s benefits outweigh its risks. Risk in this context can mean any risk relating to the quality, safety, or efficacy of the medicine, relating to patient health or public health, as well as any risk of undesirable effects on the environment. EU law also requires that risk be appropriately managed all along the therapeutic chain. Nevertheless, this occurs particularly at the time of marketing authorization and after authorization.

#### **A- At the Time of Marketing Authorization**

The regulatory authorities — whether EMA and the European Commission, or national competent authorities — assess a medicine’s risks at the time of marketing authorization,



permitting market entry only if the medicine has a positive benefit/risk balance. The authorization decision thus involves both risk assessment and risk management. More precisely, for medicines subject to the centralized procedure, the EMA assesses the risk when it reviews the application, and the European Commission manages the risk when it makes an authorization decision on the basis of the EMA's opinion. These decisions consider both the product and its associated information, meaning the Summary of Product Characteristics (SmPC), which is technical labelling for healthcare professionals, and the package leaflet, which is intended for patients. Such associated information is fully part of the marketing authorisation dossier.

Marketing authorization applications must also include risk management plans (RMPs), and the EMA's assessment of the application includes its assessment of the planned risk management. An RMP has three elements. First, it must identify or characterize the medicine's safety profile, focusing on important risks, missing information, and safety concerns that need to be managed proactively or studied further. Second, it must plan "pharmacovigilance" activities to characterize and quantify clinically relevant risks and identify new adverse reactions. As discussed in the next section, this includes routine pharmacovigilance (a passive surveillance system) but may include proactive activities such as non-clinical studies or even clinical trials. Third, it must describe the planning and implementation of risk management (or "minimization") measures. These always include the SmPC and package leaflet, the content of which is controlled and which use a standardized format; these are the primary means by which a marketing authorization informs healthcare professionals and patients about the risks associated with its medicine. Risk management measures may also include controlled access programs, such as a requirement that prescribers and dispensers document their understanding of the risks of the product or limiting the dispensing to certain registered pharmacies.

When granting a marketing authorization, the competent authority must determine whether the medicine will be available only by prescription. A medicine must be classified as prescription-only if (1) it is likely to present a danger if used without medical supervision, (2) it is frequently and often used incorrectly and as a result is likely to endanger health, (3) it contains substances that need further safety assessment, or (4) it is administered parenterally.

Competent authorities may subdivide the prescription-only category into three further subdivisions: medicines on renewable or non-renewable prescription, medicines subject to special medical prescription (typically for narcotics and other drugs that can be abused), and medicines on restricted medical prescription, reserved for use in certain specialised areas (for instance, treatments that can only be used in a hospital). Some Member States also create subcategories of non-prescription medicines, so that some medicines are available in general retail settings, others only in pharmacies, and others only after consultation with a pharmacist.

European law relating to the legal status of medicines differs profoundly from U.S. law, and the differences affect patient experiences in the healthcare system. U.S. law generally provides for two general categories of medicine: prescription medicines (including controlled substances and other prescription drugs) and non-prescription medicines, and the latter can be purchased in any retail setting.<sup>48</sup> In the EU, Good Distribution Practices apply to medicines and they are taken into account at the time of marketing authorisation (as well as Good Manufacturing Practices). They describe the minimum standards to be met from the site of manufacturer to the pharmacy or person authorized or entitled to supply medicines to the public to ensure the quality is maintained

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<sup>48</sup> [\[Insert cross reference to U.S. medicines chapter\]](#) [Zettler and Lietzan]



throughout all stages of the supply chain. Pharmacies and pharmacists in particular, whose special status has also been recognised by the European Court of Justice, play a fundamentally different role in Europe than they do in the United States. In Europe, they may be the primary healthcare professionals with whom a patient interacts. They diagnose conditions, recommend treatments, and counsel their patients. If a medicine is placed behind the counter in Europe, a patient *must* have a sustained conversation with a pharmacist about his or her condition before purchasing this medicine. And if it is available only in pharmacies, this conversation may still occur. In addition, Member States can have higher requirements regarding distribution. For instance, in France, the entire chain of development of medicines is under the so-called “pharmaceutical monopoly”: medicines are distributed in authorized pharmaceutical establishments under the responsibility of pharmacists only.

Consequently, the same medicine may well be available at a grocery store in one Member State, as it may be in the United States, while it may be available in pharmacy only in another EU Member State. These types of rules have been challenged before domestic courts and the ECJ because they could have the effect of impeding trade, but in general the ECJ recognises the public interest inherent in maintaining the special position of pharmacists and pharmacies in European societies. Notwithstanding formal regulation, even in Member States that do not have a third behind-the-counter status, pharmacists play a role providing medical advice (and thus managing the risks of medicines) that they do not play in the United States.

## **B- After Marketing Authorization**

Various rules applicable after marketing authorization also ensure that the risks associated with medicinal products are continually assessed and minimized as much as possible. Broadly speaking these fall in two categories: risks inherent to the medicine itself, and risks associated with the manufacture and distribution of a medicine.

### **1- Risks Inherent to the Medicine**

Additional information about the overall clinical profile of a medicine continues to emerge after marketing authorization. EU authorities have repeatedly strengthened EU laws governing the safety monitoring of medicines, or pharmacovigilance, including through significant legislative changes in 2010 and 2012. Every participant in the healthcare system shares responsibility for pharmacovigilance. Traditionally, the marketing authorization holder (the company or other legal entity having the authorisation to market a medicine), national competent authorities, EMA (especially its Pharmacovigilance Risk Assessment Committee), and European Commission play a role. Healthcare professionals and patients now also play a key role.

The marketing authorization holder must operate a pharmacovigilance system. Among other things, the marketing authorization holder must report adverse reactions to the EMA; this includes both expedited (15-day) reports of serious adverse reactions and Periodic Safety Update Reports (every six months for the first two years after market entry, then once a year for two years, and then every three years thereafter).

The EMA in turn operates “EudraVigilance”, an electronic system for managing and analysing suspected adverse reactions to medicines that are authorised or in clinical trials in the European Economic Area. This system allows electronic exchange of reports among the EMA, national competent authorities, marketing authorization holders, and clinical trial sponsors. It also includes a large pharmacovigilance database with search and tracking functions, containing

information on suspected adverse reactions arising from uses of medicines within or outside the terms of the marketing authorization as well as those occurring during post-authorization studies. The data in this database are publicly available in an aggregated format only.

The Member States also operate a pharmacovigilance system and are required to evaluate the information, consider options for risk minimisation and prevention, and take appropriate regulatory action concerning marketing authorization. For instance, in the case of a centrally authorised medicine, a Member State could recommend that authorization be modified, suspended, or revoked. In this case, it would inform the EMA, other Member States, and the marketing authorization holder. The European Commission would make a final decision, after consulting the EMA. A Member State may also, on its own initiative or at the Commission's request, suspend the use of medicines in its territory where urgent action is essential to protect human health or the environment. Individual Member States must also encourage doctors, pharmacists, nurses, other health care professionals, and patients to report suspected adverse reactions to the competent authorities.

Certain medicines subject to additional monitoring by regulatory authorities now have black inverted triangles in their package leaflets and SmPCs, such as Skyrizi®<sup>49</sup> or Axumin®<sup>50</sup>. This includes any medicine containing a new active substance first authorised after January 1, 2011, any biological medicine authorised after that date, medicines with conditional approval, and medicines authorised under exceptional circumstances. The inverted triangle allows patients and healthcare professionals to identify medicines that require additional monitoring and encourages them to report unexpected adverse reactions through national reporting systems. In 2018, 351 medicines were subject to additional monitoring (4% more compared to 2017). EMA publishes a list of medicines under additional monitoring that have been authorised centrally or nationally.

## 2- Risks Associated with Manufacture and Distribution

Compliance with current Good Manufacturing Practices (GMP) and Good Distribution Practices is also ensured after the marketing authorisation. Apart from licensing the manufacturer and wholesale distributor of a medicine, the competent authority of each applicable Member State must ensure that the legal requirements governing medicinal products are complied with after marketing authorisation. Regarding manufacturing surveillance, this includes repeated and unannounced inspections of manufacturing facilities to ensure compliance with good manufacturing practices. Regarding distribution surveillance, the marketing authorization holder is expected to audit the compliance of any active substance manufacturers and distributors on which it relies. However, as previously said, individual Member States may impose additional requirements on the distribution of medicines.

The marketing authorization holder also has an ongoing responsibility of “supervision” with respect to its approved medicinal products. For instance, it must continually ensure that its medicines are manufactured and controlled according to generally accepted scientific methods, which entails introducing changes as appropriate (such as substantial changes to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product, or changes in the testing procedures for active substances or the

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<sup>49</sup> A medicine intended for the treatment of moderate to severe psoriasis for which there is an EC pending decision on marketing authorization.

<sup>50</sup> A diagnostic medicine used with a body scan to check whether or not prostate cancer has returned, authorised on 21 May 2017.

starting materials/reagents/intermediates used in the manufacturing process of the active substance) to take account of scientific and technical progress. This may entail securing approval of a “variation” to the marketing authorization, which corresponds to a “supplement” in the United States. In addition, the marketing authorization holder has an ongoing responsibility to provide the EMA, the Commission, and the Member States with any new information that might require amending the particulars or documents relevant to its permission to market its medicine. This would include, for instance, new information relevant to the benefits and risks of the product, including results for clinical trials and data on the use of the medicine (including data from uses that are outside the scope of the approval).

Finally, like in the United States,<sup>51</sup> EU authorities have taken steps to address the presence of “falsified medicines”, such as for Fentanyl (a synthetic opioid originally used to treat severe pain, especially for patients with cancer) and its derivatives, in the supply chain.<sup>52</sup> A falsified medicine is any medicine accompanied by a false representation of identity, source, or history. Various measures are intended to reduce the risk of falsified medicines in the EU, including good manufacturing practice requirements, good distribution practice requirements for active substances, inspection principles, safety features for the packaging of medicinal products, and information campaigns to raise awareness of the dangers of falsified medicines. Perhaps most significantly, beginning in February 2019, most medicines in the EU will have a unique identifier (in the form of a unique sequence carried by a two-dimensional barcode) on their packaging, to allow their identification and authentication at any time on the market, as well as a device to allow verification that packaging has not been tampered with. These safety features are intended to minimize the risk of falsified medicines circulating undetected for lengthy periods of time.<sup>53</sup>

#### **IV- Innovation and Competition**

European law relating to innovation and competition in medicines takes into account both economic policy and public health policy, described in the subsections below.

##### **A- Economic Policy**

While medicinal products raise special risks, they are nevertheless considered as goods. As such, they are covered by the provisions of the EU’s Treaty on the Functioning of the EU relating to the free movement of goods within the EU’s internal market (similar to the U.S. Commerce Clause). That is why the European Court of Justice always controls whether any legal restraints on trade constitute quantitative import or export restrictions, or other measures with equivalent effect. These kinds of rules are prohibited on trade between Member States. There is, however, an exception for prohibitions and restrictions justified on public health grounds, provided those measures are proportionate to their goals.<sup>54</sup>

Moreover, five areas of EU economic policy are relevant to medicines innovation and competition in the medicines market.

First, EU intellectual property policy plays a key role in innovation and competition in medicines. In addition to brands (trademarking) that is not developed here due to limited space,

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<sup>51</sup> [\[Insert cross reference to U.S. medicines chapter\]](#) [Zettler and Lietzan]

<sup>52</sup> Directive 2011/62/EU on falsified medicines, OJ L174 /74-87.

<sup>53</sup> Commission Delegated Regulation (EU) 2016/161 laying down detailed rules for the safety features appearing on the packaging of medicines for human use, OJ L 32/ 1–27.

<sup>54</sup> Consolidated Version of the Treaty on the Functioning of the European Union, art. 34-36, 2012, OJ C 326/47-390.

EU law provides one main incentive for the development of new medicines: patents. As in the United States, branding of a medicinal product can be renewed indefinitely, but patents are limited in duration to twenty years. Patents are regulated at multiple levels in Europe. Each Member State has a national patent office that issues patents under its own patent law, which in turn is harmonized with the patent law of other Member States through an EU Directive.<sup>55</sup> Disputes arising out of national patents are handled by national Courts and by the European Court of Justice. In addition, and separate from the EU structures, since the 1970s it has been possible to apply for a European patent from the European Patent Office (EPO). The EPO was created as part of the European Patent Convention (EPC), which involves some — not all — EU Member States, as well as ten additional countries. An applicant applies to the EPO for a European patent. The resulting patent confers protection in all the contracting States designated by the applicant as long as it has been validated through complex and costly procedures by their national patent offices (for instance, implementation of national requirements such as payment of designation fee and translation of the patent in the national language).

In 2012, the EU Member States (except Spain, Poland and Croatia) agreed on a “patent package” — a legislative initiative based on an enhanced cooperation and intended to lay the ground for unitary patent protection in Europe. This package includes a regulation creating a European patent with unitary effect, a regulation on the language regime applicable to the unitary patent, and an agreement to create a single Unified Patent Court. The patent package will enter into force once the Unified Patent Court agreement has been ratified by thirteen Member States including France and Germany. Such Unitary patent will make possible to obtain a patent protection in up to 26 Member States by submitting a single request to the EPO, removing the need for national validation procedures existing for European patents.

The EU patent eligibility requirements are generally harmonized with those of the United States, with one significant exception. Any new, useful, and non-obvious invention can be patented, provided it is concrete and the claims are adequately enabled in a clear written description.<sup>56</sup> But there are several general exceptions, including one relevant to medicines: “methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body.”<sup>57</sup> While a substance or composition may be patented based on the use in question,<sup>58</sup> the method of treatment itself is not patentable. In the United States, methods of treatment can be patented.

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<sup>55</sup> Directive 98/44/EC on the legal protection of biotechnological inventions OJ 1998 L 213/13-21.

<sup>56</sup> Article 52(1) of the European Patent Convention. The following are not considered inventions within the scope of Article 52(1): (a) discoveries, scientific theories and mathematical methods; (b) aesthetic creations; (c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers; (d) presentations of information. *Id.* Art. 52(2). In addition to these patentability requirements, the full scope of a claim must be adequately enabled by disclosing methods of practicing the invention in the specification. This requires both “enablement” and a “clear written description,” although the difference between the two is not always distinct.

<sup>57</sup> Article 53(c) of the European Patent Convention. Moreover, inventions the commercial exploitation of which would be contrary to “*ordre public*” or morality are also excluded. *Id.* Art. 53(a). European patent law provides a non-exhaustive list of these inventions: processes for cloning human beings; processes for modifying the germ line genetic identity of human beings; and uses of human embryos for industrial or commercial purposes, processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes. Rule 28 of the implementing regulations to the European Patent Convention and Article 6(2) of Directive 98/44/EC.

<sup>58</sup> European Patent Convention and Recital (35) of Directive 98/44/EC, Article 53(c).

Since 1992 EU law has also provided for a Supplementary Protection Certificate (SPC), which extends the term of patents associated with certain medicines, in order to compensate in part for the loss of patent life during premarket research and development.<sup>59</sup> One SPC is available per product, and it is available only if (1) the patent has not expired, (2) the product is authorised, and (3) the authorization is the first authorization to place the product (meaning, active ingredient) on the market as a medicine. Although the language in the Regulation is simple, application of the “one SPC per product” and “first authorization of the active ingredient” rules has proven complex, for instance with respect to ingredients that may or may not be active ingredients and with respect to combination products that include both new and previously approved active ingredients.<sup>60</sup>

Furthermore, Regulation (EU) 2019/933 introduced an exception, known as the “manufacturing waiver”. It allows companies to manufacture generics and biosimilars during the term of the SPC for the purpose of export to non-EU markets where patent or SPC protection has expired or never existed, but also for the making (no earlier than six months before the expiry of the certificate) of a product, and storing it in the Member State of making for the purpose of entering the market of any Member State upon expiry of the corresponding certificate. As “The timely entry of generics and biosimilars into the Union market is important, particularly in order to increase competition, to reduce prices and to ensure that national healthcare systems are sustainable and that patients in the Union have better access to affordable medicines”, Regulation (EU) 2019/933 aims to correct the significant competitive disadvantage for makers of generics and biosimilars established in the EU in comparison with makers based in third countries that offer less or no SPC protection and who could enter the Union market immediately after expiry of the certificate. This Regulation also aims to “strike a balance between restoring a level playing field between those makers and ensuring that the essence of the exclusive rights of holders of certificates (...) is guaranteed in relation to the Union market”. As such, it is likely to have a positive impact as leading to more manufacturing activity in the EU. Most importantly, it will allow generics to reach the market in non-EU countries, and in EU Member States after SPC expiry, as a relevant step for quicker patients’ access to medicines with a more affordable price.

Second, EU competition policy focuses on four topics relevant to the regulation of medicines: concerted practices, abuse of a dominant position, generic medicines, and parallel trade. Only parallel trade will be briefly mentioned here. Parallel trade — also called “parallel import” — refers to the transfer of a supply of medicine from one EU country to another EU country outside of the distribution network established by the medicine’s manufacturer. For example, a wholesaler buys medicinal products in Spain and sells them in Germany. Parallel trade can be explained by the variation in medicine prices throughout the EU since individual Member States reach different negotiated prices for their national health systems with the pharmaceutical industry. Under the EU principle of free movement of goods within the EU, parallel trade gives patients greater access to lower prices for their medicines. Parallel trade is permitted where the

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<sup>59</sup> Council Regulation (EEC) 1768/92 (OJ 1992 L 182/1–5) and Regulation (EC) 469/2009 on the supplementary protection certificate for medicinal products, OJ 2009 L 152/1-10.

<sup>60</sup> Case C-322/10 Medeva BV v Comptroller General of Patents, Designs and Trade Marks [2011] ECR I-12051 ; Case C-493/12 Eli Lilly and Company [2013] EU:C:2013:835; Case C-443/2012 Actavis et al. v Sanofi et al [2013] ECLI:EU:C:2013:833; Case C-577/13 Actavis Group PTC and Actavis UK v. Boehringer Ingelheim Pharma GmbH & Co., KG [2015] EU:C:2015:165.

concerned product is the same or very similar<sup>61</sup> to a product already authorised for sale in the destination Member State. The European Commission's position is that parallel imports increase price competition and benefit consumers, but the practice has critics. Medicines tend to flow from countries with lower prices to countries with higher prices, and some believe it contributes to shortages in the lower income countries. Finally, manufacturers object to parallel trade on the ground that price discrimination is more economically efficient than unitary pricing.

Third, as a matter of industrial policy, the EU aims to boost the competitiveness of the European pharmaceutical industry: “one of the cornerstones of a knowledge-based economy”, and “important for European public health, economic growth, trade, and science.”<sup>62</sup> The European Commission has therefore promoted activities designed to create incentives and rewards for a sustainable and competitive pharmaceutical sector while prioritizing and improving patient access to medicines, and it has identified numerous areas for future development. It supports cooperation between Member States in the implementation of Health Technology Assessments, for instance, while also strengthening industry competitiveness with special legislation to encourage the development of paediatric and orphan medicinal products. It aims to foster transparency and ethical behaviour in the pharmaceutical sector, to improve access to medicines worldwide, and to reinforce the presence of the European pharmaceutical industry in the global market.

As part of this initiative, the Commission has identified public-private cooperation as critical to the long-term sustainability of the pharmaceutical sector. It established a Joint Technology Initiative (JTI) for innovative medicine. A JTI combines private sector investment with European public funding, and fosters trans-national cooperation through the creation and management of a common Strategic Research Agenda. The current Innovative Medicines Initiative 2 (IMI 2) has an operating budget of 3.3 billion euros for the ten-year period from 2014 to 2024,<sup>63</sup> and is viewed as implementing the world's largest public-private partnership in the field of life sciences.

The EU also aims to support small to medium sized enterprises (SMEs), “the backbone of Europe's economy” as the vast majority of business in the EU (99%) are SMEs, and these companies employ two-thirds of the private sector. SMEs play an important role in the development of new medicines, accounting for 10 to 15 percent of all applications, more than half of which are for new active substances. The EMA provides administrative, regulatory, and financial support to SMEs, through an SME office with dedicated personnel. Its current action plan includes expanded outreach to newly created companies (for example to increase awareness of SME support services), strengthened training of SMEs, and promoting the use of regulatory development support tools (such as the PRIME scheme).

Fourth, the European Commission has numerous policy initiatives and practices designed to support European research and innovation. The current Framework Programme for Research and Innovation (2014-2020) (also known as “Horizon 2020”) notes that biotechnology is poised to deliver a “stream of new applications” and thus identifies strategic investment in biotechnology

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<sup>61</sup> The medicines have a common origin (i.e. they are both manufactured pursuant to agreements concluded with the same licensor) and the same composition (without having to be identical in all respects, they are manufactured according to the same formulation, using the same active ingredient and also have the same therapeutic effects). Case C-201/94 Smith & Nephew Pharmaceuticals and Primecrown v The Medicine Control Agency [1996] ECR I-5819.

<sup>62</sup> Commission Staff Working Document, Pharmaceutical Industry: A Strategic Sector for the European Economy (SWD(2014)216/F1), 26 June 2014 ([here](#)).

<sup>63</sup> IMI, Introducing IMI, The budget ([here](#)).

research and development as a priority. Some of this work overlaps with the policy initiatives intended to boost the competitiveness of the pharmaceutical industry. For example, the Commission identifies support of SMEs and the Innovative Medicines Initiative as among its policies relating to health research and innovation. The Horizon 2020 work programme for health, demographic change, and wellbeing solicits proposals in numerous areas of medicine, such as proposals relating to use of the human microbiome in treatment of disease, proposals focusing on the development of regenerative medicine, and proposals exploiting the full potential of in-silico medicine research for personalized diagnostics and therapeutics.

Finally, the EU's external policy includes various undertakings that directly affect the pharmaceutical sector. These include, for instance, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the Convention on the Elaboration of a European Pharmacopoeia. The goal of the European Pharmacopoeia was to harmonize specifications for medicines to enable free circulation of high-quality medicines throughout Europe.

## **B- Public Health Policy**

EU public health policy also affects innovation and competition in medicines. Broadly speaking EU public health policy aims to protect and improve the health of EU citizens, support the modernization of health infrastructure, and improve the efficiency of Europe's health systems. The EU "Health Programme" outlines the EU's strategy for ensuring good health and healthcare. The current programme, applicable for the years 2014 to 2020, has four specific objectives: health promotion; protection from serious health cross-border health threats; capacity building; and access to improved healthcare. The special regulatory frameworks for three types of medicine — orphan medicines, paediatric medicines (discussed below), and advanced therapy medicinal products (discussed in section V) — fall within the broad scope of this programme.

Like U.S. law, EU law offers incentives for the development of orphan medicines — drugs that are intended to treat rare diseases or which are not otherwise expected to generate sufficient return in the marketplace to justify their development.<sup>64</sup> To receive orphan designation the company also must show that there is no satisfactory alternative medicine authorised for the market, or that the proposed orphan medicine will be of significant benefit. Orphan medicines must be authorised through the centralized marketing authorization procedure. Companies developing orphan drugs benefit from protocol assistance and may be exempted from marketing authorization fees. After approval, an orphan medicine enjoys ten (rather than eight) years of market exclusivity, during which neither the Commission nor an EU Member State may approve a "similar" medicinal product for the "same" therapeutic indication. This period may be reduced to six years if the designation criteria are no longer met. Between 2000 and 2015, the Commission granted 1544 orphan designations and granted marketing authorization to 117 orphan medicines.<sup>65</sup> Orphan medicines can be very expensive and present a challenge to the sustainability of the national health

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<sup>64</sup> Regulation (EC) 141/2000, *op. cit.* A medicine is eligible for orphan designation if it is (1) intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community; or (2) it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community, and without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment. For instance, Mepsevii®, a medicine to treat the Sly syndrome that has been authorized under 'exceptional circumstances' 23 August 2018 as mentioned above, was designated an orphan medicine.

<sup>65</sup> European Commission, Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products, State of play 2015, SWD(2015)13 final.



systems, as noted regularly by Eurordis (the voice for rare disease patients in Europe), and for this reason orphan exclusivity remains very controversial in Europe, just as in the United States, despite its apparent success in incentivizing development of these medicines.

The regulation on paediatric medicine was adopted in 2006, to improve the health of children under 18 years of age in the EU through the promotion of research, development, and marketing authorization of medicinal products for paediatric use.<sup>66</sup> Like U.S. law, EU law aims to increase paediatric research through a combination of obligations and incentives. Today every new medicine in Europe must also be studied in children, and this research is grounded in a “paediatric investigation plan” (PIP) that must be developed early in the preauthorization clinical development program. The PIP, in turn, is “a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population.”

Paediatric medicines benefit from strengthened incentives. The Paediatric Regulation also created a new type of marketing authorization, the Paediatric Use Marketing Authorization (PUMA), for a medicine to be developed exclusively for use by children (following a PIP approved by the PDCO). For instance, Slenyto® has obtained a PUMA on 20 September 2018 for the treatment of insomnia in children and adolescents with autism spectrum disorder or Smith-Magenis syndrome. If there is a corresponding product authorised for adults that is no longer covered by intellectual property rights, the manufacturer may pursue a Paediatric Use Marketing Authorization, using the same brand name in order to capitalise on existing brand recognition, while benefiting from the “eight plus two” years of exclusivity normally associated with new marketing authorizations. If there is a corresponding product authorised for adults covered by intellectual property rights, the holder of the patent or supplementary protection certificate is entitled to a six-month extension of the SPC’s duration (except in the case of an orphan drug). If the paediatric medicine is also an orphan drug, the ten-year period of orphan market exclusivity is extended to twelve years. For instance, Amglicia® to treat newborns and children with neonatal diabetes is both a paediatric and an orphan medicine.

### **C- Advertising and Promotion**

Unlike U.S. law, European law uses the term “advertising” to refer broadly to any kind of promotion of a medicinal product — thus not only advertising to the general public and advertising to prescribers, but also visits by medical sales representatives to prescribers, supplying of drug samples, sponsorships of promotional meetings attended by prescribers, and sponsorship of scientific congresses attended by prescribers.<sup>67</sup> Like U.S. law, EU law prohibits advertising of any medicine that has not yet been authorised for the market.

Also unlike U.S. law, EU law prohibits direct-to-consumer advertising of prescription medicines. This prohibition raises particular difficulties where advertising is through the internet so consumers can also access it. Indeed, the dissemination on a website of information relating to medicines available on medical prescription only, where that information goes beyond “the literal and complete reproduction of the package leaflet or the summary of the product’s characteristics, which have been approved by the [competent] authorities” is prohibited as well as information “selected or rewritten by the manufacturer, which can be explained only by an advertising

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<sup>66</sup> Regulation (EC) 1901/2006, *op. cit.*, and Regulation (EC) 1902/2006, *op. cit.*

<sup>67</sup> Directive 2001/83/EC, Arts. 86 et seq.

purpose”.<sup>68</sup> Direct-to-consumer advertising of non-prescription medicines that contain narcotics or psychotropic substances is also prohibited. There is an exception for vaccination campaigns approved by the competent authorities of the Member States.

EU law similarly prohibits industry from distributing medicinal products directly to the public for promotional purposes. It further permits Member States to ban the advertising of any medicinal product subject to reimbursement, which several have done, including France.<sup>69</sup> It does, however, expressly authorise advertising of medicines “which, by virtue of their composition and purpose, are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary.”<sup>70</sup> For instance, this is the case in France for cough or cold medicines that are not submitted to prescription and not reimbursed by national health insurance, such as Actifed® or NurofenFlash®. This advertising is subject to various requirements imposed under EU law. For instance, it must be clear that the message is an advertisement and that the product in question is a medicinal product, and the advertising must include the information necessary for correct use of the product. Some additional principles are similar to those applied by the US FDA, including the rule that advertising must not suggest that the effects of a medicine are guaranteed or that they are unaccompanied by adverse reactions, but others are unique to Europe, such as the rule that advertising may not suggest that the health of a person can be enhanced by taking the medicine and may not give the impression that a medical consultation is unnecessary.

In contrast to direct-to-consumer advertising, advertising to persons qualified to prescribe or supply medicines is generally permitted under EU law. Two basic rules apply and are broadly speaking analogous to rules that apply in the United States. First, all parts of the advertising of a medicinal product must comply with the particulars listed in the product’s summary of product characteristics. Second, the advertising must present the medicine objectively, without exaggerating its properties and without being misleading. In addition, advertising to prescribers and suppliers must include essential information compatible with the summary of product characteristics and the supply classification (nonprescription versus prescription) of the medicinal product. Member States may add supplementary requirements such as that the advertising must state the selling price. Finally, a Member State may instead decide that the advertising of a medicinal product to persons qualified to prescribe or supply the product may include *only* the name of the medicinal product, or its international non-proprietary name, where this exists, or the trademark, if it is intended solely as a reminder.

## **V- A Special Framework for Advanced Therapy Medicinal Products**

In 2007, the EU established a specific legal framework for medicines based on genes, cells, or tissues of human or animal origin, also known as “advanced therapy medicinal products” (ATMPs).<sup>71</sup> ATMPs include four categories of product: gene therapy medicinal products, cell therapy medicinal products, tissue engineered products, and the combination of any of these with medical devices as combined advanced therapy medicinal products. Many of these products, like stem cell therapies, would be considered “regenerative medicines” in the United States. Cell and tissue products that are minimally manipulated or intended for homologous use (that is, for the

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<sup>68</sup> Case C-316/09 MSD Sharp & Dohme GmbH v Merckle GmbH [2011] ECLI:EU:C:2011:275.

<sup>69</sup> Article L5122-6 of the French Public Health Code.

<sup>70</sup> Directive 2001/83/EC, Art. 88.2.

<sup>71</sup> Regulation (EC) 1394/2007 on advanced therapy medicinal products, OJ L324/121-137.

same purpose in the recipient as in the donor) are *not* considered ATMPs.<sup>72</sup> A classical blood transfusion would not constitute an ATMP. ATMPs tend in fact to be developed for the purpose of preventing or treating, or even curing, rare diseases, acquired diseases such as cancers, central nervous system degenerative conditions (such as Alzheimer's and Parkinson's disease), and genetic diseases. For instance, Strimvelis® is a gene therapy ATMP authorised from 26 May 2016 to treat severe combined immunodeficiency due to an enzyme (adenosine deaminase) deficiency (ADA-SCID), a rare inherited condition. Such enzyme deficiency leads to an immune system deficiency where patients rarely survive more than 2 years without effective treatment.

Broadly speaking, the ATMP framework is intended to foster the competitiveness of European pharmaceutical companies in the field, facilitate the flow of goods throughout the European market, *and* protect public health. In addition to the primary Directive (2001/83/EC) that applies to all medicinal products in the EU, these medicines are subject to a Regulation specifically relating to ATMPs (as well as many guidelines). Together these documents create a stricter legal regime for ATMPs than apply to other medicines in the EU and, indeed, than apply to tissue-based products in the United States.

ATMPs must be authorised under the centralised procedure discussed in section II.A above. Within the EMA, the Committee for Advanced Therapies (CAT) has responsibility for every issue relating to ATMPs, including recommending their classification and assessing the resulting marketing authorization applications. Small to medium sized enterprises (SMEs) frequently perform the earliest work relating to new ATMPs, such as proof of concept and feasibility studies. These companies do not necessarily have the means to carry out the clinical trials needed for authorization. The Regulation on ATMPs therefore creates a procedure for the EMA to review and certify the quality and non-clinical information generated by an SME, which in theory will facilitate a partnership between the SME and a larger company with the resources to carry out the expensive and risky clinical trials needed for centralized authorization.<sup>73</sup> This procedure has been used very little. There is some discussion of extending it to academics who also develop feasibility studies. ATMPs are subject to additional regulatory requirements – beyond those applicable to other medicines – relating to clinical trials, manufacturing, pharmacovigilance, and traceability.

In a 2014 report on the ATMP regulation, the European Commission highlighted that few-only four- ATMPs have received marketing authorization. It also suggested clarification of the legislation in order to help the translation of research into medicines available to patients in the EU. Nevertheless, it also reported an increase in the activity of the CAT, revealing the dynamics of this sector. Indeed, since adoption of the Regulation, the Commission has finally granted fourteen marketing authorizations for ATMPs.<sup>74</sup> However, the four ATMPs that were first authorised were later withdrawn by their marketing authorization holders for commercial reasons.<sup>75</sup> Such ATMPs' market failures may be because they are very costly and they may not

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<sup>72</sup> They are covered instead by the Directive 2004/23/EC on tissues and cells (OJ L102/48-58), or the Directive 2002/98/EC on human blood and blood components (OJ L33/30-40).

<sup>73</sup> The Regulation also allows SMEs a 90% reduction in the fees (and other applicants a 65% reduction in the fee) that would otherwise be payable to the EMA for scientific advice.

<sup>74</sup> The thirteen authorized products are: ChondroCelect, Glybera, MACI, Provenge, Holoclax, Imlygic, Strimvelis, Zalmoxis, Spherox, Alofisel, Yescarta, Kymriah, Luxturna, and Zynteglo.

<sup>75</sup> Marketing authorizations for Provenge, Chondrocelect, MACI and Glybera were withdrawn at the request of the marketing authorization holders.

be reimbursed by national health insurance systems. In addition to the high cost of ATMPs and general lack of health resources, the reimbursement challenges may reflect the limited evidence of long-term cost/effectiveness to date and the lack of flexibility in reimbursement regulatory pathways. Moreover, there are differing views of the value of ATMPs among stakeholders.

There may be ways to address some of these challenges. For instance, the iterative adaptive pathways approach to market (discussed above in section II.B.2), already used for some ATMPs, was established in part to fill the gap between entering the market and being reimbursed by national health insurances, given that these two aspects are discussed both earlier and together with the various stakeholders involved. In addition, the European Commission has adopted a proposal for a Regulation on health technology assessment especially to improve the availability of innovative health technologies for EU patients, to ensure efficient use of resources and strengthen the quality of HTA across the EU and to improve business predictability. Various regulatory flexibilities described in this chapter have been used – or could be used – for ATMPs. For instance, the PRIME scheme aims to support medicines development, including ATMPs. The most recently authorised ATMPs, Yescarta® and Kymriah® used for the treatment of blood cancer, were reviewed under the accelerated assessment scheme, discussed in section II.B.1 which allows for faster review at the EMA.

The development of ATMPs involves also other challenges. First, the scope of the regulation remains uncertain. The Regulation on ATMPs applies only to medicines that are “intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.”<sup>76</sup> Consequently, this regulation, as for all European pharmaceutical, does not apply to magistral or officinal formula. Further, ATMPs are not covered if they are “prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.”<sup>77</sup> Instead, they are regulated at the national level. The individual Member States interpret this ‘hospital exemption’ differently, especially the notion that the exemption applies to ATMPs prepared on a “non-routine basis.” Some will authorise an ATMP under the hospital exemption only if it is provided to a single patient, or a single patient at a time, while others will authorise ATMPs intended for several patients (with different upper limits varying more or less between 5 and 100 according to unofficial discussions with various national competent authorities). As a result, there is competition, which was not anticipated, between ATMPs authorised under the European centralised marketing authorization and ATMPs that are authorised nationally under an exemption for hospitals. Clarification of the scope of the hospital exemption would be helpful.

In addition, the definition of “ATMP” itself raises concerns: for example, regarding the distinction between gene therapy medicinal products (which are included) and vaccines (which are not).<sup>78</sup> In addition, as noted, the Regulation covers only cells and tissues that have been

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<sup>76</sup> Directive 2001/83/EC, Art. 2(1).

<sup>77</sup> Regulation (EC) 1394/2007, Art. 28(2).

<sup>78</sup> For instance, live recombinant viral vectors intended to treat pathologies caused by infection (e.g. malignancies) in oncology should be Gene Therapy Medicinal Products, while similar products intended as prophylactic against infectious disease should be vaccines.

“substantially manipulated”<sup>79</sup> or that are not intended to be used for the same essential function or functions in the recipient as in the donor. These criteria have proven difficult to interpret, and it can be hard to predict a product’s classification in advance. Another challenge relates to differentiating between combined ATMPs covered by the ATMPs framework, on the one hand, and medical devices containing tissues and cells covered by the medical devices legislation, on the other hand. The CAT provides recommendations on the classification of ATMPs and has adopted various guidelines on the topic, which have been very helpful, but the challenge remains. Therefore, it seems necessary to accept the definition status will always rely on case-by-case analysis.

Second, the biological nature of the ATMPs and the complexity of their processes make manufacturing requirements very specific and costly. In addition, special qualifications and training are often required for the clinical delivery of ATMPs. This has led to the development of new structural arrangements in the EU for the manufacture and delivery of these products. For instance, some large manufacturing centres specializing in ATMPs provide their services to multiple ATMPs developers as well as specific treatment centres targeting specific diseases. They sometimes also combine with manufacturing centres especially for autologous products, those in which the patient’s own cells are used.

### **Conclusion**

European Union medicines law is trying to find the best balance between risks of (new) medicines and patients’ access to them, costs to national health systems of novel medicines and treating conditions for which there is no cure, incentivising innovation and creating a single European market while ensuring a high level of protection of patients in the EU. This is to be done taking into account three contextual challenges.

First, as new kinds of medical treatment are developed, it is not always clear where they fit into existing legal categories, as with microbiome-based products. This is especially true for medicines that have to be delimited from other health products covered by other legal regimes (such as medical devices) and that also include many subdivisions (for instance, orphan drugs, paediatrics, ATMP), often complementary and potentially cumulative. As a result, it becomes difficult to ensure that innovations are subject to the appropriate regulations to protect patients’ welfare, as well as whether they receive appropriate incentives or regulatory support from health agencies to properly promote their development. This is part of the complexity of the EU system.

Second, the particularity of Europe is to combine both national law and European Union law. For medicines, this challenge is emphasised as long as management of health care systems and their resources are regulated at the national levels. Consequently, despite strong European Union law regarding the creation of a single European market for medicines, the promotion of research and innovation, and the limitation of unfair practices, the last steps, i.e. directly supplying medicines to patients or making them accessible as a matter of practical reality to patients within the health care systems, rely on heterogeneous national systems with different resources and different approaches.

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<sup>79</sup> Annex I of Regulation (EC) 1394/2007 provides a non exhaustive list of manipulation that are not substantial : cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification.

Third, the wider context needs to be taken into account, and especially the promotion of the European pharmaceutical sector worldwide. Of course, the internal limits above-mentioned have consequences here as well. For instance, it is impossible to promote a European system that is not one but the sum of various national systems regarding health care management. Nevertheless, the pharmaceutical sector is also regulated to compete globally as a key European industry.

The EU approach has clearly focused on the medicines' access to the market, including as part of a public health objective of patients' health protection. As such, the legal system has been more and more strengthened regarding safety (notably pharmacovigilance legislation) and removal of barriers for common and profitable mechanisms (for instance, new regulation on clinical trials). Nevertheless, such approach by stratum has led to a system that is quite fragmented (regarding the different medicines or the different steps of medicines development (specifically) regulated) and lacks a global view on the entire life cycle of medicines, as a continuous, although long, process. Particularly, and despite several attempts, it lacks a coherent part on patients' access to medicines, while it has been quite successful in fostering medicines' access to the market. One main reason for that is to protect Member States competency regarding the organisation of their national health systems. One example here is the Commission's proposal of a Regulation on HTA that would contribute to a more efficient use of resources and to a homogeneous and, to a more or less wide extent according to the Member States experiences in this field, to a higher quality of HTA within the EU. Unfortunately, the current rise of nationalism within the EU, added to constraints over austerity-limited budgets, are not good parameters for these problems to be solved.

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