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Is regulatory innovation fit for purpose? A case study of adaptive regulation for advanced biotherapeutics

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Abstract

The need to better balance the promotion of scientific and technological innovation with risk management for consumer protection has inspired several recent reforms attempting to make regulations more flexible and adaptive. The pharmaceutical sector has a long, established regulatory tradition, as well as a long history of controversies around how to balance incentives for needed therapeutic innovations and protecting patient safety. The emergence of disruptive biotechnologies has provided the occasion for regulatory innovation in this sector. This article investigates the regulation of advanced biotherapeutics in the European Union and shows that it presents several defining features of an adaptive regulation regime, notably institutionalized processes of planned adaptation that allow regulators to gather, generate, and mobilize new scientific and risk evidence about innovative products. However, our in-depth case analysis highlights that more attention needs to be paid to the consequences of the introduction of adaptive regulations, especially for critical stakeholders involved in this new regulatory ecosystem, the capacity and resource requirements placed on them to adapt, and the new tradeoffs they face. In addition, our analysis highlights a deficit in how we currently evaluate the performance and public value proposition of adaptive regulations vis-à-vis their stated goals and objectives.

Keywords: adaptive regulation, advanced therapy medicinal products, biotherapeutics, health policy, innovation, regulatory change.

1. Introduction: Regulating biomedical innovation

Over the years, cycles of regulatory reforms have focused on the introduction of better or smarter regulations as new approaches to achieving regulatory proportionality, transparency, and responsiveness. These reforms, their consequences, and the extent to which they achieve their desired objectives have been extensively documented in the literature (Alemanno, 2015; Baldwin, 2010; Black et al., 2005; Black & Baldwin, 2010; Gossum et al., 2010; Radaelli & Meuwese, 2008; Sarpi, 2015).

Less attention, in both practice and theory, has been paid to the introduction of planned, yet flexible or adaptative regulations aimed at addressing the often challenging balance between promoting scientific and technological innovation, and their emerging risks (Brass & Sowell, 2021; McCray et al., 2010). Adaptive regulatory models are an important approach to managing the introduction of innovations on the market (Blais & Wagner, 2008; Greer & Trump, 2019; Syrett, 2020), yet their intended and unintended consequences have been less explored in the specialist literature.

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This paper provides an in-depth exploration of the rationale, construction, and main consequences created by the introduction of adaptive regulation using a less documented case study: the regulation of advanced biotherapeutics in the form of advanced therapy medicinal products (ATMPs) in the European Union (EU). ATMPs include cell therapies, gene therapies, and tissue-engineered products (TEPs) that are currently prime examples of biomedical innovation and regenerative medicine. When these products began to be clinically tested, regulators in Europe and elsewhere were adopting a new mission that included not only consumer protection, but also supporting needed innovation especially for unmet medical needs, such as rare diseases. Existing risk regulatory frameworks were considered less suited for advanced biotherapeutics because their starting materials, their modes of production and administration, and the way they interact with the human body are considerably different from other medicines. In addition, knowledge about their actual mechanism of action and long-term consequences are only beginning to emerge. Therefore, an adaptive model of regulation was adopted to provide expedited market access for these unique therapies and to redistribute risk management throughout the entire lifecycle of these products, from a heavy emphasis on comprehensive pre-marketing trials to pre- and post-marketing evidence evaluation and risk management. The adaptive approach also allows for continuous specification and revision of technical requirements, thus enabling regulators to keep pace with emerging knowledge and evidence, while being flexible in assessing the specific risks and benefits of each individual innovation in this field.

Our article is structured in six parts. In Section 2, we present the main features and objectives underpinning the introduction of adaptive regulation, based on existing literature. In Sections 3 and 4, we provide detail of how this translates to the regulation of advanced biotherapeutics, focusing on the unique rationale, features, and mechanisms of regulatory change needed to implement an adaptative regulatory regime for ATMPs in the EU. In Sections 5 and 6, we provide a critical analysis of the implications and consequences of this regulatory adaptation for key regulatory stakeholders. Section 7 concludes the article with key learnings from our case analysis that can be used to inform our evolving understanding of adaptive regulations.

Our article finds that, overall, the EU ATMPs regulatory regime exhibits the main features of adaptive regulation, from institutionalized processes of planned adaptation that allow regulators to gather, generate, and mobilize new scientific and risk evidence about innovative products, to iterative approaches for evidence assessment throughout the lifecycle of these products (Brass & Sowell, 2021; McCray et al., 2010; Syrett, 2020). Yet, our in-depth analysis of the regulation of biotherapeutics highlights that more attention needs to be paid to the consequences of these reforms for critical stakeholders involved in an adaptive regulations ecosystem and the capacity and resource requirements placed on them to adapt. As adaptive regulations are introduced, regulators can face legitimacy challenges given their new role of balancing the promotion of innovation with consumer protection; developers and manufacturers might get benefits from earlier market access and less comprehensive authorization requirements, but also face costly, burdensome commitments and sometimes unclear requirements when surveilling the performance of their product throughout its lifecycle. Equally, national healthcare systems (HCSs) and public agencies such as health technology assessment (HTA) bodies have to make critical reimbursement decisions, balancing a product's safety and effectiveness with its justifiable use of public resources. Furthermore, our case analysis highlights that more attention needs to be paid to how we evaluate the performance and public value of adaptive regulatory interventions vis-à-vis their expected goals and objectives. In the case of the regulation of advanced biotherapeutics in the EU, we find mixed and insufficient evidence to assess whether the adaptive pathways introduced by the regulator achieve the goal of bringing innovative therapies to a substantial number of patients in need, at a faster rate. Thus, we conclude that more in-depth analysis of the implications and effects of adaptive regulations on critical stakeholders and their value propositions needs to be conducted before we can make any substantial claims about the benefits of these reforms.

2. Analytical framework and research design

2.1. Analytical framework: Adaptive regulation

Regulatory adaptation, agility, and flexibility are increasingly recognized as drivers of regulatory reform designed to address the balancing act between fostering scientific and technological innovation while ensuring consumer protections against emerging risks and uncertainties. For instance, in 2020, six countries signed the Agile Nations Charter (2020), an intergovernmental network for regulatory cooperation to anticipate and identify scientific and

technological breakthroughs, and ways to manage their opportunities and risks in a timely, targeted, and proportionate manner. Similarly, in response to the Covid-19 pandemic, attention has focused on global regulatory agility during health emergencies in order to facilitate expedited, effective, and safe authorization of health products such as vaccines (Bolislis et al., 2021; Mak et al., 2020).

Regulatory reforms designed to achieve more flexibility and agility are not necessarily new and can be traced back to policy changes supporting smarter, better, or responsive approaches to regulatory design and implementation. The concept and practice of "smart regulation" were advocated as a means of promoting pluralism in both the selection of regulatory instruments and across stakeholders implementing requirements throughout the entire regulatory cycle (Gunningham et al., 1998). The "better regulation" reforms, promoted heavily across the EU and by international organizations, introduced a commitment to transparency, accountability, and proportionality across the regulatory process, supported by measures designed to simplify requirements and compliance costs through the use of techniques such as Regulatory Impact Assessments (Chase & Schlosser, 2015; Radaelli & Meuwese, 2008; Scott, 2018). "Really responsive risk-based regulations" promoted the use of regulatory mixes in ways that are flexible and sensitive to emerging risks and their impact on enforcement and compliance (Black & Baldwin, 2010).

Yet, the adaptive regulations approach developed its own distinctive features. Adaptive regulations generally target science and technology policy areas characterized by a fast pace of innovation that require regulators and other critical stakeholders to keep pace with growing scientific evidence and understanding, emerging technologies, and their risks. This generally requires continuous data collection, new analytical techniques, and dynamic risk metrics and thresholds that allow "regulators to modify regulations as science and uses change without having to pass new legislation. Adaptive regulation allows them to become more restrictive should new evidence suggest previously unknown negative consequences or to become less restrictive for technologies that prove to be less risky than imagined" (Greer & Trump, 2019, p. 506).

Recognizing some of the institutional barriers to assimilate new scientific and technological information, McCray et al. (2010) introduced the concept of "planned adaptation" in risk regulation to highlight the importance of institutional mechanisms and processes that facilitate new knowledge capture, generation, and analysis. Thus, for "planned adaptive risk regulation" to work, two features have to be present: "[a] a priori commitment to subject an existing policy to *de novo* re-evaluation and [b] systematic effort […] to mobilize new factual information for use when the re-evaluation takes place" (McCray et al., 2010, p. 952). Sowell (2019, p. 291) and Brass and Sowell (2021, p. 1095) added an extra feature to this model of planned adaptive regulation, emphasizing the importance for critical regulatory stakeholders to also adapt their capabilities and capacities to new requirements for evidence generation and information provision over the lifecycle of new products and services whose risks are not fully known.

The adaptive regulation approach has seen some popularity in the healthcare sector, especially through the creation of new pathways that facilitate expedited market access for innovative medicines and therapies targeting unmet clinical needs (Eichler et al., 2008, 2015; Syrett, 2020). Looking specifically at the adaptive regulations approach in the licensing of pharmaceuticals, Syrett identified a number of characteristics that also correspond to the planned adaptive regulation features listed above (2020, p. 275):

- **a.** "a non-binary approach to regulatory evaluation of the safety, efficacy and quality of drugs," departing from a predominant focus on the provision of comprehensive clinical trial data prior to a product gaining market authorization;
- **b.** "an iterative approach to evidence generation" relying on data collected post clinical trial and market authorization, which helps the regulator evaluate the continuous performance and emerging risks of a product;
- **c.** "a more holistic approach to drug development with multiple stakeholders being involved throughout rather than only subsequent to the licensing decision," which corresponds to the distributed nature of evidence generation and risk management associated with flexible regulatory pathways;
- **d.** cost reductions as a result of shorter clinical trials and early market access benefits for companies developing innovative products.

While these features are becoming recognized in both regulatory practice and theory, the specialist literature provides less critical engagement with the consequences of adaptive regulations, the implications of these reforms

for critical stakeholders and for the overall goals and objectives underpinning them. Blais and Wagner (2008, p. 1704) observed that regulatory agencies require structural changes and "institutional capacity to assimilate and encourage information breakthroughs in general, and to revise rules in accordance with this information in particular […]." Syrett (2020, p. 282) highlights the presence of stakeholder contestation when new adaptive regulation approaches are introduced, disrupting "business as usual" practices between the regulator and regulated, thus challenging the legitimacy of the regulator and the reform itself. Yet, much more needs to be understood about the implications of adaptative regulatory initiatives at systemic level in certain policy domains, especially how critical stakeholders other than regulators respond to these changes, and whether the reforms themselves are meeting their intended objectives.

In this article, we explore a form of adaptive regulation less documented in the specialist literature: expedited, or what we call *facilitating pathways* adopted by medicines and healthcare regulators in response to biomedical innovations targeting mostly unmet medical needs. Our analysis and findings aim to uncover what is unique about this form of adaptative regulatory practice, how it takes shape in medicines regulation, and whether it brings new and/or similar challenges to those identified in the scholarship presented above.

The growth of adaptive pathways in the regulation of innovative medicines offers a befitting case study for investigating the real-life performance and implications of adaptive regulations. A feature that makes our case study especially interesting is the mix of a well-established regulatory tradition in medicines regulation and the far-reaching technological and scientific innovation we are witnessing with the introduction of advanced biotherapeutics. Hence, both regulatory and technological innovation show their full disruptive potential. We focus our analysis on two critical aspects:

- **i.** How the concept of adaptive regulations is actualized in a particular regulatory context, one highly structured and characterized by long standing practices, such as medicines licensing. We analyze whether the main rationale and features of adaptive regulation are present, and how they take shape in this case study. We give special emphasis to issues resulting from the institutionalization of an iterative approach to evidence gathering and risk monitoring through the ATMPs lifecycle, as well as the plurality of stakeholders involved in the process.
- **ii.** The main consequences (intended and unintended) of adopting and implementing adaptive regulations to promote innovations in medicines and healthcare. We give special emphasis to systemic changes, especially: (a) changes in communication structure, evidence-gathering, and information flows between the regulator and other critical stakeholders; (b) effects on resource allocation and organizational capacity for critical stakeholders, including regulatory agencies; (c) public value considerations addressing the extent to which the introduction of these reforms has achieved the intended outcomes of bringing needed medicines to more patients, sooner.

2.2. Research design and methods

This article provides a detailed analysis of facilitating regulatory pathways established to provide expedited market authorization for advanced biotherapeutics—cell and gene therapies, and tissue-engineered products. We focus mostly on the EU regulatory regime and its reform to facilitate the expedited authorization of these therapies, although we also draw comparisons with similar regime changes in the United States.

Our article builds on empirical research conducted between November 2017 and December 2019 in the Future Targeted Healthcare Manufacturing Hub in the United Kingdom—a large multidisciplinary research hub investigating manufacturing, regulatory, and reimbursement opportunities and challenges for targeted healthcare, focused on bioengineering solutions. The primary research supporting our analysis and findings is based on: (a) 11 semi-structured interviews with key stakeholders (Table 1), which addressed the main features and consequences of this regulatory change; (b) six Regulation and Reimbursement Specialist Working Group meetings that we coordinated, with equally mixed representation across therapy developers/manufacturers, regulatory specialists, and healthcare provider representatives, where the impact of this regulatory change was discussed in depth; and (c) participant observation in technical Working Groups within the research hub specializing on formulation, supply chain, and decisional tools for the manufacture of advanced biotherapeutics. An in-depth

Table 1 Professionals interviewed as part of this study (December 2017–August 2018)

Category	Interviewees
Regulatory advisors	2
Companies	3
Regulatory agencies	2
Charities and patient groups	2
GMP manufacturing facilities	1
Innovation facilitator	1
Total	11†

†Seven UK-based, three based in other European countries, and one US-based.

examination of primary regulatory and legislative documents for advanced biotherapeutics in the EU and the United States was also conducted to support our analysis.

The examination and findings provided in this article are analyzed through the adaptive regulation analytical framework introduced in Section 2.1. Thus, the data extrapolated focuses on two critical aspects: (a) the features of the adaptive regulatory regime for advanced biotherapeutics, and (b) the intended and unintended consequences and implications of implementing adaptive regulations for critical stakeholders, the systemic changes that occur, and the extent to which these regulatory innovations perform according to their expected objectives and outcomes.

3. Background: Reasons and drivers for regulatory change

3.1. The first driver: Biomedical innovation

Engineered human cells, genes, and tissues constitute the new generation of biomedical innovation in healthcare. Following the terminology used in European regulations, we refer to them as ATMPs. The cell-based products are based on human biological material, which is sourced from either donors (allogeneic therapies) or the patient (autologous therapies), then manipulated, expanded, and administered to the patient in order to either regenerate a damaged tissue, restore it, or enhance a function that is compromised.[1] These biotherapeutics generate great hopes to cure serious diseases and restore injured tissues or organs to their full functionality and health.

The greatest challenges posed by cell-based ATMPs (including ex vivo gene therapies) come from their being living products: their therapeutic potency depends on their being alive and active, but this means that their state can change and affect patients differently - they can lose effectiveness or have undesirable and harmful effects. Living products come with some inherent complexities: potential for contamination, instability, and unpredictability. This makes it more challenging to achieve the consistent quality required for patient safety in established medicines regulatory frameworks. In order to mitigate this risk, and make those products acceptable, it is essential to understand how they achieve their therapeutic benefit, which features they need to have (and not have) in order to be safe and effective, and how these features can be removed (if harmful), augmented (if necessary), and preserved. All these tasks pose formidable difficulties at the level of scientific understanding, sourcing, and processing of the starting materials, tests and controls, preservation, and delivery and administration of the final product (Salmikangas et al., 2015). Similarly, at all stages, regulating these products raises new challenges and requires ad hoc solutions. For instance, testing may require a time longer than the shelf life of the product, making it impossible to test before administration to patients. At the level of clinical trials, standard practices are often impossible. For example, preliminary testing in animals, or in healthy volunteers may not be feasible, and controlled trials are sometimes not possible. Finally, tissues, cells, and genetic material may remain in the body for a long time, may undergo transformations, and move away from the target area, organ, or gene; such effects may manifest after the end of a trial (The Committee for Advanced Therapies [CAT], 2010).

For all these reasons, advanced biotherapeutics represent innovative and disruptive technologies. Therefore, when they began to be tested or administered in clinical settings, questions arose whether existing regulations could adequately govern the risk controls required by these live therapies, while preserving the usual level of

quality, safety, and effectiveness (Brévignon-Dodin & Livesey, 2006). The ensuing European legislative and regulatory response is described in Section 4 below.

3.2. The second driver: From health protection to health promotion

Historically, the regulation of medicinal products emerged reactively in an attempt to protect patients from the commercialization of harmful products. The modern system of regulatory oversight of new drugs emerged in the 1960s, following the Thalidomide disaster (Comanor, 1986; Krapohl, 2007). The paragon was represented by the US system, where the FDA applied the most advanced scientific methods for licensing any product entering the federal market. Namely, they demanded three stages of clinical trials culminating in the larger phase III randomized controlled trials (RCTs) that are still widely regarded as the gold standard of clinical evidence for safety and effectiveness (Carpenter, 2014).

The unintended consequence of this robust system was that it made the development and marketing of new drugs slower and very expensive (Comanor, 1986; Peltzman, 1973; Wardell, 1973; Wiggins, 1981). When industry complaints were bolstered by patients' grievances that the agency was delaying access to potentially life-saving treatment, the precautionary view of regulators' role began a transformation, leading to a new vision that included the task of promoting innovation and speeding up patient access to promising therapies. So, when the FDA proposed its framework for cellular and tissue-based products in 1997, their goal was to secure the safety of new and innovative products, to foster the public's trust in these rapidly evolving and promising technologies, and to make sure that innovation and efficient development "could proceed unhindered by unnecessary regulations" (FDA, 1997, pp. 7 and 8).

In Europe too, several countries established pre-marketing testing (Krapohl, 2007) and the European Community, with Directive 65/65/EC, laid down the principles of safety, efficacy, and therapeutic benefit as the criteria for market authorization (Chowdhury, 2014). The creation of the common market led to the establishment of the European Medicines Evaluation Agency (EMEA) in 1995, renamed the European Medicines Agency (EMA) in 2005. Since its inception, the Agency had a dual orientation aimed at promoting both public health and a common market for innovations—even more so under the influence of the Lisbon Agenda. Tellingly, the agency was initially under DG Enterprise until 2009, when it was moved under DG Sanco (Health and Consumers), which "until then had been one of EMA's greatest critic" (Vestlund, 2015, p. 356). An attempt to bring it back under DG Enterprise in 2014 was defeated (Martin, 2014), but demonstrates that the Agency is subject to competing expectations. So, the EMA too—like the FDA—approached emerging therapies by trying to reconcile multiple goals: patients' safety, economic growth, and medical progress. In pursuing this broad agenda, the European Commission noted that "too burdensome requirements could have detrimental consequences for public health as it could prevent the appearance of valid treatments for unmet medical needs. Regulation in this area should contribute to creating conditions that facilitate the appearance of new medicinal products, while ensuring a high level of health protection" (EC, 2014, p. 13). The "better regulation" agenda and its focus on business impact and cost–benefit analysis had reached medicinal products (EC, 2007, 2016).

3.3. The third driver: Facilitating pathways for unmet needs

The third driver of change was the emergence of a new orientation in medicines regulations to establish special conditions for certain classes of products in order to steer innovation where needs were most urgent. We call these regulatory frameworks "facilitating pathways" because they enable accelerated or facilitated market approval for therapies targeting unmet medical needs and filling therapeutic gaps.

These programs follow two special regulatory provisions: shortening the time needed to achieve marketing authorization and increasing interaction with the regulators to improve the chances of satisfying their requirements. These facilitations are attractive for developers because they mitigate two main disincentives on R&D: the long interval between investments and their recoupment, and the low success rate. In short, they reduce costs and risks. But they do so selectively: only for those products that will improve the therapeutic options available to patients. New products that will simply compete for market shares with existing ones are not eligible. This selectivity is needed because new drugs are not necessarily innovative drug, and the most profitable drugs are often products targeting common conditions for which similar products exist. So, the market does not necessarily deliver the innovation most needed by patients.

Table 2 The range of facilitating programs in the United States and EU

Program main purpose and main mechanism	United States	EU
MF. Financial incentives, lower evidence requirements	*Orphan designation* (1983)	*Orphan designation* (2000)
RB. Shorter reviewing time (faster market access)	*Priority review* (1992)	*Accelerated assessment* (2004)
RB. Delaying the collection of part of the safety and efficacy evidence to the post-marketing phase (faster market access)	*Accelerated approval* (1992)	• *Approval under Exceptional circumstances* (2004) • *Conditional marketing authorization* (2006) • *Adaptive pathways* (2014)
RB. Special agency commitment to advise, support development and tailor the evaluation to the product profile (development de-risking)	• *Fast track* (1997) • *Breakthrough* (2012) • *Regenerative Medicine Advanced Therapy* (2017)	*PRIME* (2016)

The first column shows whether the scheme addresses a market failure (MF) or eases the regulatory burden (RB). All schemes are meant to support innovation that address unmet medical needs. The second and third columns list the facilitating pathways currently offered in the United States and in the EU.

The first example of a facilitating pathway, the *orphan drug designation*, addressed this market failure: it offered financial incentives, downsizing of clinical trials, and providing special stewardship from the regulator to products for very small target populations (for instance, rare diseases). Afterwards, a range of new programs addressed the disincentive represented by regulations themselves (Table 2). They lowered the regulatory barrier to market entry through the following mechanisms: (a) speeding up regulatory review, (b) moving part of the evidence collection after market authorization, and (c) increasing interactions with regulators and their advice. Shifting some evidence collection after marketing is the mechanism with the more substantial impact, since it typically means that large, long, and very expensive phase III trials are not required before authorization. In principle, facilitating pathways should meet the demands of both stakeholder groups whose interests they are expected to serve: patients and product manufacturers. Yet, critics claim that, more often, they serve industry rather than patient interests (Banzi et al., 2017; Davis & Abraham, 2013; Davis et al., 2016; Herder, 2019).

Table 3 provides examples of some advanced therapies that recently received marketing authorization in the EU and the United States, and which facilitating pathways they used. Not all facilitating pathways have met with the same success. For instance, sponsors do not seem to have been eager to choose the Conditional Marketing Authorization, or the Adaptive Pathways, while the PRIME scheme has proved much more popular (Detela & Lodge, 2019; Sabbah-Petrover et al., 2019). Currently, in Europe, PRIME has become very attractive for ATMP developers—40% of products granted access to the scheme are ATMPs (Detela & Lodge, 2019)—and in the United States, the RMAT scheme is meeting with a similar success (Sabbah-Petrover et al., 2019). Orphan designation remains an important and popular resource for advanced therapies.

4. Regulatory adaptation in the approval of advanced therapies in the EU

Emerging regulatory frameworks for ATMPs, especially in the EU and the United States, have been informed by the three drivers of change explained above. In this section, we highlight the regulatory adaptations implemented in the EU to facilitate early market approval of advanced therapies. We show that the resulting regulatory regime for advanced therapies emerges from the combination of the following three regulatory pillars with significant adaptive regulation features:

a. the *facilitating pathways* described above (Section 3.3);
b. the *dedicated ATMP Regulation* 1394/2007 and the Directives on cells and tissues (Section 4.1);
c. the *new pharmacovigilance system* (Section 4.2).

Table 3 Combinations of facilitating programs used by different ATMPs

Product and jurisdiction of approval	Facilitating programs used				
	Fast track (US)	Orphan designation (US and EU)	Breakthrough (US)/ PRIME (EU)	Priority review (US)/accelerated assessment (EU)	Conditional approval (EU)
Holoclar, TEP (EU 2015)		Y			Y
Zalmoxis, CT (EU 2016)		Y			Y
Spherox, TEP (EU 2017)					
Kymriah, GT_e (US 2017)		Y	Y	Y	
Kymriah, GT_e (EU 2018)		Y	Y	Y	
Luxturna, GT_i (US 2017)		Y	Y	Y	
Luxturna, GT_i (EU 2018)		Y			
Zolgesma, GT_i (US 2019)	Y	Y	Y	Y	
Zynteglo, GT_e (EU 2019)		Y	Y	Y	Y

The table shows that developers may use several combinations of facilitating pathways. Notice that the only product that did not use any facilitation (Spherox) had an exceptionally long time between the submission of the MAA (December 2012) and the final MA (July 2017). The company took nearly 42 months to answer the questions from the EMA. CT, cell therapy; GT_e, gene therapy (ex vivo); GT_i, gene therapy (in vivo); TEP, tissue-engineered product.

The interplay between these three pillars constitutes a system of *adaptive regulations*, designed to facilitate iterative evidence generation and learning by incorporating new knowledge into the evaluation of products and in the management of their use and risks. Each of these pillars has features designed to enable the fine-tuning of regulatory activity to the emergence of new scientific and risk evidence, as seen in the features of adaptive regulation identified in Section 2.1 (Blais & Wagner, 2008; Brass & Sowell, 2021; McCray et al., 2010; Syrett, 2020). Because the regulatory frameworks do not stipulate technical requirements and leave their specification to guidelines and supporting documents periodically released by the EMA, the ATMP Regulation can adapt to new technical and scientific advances without changing its legal basis. The facilitating pathways' adaptive character also stems from the fact that early and repeated interactions between developers and regulators are aimed to customize regulatory requirements for specific therapies, highlighting the "non-binary approach to regulatory evaluation of the safety, efficacy and quality of drugs" that Syrett identified (2020, p. 275). This is possible because the evaluation of the acceptable balance between risk and benefit is ultimately a matter of regulatory discretion. Finally, the pharmacovigilance and risk management tools mandate the collection and evaluation of further evidence post-market authorization, and thus enable the update of regulatory decisions as more evidence is gathered throughout the lifecycle of a product, pointing once more at the institutionalization of processes for iterative evidence gathering to inform regulatory decision-making about the safety, quality, and efficacy of these products. Facilitating pathways and enhanced pharmacovigilance are not exclusive to advanced therapies, but their adaptive elements are especially valuable for this class of products, which represent the ideal testbed for adaptive regulations, since flexibility is needed not to stifle their development, and ongoing monitoring is necessary to mitigate the risks of technology not yet widely tested and whose unintended and long-term biological effects are not yet fully understood.

ATMPs are paradigmatic examples of products that need special pharmacovigilance and are put under additional monitoring. They typically meet two or more of these post-marketing monitoring conditions: being a biological product; being a new active substance; having been required to produce a Post Authorization Safety Study (PASS); and/or having received a conditional or under exceptional circumstances approval. In short, because of their new mode of action, ATMPs' long-term safety and efficacy are typically hard to demonstrate before marketing, and hence they need to have an especially demanding post-marketing surveillance program, which is regulated by the new pharmacovigilance legislation.

Thus, what we describe as adaptive regulation is a regime much wider than the "adaptive pathways" program of the EMA—itself a form of facilitating pathway. The ATMPs regulatory regime in the EU is the result of adaptive features spread along the regulatory cycle and acting at various levels. The first and second pillars—the

facilitating pathways and the *ATMP regulation*—enable the updating of technical requirements without changing the legal basis or waiting for new legislative initiatives, and help in determining which evidence will satisfy regulatory requirements in particular cases. The third pillar—*pharmacovigilance*—prescribes the steps for collecting further evidence after marketing and adapts the terms of the regulatory authorization if new evidence comes to light. So, the presence of adaptive regulation features at different stages of the regulatory activity justifies the description of the ATMPs regulatory regime as adaptive.

4.1. The ATMP regulation

"The ATMP regulation was designed to ensure a high level of human health protection as well as the free movement of ATMPs in the EU" (EC, 2014, p. 2). The regulation was triggered by the growing number of TEPs that were appearing in Member States, either as commercial products or as clinical procedures. It addressed two fundamental issues: regulatory approval discrepancies across EU Member States, and ambiguity about the product category under which these biotherapeutics would fall: devices, medical procedures, or medicinal products (Brévignon-Dodin & Livesey, 2006; Dupraz Poiseau et al., 2006; Faulkner et al., 2003; Kent et al., 2006). The first impulse was therefore toward creating a unified market through a mandatory centralized authorization procedure and to consolidate expertise by instituting a Committee for Advanced Therapies (CAT), charged with evaluating these products. As the regulation was discussed among EU legislators, safety and trust issues became increasingly prominent and led to the decision to bring all ATMPs under the "medicinal products" category: the one regulated more strictly (Faulkner et al., 2008; Geesink, 2006). To compensate developers—mostly hospitals, Small and Medium Enterprises (SMEs), and universities—from the considerable burden that this choice imposed on them, a number of incentives and facilitations were introduced for SMEs and hospitals (see Mansnérus, 2015, p. 452).[2]

A distinctive feature of the ATMPs Regulation is its flexibility (Åkerblom, 2008)—a fundamental aspect of adaptive regulations. Legislators and regulators wanted to provide a clear and comprehensive legal and regulatory framework, but they were well aware that the sector was still young and rapidly evolving, and that products are diverse and pose different challenges. Furthermore, techno-scientific advances in this field are pervasive, pertaining not only to biotherapeutics but also to manufacturing techniques, assays and tests, reference materials for quality controls, and finally clinical trials design, methods, and real-world evidence collection (Hourd et al., 2008; Schilsky, 2018). Flexibility and adaptation appeared the only answer consistent with staying abreast of techno-scientific progress. Comitology was adopted (Faulkner et al., 2008) so that the technical guidelines complementing the ATMP Regulation "can be updated and revised in a flexible and rapid manner" (Mansnérus, 2015, p. 455) to respond to new evidence and better understanding without changing the legislation.

In addition, a risk-based approach was introduced to increase regulatory flexibility.[3] This instrument allows applicants to depart from the dossier template, and tailor the evidence and quality controls to be presented in support of a product on a detailed product-specific multifactorial analysis (Directive 2009/120/EC), (Cohen-Haguenauer, 2013; Salmikangas et al., 2015).

4.2. The new pharmacovigilance system

The new European pharmacovigilance system[4] is designed to monitor medicinal products' safety and efficacy throughout their lifecycle. This mechanism of risk-based, planned adaptation works in three steps. It begins with data collection from multiple sources, continues with a range of scientific evaluations performed by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), and concludes with a set of regulatory actions, which can range from updated labels to product withdrawal. Currently, medicinal products in the EU are mandated to have a risk management plan and they are subjected to proactive lifelong monitoring, whose mechanism is also subject to planned quality control and improvement (Regulation 520/2012 and EMA, 2018). Besides, this renewed pharmacovigilance system aims at accelerating "access to new and innovative medicines" (Santoro et al., 2017, p. 867). Evaluators can accept less upfront evidence trusting that the improved pharmacovigilance is a powerful risk mitigation mechanism (Arlett et al., 2014; Eichler et al., 2012, 2013).[5] This is what makes the new European pharmacovigilance framework especially relevant for ATMPs: as a product whose market authorization would be substantially delayed if full evidence of long-

Table 4 Adaptations and implications of the new ATMPs regulatory regime

Old regulatory regime	New regulatory regime	Implications of the change
Focus on product-associated risk *Goal*: Risk minimization Protecting public health	Dual focus: - Disease-associated risks - Product-associated risks *Goal*: Risks balance optimization Promoting public health	Risk versus risk framework Inevitability of tradeoffs Risk tolerance Value-judgments required
Focus on evidence robustness *Goal*: Maximizing pre-marketing evidence	Focus on evidence generation opportunity costs and diminishing returns *Goal*: Satisficing pre-marketing evidence supplemented post-marketing	How to make and justify value-judgments on risks and benefits? Need for enhanced pharmacovigilance
Focus on scientific evaluations of quality, safety, and efficacy *Goal*: Providing technical evaluations	Focus on facilitating innovation and patients' access to it *Goal*: Addressing unmet medical needs	Extensive engagement with other stakeholders, capacity building Getting the mandate and capacity to lead innovation

The table summarizes some of the most important consequences of the move from a precautionary approach to an approach that takes into consideration unmet needs and support for innovation.

term safety and efficacy was demanded, their safety assurance is partly entrusted to carefully monitoring and assessing evidence produced after marketing. However, this is also what generates controversy. For, while it is agreed that the new pharmacovigilance makes post-marketing decisions faster and more robust, its goal to facilitate faster product approval raises concerns. Marketing decisions based on less evidence and more uncertainty can lead to more mistakes by regulators and less informed decisions by clinicians and patients (Davis et al., 2016; Tao et al., 2019). Furthermore, as Begg and Ellenberg (2018, p. 218) note, post-marketing evidence and research "cannot fully compensate for the kind of evidence that can only be assembled in the pre-marketing setting."

We summarize the adaptive features and consequences of the adaptive regulation regime for emerging biotherapeutics in the EU in Table 4.

In Sections 5 and 6, we explore in more depth the implications and consequences of the introduction of the ATMPs adaptive regulation regime for critical stakeholders that shape and are affected by this reform: the regulators, developers, national health technology assessment (HTA) bodies, payers, and the healthcare system (HCS), including patients, as a whole.

5. Implications for regulatory agencies

Balancing the promotion of biomedical innovation for unmet needs with the established requirements for quality, safety, and efficacy in medicines regulations has altered the role and engagement of regulators in the market authorization process and post-marketing surveillance for ATMPs. This adaptation had two effects. First, this new generation of technology demanded new assessment criteria and keeping pace with emerging scientific and risk knowledge. Second, overcoming the limits of a precautionary approach has made the task of regulators broader, forcing them to reinvent their role, which, as Syrett (2020) mentioned, can affect their legitimacy. In this section, we show that these two challenges have been addressed with the same instrument: an intensified use of discretion and engagement with industry and other stakeholders (Fig. 1). However, this strategy has brought challenges and criticisms to the regulators, placing new pressures on their capacity to continuously engage not only with a broader range of stakeholders but, equally, with emerging scientific and technical knowledge, including new risk knowledge.

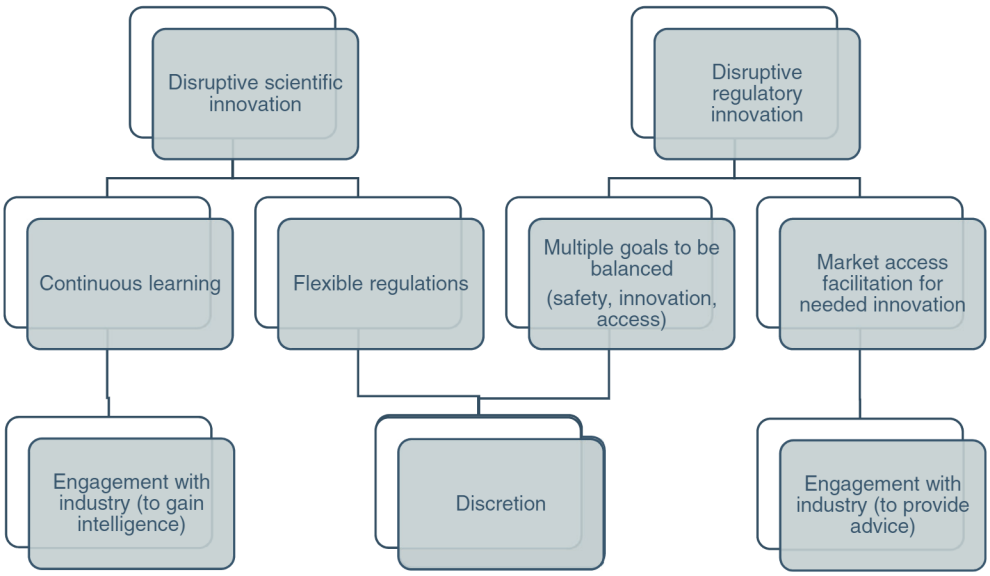

Figure 1 Responses to disruptive scientific and regulatory innovation.

5.1. The new role of regulatory agencies: Balancing effective stewardship and trust

Generally, procedural regulatory flexibility and the need to balance different goals (Lumpkin et al., 2012) can increase regulators' discretion (Fig. 1). The need to facilitate product innovation and to understand what kind of evidence requirements are appropriate for each product has led to more engagement with industry in the early stages of trial design and dossier preparation. However, this engagement process encounters two serious challenges. First, regulators are not the only gatekeepers on the path from bench to clinic, so that facilitating marketing authorization does not automatically lead to patient access: payers have to cover, clinicians to uptake, and patients to trust (Abou-El-Enein et al., 2016; Driscoll et al., 2017; Maschke et al., 2017; Tao et al., 2019), and if regulators accept tentative evidence, other stakeholders will have weaker reasons to trust the value of innovation. Second, increased engagement with industry exposes regulators to the contentious issues of regulatory capture, which can undermine the public trust in a sector that is already perceived as dominated by a small number of players with significant market power (Bramley et al., 2017; Davis & Abraham, 2013; Davis et al., 2016; Garattini, 2016).

5.2. Stakeholder engagement and its challenges

Trust challenges may be addressed by regulators taking the further step of engaging not only with industry, but with a broader variety of stakeholders, including patients, clinicians, and health technology assessors. As Francesco Pignatti of EMA said:

> *"There's a clear opportunity to design the development in such a way that all stakeholders maximise the chances of fulfilling their objectives as quickly and rationally as possible." (Crompton, 2015, p. 7)*

Both the Adaptive Pathways and the PRIME scheme exemplify this attempt of promoting and coordinating multi-stakeholder engagement. Extended dialogue may both enable developers to meet the demands of all stakeholders who need to be convinced of the value of new products, and promote more openness, thus dispelling the perception that regulators have been captured by the regulated industry. On the other hand, new challenges emerge: the capacity needed to promote this coordination exercise, the transparency of the process, the fairness and balance in the representation of interests, the legitimacy of this role, and the responsibility and accountability structure that it generates need to be more carefully considered.

5.3. Regulatory capacity and legitimacy

Continuous stakeholder engagement needs capacity not only from the EMA but also from all participants, since the effectiveness of the exercise will be limited if some participants lack capacity to keep up. Currently, this is a greater challenge than the capacity of the EMA itself. For instance, both our research and other studies have shown that the idea of parallel consultations with regulators and HTA bodies did not work as well as expected because HTA bodies were not always able to give feedback in a timely manner and with the same level of quality and specificity as the regulator (Bramley et al., 2017; Mayer-Nicolai et al., 2014).[6] Similarly, lack of capacity has also limited the participation of SMEs in this continuous consultation process (Warner & Sibal, 2015).

In addition, the selection criteria for stakeholder consultation are not fully transparent, so that it is unclear if all relevant interests are fairly and proportionately represented. This is a sensitive issue because EU consultation processes around regulations are often criticized for consulting "the 'usual suspect', organized interest groups as opposed to 'missing stakeholders'," and to recruit on the basis of their technical expertise rather than by being the most affected (Alemanno, 2015, p. 349). Furthermore, in the medicines sector, concerns have been raised repeatedly about the industry's ability to influence the agenda of patient groups (Batt, 2017; Jones, 2008; Lieberman, 2016). Finally, it is not clear whether regulators have legal mandate to exercise this coordination role. Regulation 726/2004 indicates that the Agency's task is to provide science-informed opinions on the safety, efficacy, and quality of medicines, and it may be argued that becoming an innovation broker oversteps this original mandate, a worry that has been expressed during the primary research conducted during this study by a regulator working with the EMA. On the other hand, the European legislator has mandated the presence of some stakeholders in recently established committees: the CAT features two patient and two clinician representatives, and the PRAC features one patient and one healthcare representative (Regulation 1394/2007, Art 21; Regulation 726/2004, Art 61a). This may be read as a sign that the legislator encourages broader stakeholder engagement in the work of the EMA, but disparities between engagement requirements across regulatory frameworks raise questions about the role and discretion of the EMA in this process.

6. Implications for other regulatory stakeholders: Leaving healthcare providers behind?

6.1. Implications for developers: The hidden capacity costs of facilitation

The centralized procedure and the establishment of the CAT have provided a unified European assessment of ATMPs marketing authorization applications (MAAs). However, a remaining problem comes from the division of competence between the EMA and National Competent Authorities stemming from the subsidiarity principle in the EU. National differences in interpretation, enforcement, and implementation of EU legislation are the most frequently criticized regulatory hurdles (Pearce et al., 2014; ten Ham et al., 2018). The regulatory consistency offered by the FDA in the United States has not been achieved in the EU, where national competent authorities play an important part in the implementation of EU regulations and directives and, often, fail to do so uniformly.

In contrast, the flexibility of the ATMPs regulatory regime can be helpful in accommodating product specificities and more tailored marketing authorization processes, but it also creates new uncertainties. In the development of advanced biotherapeutics, SMEs, hospitals, universities, and their spin-offs have played a major role, while large companies have mainly stepped in at the later stages of development (EC, 2014; Pearce et al., 2014; Phacilitate, 2017). Given the specificities of these therapies and regulatory flexibility, product development risks can be mitigated by developing a very thorough scientific understanding of the product, and by engaging with regulators early and frequently ("come early, come often"). Yet these strategies require considerable resources and capacities and are thus less available to small developers. As Carvalho et al. (2019, p. 826) observe "prior experience and the resources of the applicant are key factors in regulatory approval."

Furthermore, our primary research shows that early engagement with regulators for more scientific advice comes with a tradeoff. The early MAAs submitted by ATMP producers had a high number of shortcomings that led to several questions and concerns from the regulators (Bravery et al., 2019; de Wilde et al., 2018; Seimetz, 2016). The novelty of the products and inexperience of developers were the likely causes, which might be mitigated through closer engagement with regulators. However, research has shown that scientific advice is a double-edged sword: when not followed it increases the likelihood that the Agency rejects the MAA (Hofer et al., 2015; Regnstrom et al., 2010). Yet, following the regulator's guidance often requires further time and

Table 5 EMA post-marketing requirements for CAR-T cell therapies

	CAR-T product	
	Kymriah	Yescarta
Safety requirements	Risk management plan Administration only in centers qualified to dispense Educational program for patients and healthcare professionals	
Post-marketing surveillance	Periodic Safety Update Reports (PSURs) Post-Authorisation Safety Study (PASS) until December 2038 Required patients' registry Post-Authorisation Efficacy Study (PAES)	

The table provides a good illustration of how much work companies need to do in bringing products to the clinic and in the post-marketing phase.

resources, and it can even require further basic research into the biological attributes of biotherapeutics (ten Ham et al., 2018). Hence, "applicants may prefer not to ask questions where the answer could be unpalatable" (Bravery et al., 2019, p. 788). Moreover, a product that addresses an unmet need and shows significant benefit might get away with an imperfect dossier, as Hauray (2017) has shown. As a regulatory consultant explained during our primary research, limited engagement with regulators may be driven by financial pressure to meet a milestone or to get to the market before a competitor, hence the desire to avoid burdensome demands that could delay submission. So, while in principle, it is safer to follow a development plan that maximizes the quality of the dossier and the likelihood of authorization, in fact this may be impossible for resource-limited sponsors whose first need is to raise capital.

Facilitating pathways and adaptable requirements offer to developers the attractive opportunity of smaller and shorter clinical studies, so as to reduce upfront development costs, accelerate recoupment of investment, and capitalize on patent protection. This constitutes a critical feature of adaptive regulations in licensing medicines, as identified by Syrett (2020, p. 275) and presented in Section 2.1 above. However, this advantage implies increased demands for post-marketing vigilance, whose burden is seldom adequately appreciated. Yet, pharmacovigilance and risk management plans "cost time and money" (Tsiftsoglou et al., 2013) and "can be unaffordable for small companies" (EC, 2014, p. 13). Through listing the safety and post-marketing requirements of the most commercially promising ATMPs, Table 5 offers a telling example of how demanding safety and post-marketing obligations can be.

Furthermore, being granted marketing authorization does not equate with success. Receiving authorization for a very restricted indication, with burdensome post-marketing commitments and without evidence to convince payers, may lead to commercial failure—as the examples of Provenge (Jarosławski & Toumi, 2015) and Glybera (Anonymous, 2017) show—and even bankruptcy.

The ATMPs' adaptive regulation regime affects advanced biotherapeutics developers in different ways. Despite all the attempts to support SMEs, small developers often cannot take full advantage of the supporting mechanisms offered by the European regulator, although they are becoming more aware of their importance. In many cases, small developers have later partnered with larger companies (e.g., San Raffaele hospital partnered with GSK for Strimvelis, Holostem with Chiesi for Holoclar, University of Pennsylvania with Novartis for Kymriah), whose capacities can improve the success rate of MAAs and bear the financial burden of pharmacovigilance and delayed adoption. The early developers of Strimvelis and Holoclar acknowledge that partnering with experienced companies was necessary for their success, a position also confirmed in our primary research[7] (Milazzo et al., 2016; Pellegrini et al., 2018), whereas the case of Kite—the developer of Yescarta, bought by Gilead for $11.9 billion (de la Merced, 2017)—shows that financial payoffs for early developers can be considerable.

This handover model is not exclusive to advanced therapies, but in this area can become even more prominent. There are three reasons why taking advanced therapies through regulatory approval and commercialization poses unique challenges to small developers. First, adaptive regulations require that regulatory concerns are heeded earlier and throughout the lifecycle of the product, and hence need higher capacity of understanding and negotiating regulatory issues and of integrating them in product development. Second, advanced therapies face

unique challenges in scaling up production and in logistics (preserving, shipping, and delivering products)—challenges that are both technical and regulatory. Hence, expertise and capital are needed to a higher degree. Finally, advanced therapies emerge very often from research hospitals where the needs of patients and scientists do not always align with the needs of a product development process oriented to regulatory approval. Against this background, the handover model may be especially compelling for advanced therapies. The intricacy, costs, and uncertainties of managing the requirements of adaptive regulations throughout the lifecycle of an advanced therapy are a substantial market entry barrier and can create a quasi-monopoly over entry capacities in favor of established players, as well as an unbalanced distribution of development risks.

6.2. Implications for patients: A new valley of death between approval and access?

The ultimate justification for the introduction of adaptive regulations for ATMPs rests on its ability to benefit patients faster: are patients getting more innovation and earlier access to it? Both questions are currently very difficult to answer with clear empirical evidence, so more data need to be produced to assess the performance of the regulatory regime.

Currently, we do not have robust evidence for measuring the impact of regulatory reforms such as the introduction of adaptive regulations on the rate of innovation. Reports on R&D in this field (ARM, 2019a; ARM & BIA, 2019; Phacilitate, 2017) suggest that the sector is vibrant and that the worst fears of early critics (Kirkland, 2010; Pirnay et al., 2012, 2013) did not materialize. However, comparison with the United States (ARM, 2019a) suggests that there many more biotherapeutics are entering the clinical development stage than in the EU.

A second issue that requires further research is whether regulatory support for facilitating and accelerating market access for biotherapeutics is leading to faster and broader patient access. Currently, the earliest opportunities for patient access to innovation are provided by clinical trials, but this form of access is numerically limited and further constrained by the enrolment criteria set out by trial protocols. Trials are designed to test hypotheses, not to provide wide access or equal opportunities to all patients. For these reasons, new pathways for pre-market authorization access to medicines have been introduced in many jurisdictions (including the EU) as Compassionate Use and Expanded Access schemes. These schemes cannot provide equal and universal access to all patients in need, but they provide additional pre-authorization access without affecting the stringency of conventional authorization requirements. Therefore, they can provide a useful benchmark to measure the success of facilitating pathways to market: if these pathways do not offer a substantial advantage in terms of the volume of patients getting access, then the disruption and increased uncertainty they bring with them are hardly justified. Collecting the data for this comparison and making them publicly available is a necessary condition for a rigorous and evidence-based assessment of the regulations' fitness for purpose.

In the absence of the needed data, we have attempted a rough comparison. The only information we found on the number of patients who have received ATMPs in the EU is an aggregate figure provided in a presentation by an EMA representative who stated that, at the time (December 2017), circa 111 patients had been treated. We have calculated how many months the ATMPs approved at that time had been on the market and divided by the number of patients treated, to have the ratio of patients treated per month with ATMPs available on the market. We have then compared this figure with the ratio of patients treated per month during the pivotal trial(s) of some ATMPs and until the time of MAA application. The results, reported in Table 6, raise the question whether flexible marketing authorization has brought ATMP products to more patients than those who were receiving them through clinical trials before market authorization. Given the small sample size, and the limitations of the methodology and data sources, robust conclusions cannot be drawn at this stage. However, this highlights an underexplored yet critical aspect by which to evaluate the performance of the new adaptive regulatory regime: more rigorous comparison is required between the level of patient access afforded by clinical trials and compassionate use programs, and the level of patient access achieved in the first years after authorization.

Two more issues are worth mentioning in relation to implications of adaptive regulations for patients. First, regulations allow ATMP products on the market with limited information about their side effects and comparative efficacy, although in some cases there may not be appropriate comparators. This makes therapeutic choices by patients and clinicians less well-informed and more risky (Abou-El-Enein et al., 2016; Tao et al., 2019). In fact,

Table 6 Patients treated per month—before and after marketing authorization

Product	Months on the market (until December 2017)	Patients treated (ratio per month on the market)	Months from beginning of earliest pivotal trial to MAA submission	Patients treated (ratio per month on trial)
ChondroCelect	66	Aggregate	64	51 (0.79)
Glybera	57	111 (0.45)	56	27 (0.48)
Maci	9		46	72 (1.56)
Provenge	19		145	477 (3.29)
Holoclar	32		120	133 (1.1)
Imlygic	23		37	291 (7.86)
Strimvelis	18		108	11 (0.1)
Zalmoxis	14		113	30 (0.26)
Spherox	4		29	125 (4.31)
Total	242	111 (0.45)	718	1217 (1.69)

The table shows that products often do not reach more patients after marketing authorization. *Sources*: Presentation from EMA representative Ana Hidalgo-Simon available at: https://www.ebe-biopharma.eu/wp-content/uploads/2017/12/2017-AHS-pesentation-6th-EBE-Annual-Regulatory-Conference-5-Dec-17.pdf (accessed January 14, 2020). Products EPARs (European Product Assessment Reports) available on the EMA website. Trial repository Clinical.Trials.gov. For Glybera also the trial protocol https://docplayer.net/14912703-Protocol-number-ct-amt-010-01.html (accessed January 9, 2020).

regulators themselves have acknowledged that drugs approved through facilitating pathways need to have constraints on how they are prescribed. As the Executive Director of EMA stated in an interview:

> *"We would need to be able to apply certain restrictions around prescribing the drugs that are approved via any new pathway because otherwise we are only lowering the evidence standards." (Mullard, 2012, p. 182)*

This means that authorization based on limited evidence will not lead to universal access for all patients in need, but only for those expected to be good responders to the therapies. This reinforces our claim that a comparison with the access afforded by compassionate use is appropriate. Furthermore, it is worth inquiring how the limited evidence will affect patients' and doctors' decisions, especially as some clinicians have contested the assumption that patients with unmet needs only want faster access and reported that patients are also concerned about risks and benefits (Lieberman, 2016; Murray, 2017). So, what applies to desperate patients with no alternative cannot be generalized to all ATMP patients: in some cases, better-informed decisions may be valued more than additional therapeutic options.

Finally, we need to consider which patients we are considering. If very expensive treatments like ATMPs (Seoane-Vazquez et al., 2019) are adopted by healthcare providers without considerably increasing their total budget, there will be a substitution effect; some other treatments will be discontinued and other patient groups could suffer as a result. Therefore, there will be what in risk tradeoff analysis is called risk transfer (Graham et al., 1995): the risk of not having access to useful therapies would be transferred from the patient population addressed by the ATMPs, to the patient population(s) that will lose access to formerly reimbursed therapies (De Grandis et al., 2018).

6.3. Implications for health technology assessment and payers: Left holding the bag?

Because of their hefty prices and clinical mode of administration, ATMP products can only reach patients through the mediation of HCSs. Payers' reimbursement and clinical preparedness are therefore necessary conditions for patient access. Reimbursement decisions are taken at national (or regional) level, typically through an exercise called HTA, which assesses whether there is enough evidence supporting a product's effectiveness and whether a product represents an efficient and justifiable use of limited resources. After regulators, payers are thus the next gatekeepers and are now becoming the main target of the charge of stifling innovation, especially in the United Kingdom (House of Lords Science and Technology Committee, 2013, §§ 139–141; Gardner &

Webster, 2016). Recent reports (ARM, 2019b; GAUK, 2019; ICR, 2018) and various studies (Corbett et al., 2017; Leyens & Brand, 2016; Vella Bonanno et al., 2017; Woolacott et al., 2017) provide evidence that currently HTA and reimbursement decisions are the main obstacle to patient access to new products. Reports by the Institute of Cancer Research and by Genetic Alliance, which focus exclusively on the United Kingdom where access is more limited than in other major European countries, show clearly how, after market authorization, a significant percentage of innovative drugs for cancer and rare diseases never reach patients. The Alliance for Regenerative Medicine report shows that the availability of EMA-approved ATMPs in six EU countries ranges from patchy (in Germany, the United Kingdom, and France where scarcely half of the approved products are reimbursed) to limited (in Italy three products are reimbursed) to virtually non-existent (in Spain and Sweden). These data support our conjecture that authorized ATMPs are reaching few patients. On the other hand, the report is very appreciative of the EMA's effort to facilitate ATMP access to market.

Regulatory efforts to accelerate marketing authorization are not sufficient for speeding up patient access (Leyens & Brand, 2016) especially in the case of ATMPs, whose claimed long-term benefits are both not demonstrated with the limited evidence needed for their MA and ill-suited to be properly valued by current reimbursement models (ARM, 2019b). Moreover, there is a pricing problem: companies are struggling to find a price tag that can secure both market penetration and profitability. Consequently, some products have failed on the market (Abou-El-Enein et al., 2016; Eder & Wild, 2019). Payers and observers, on the other hand, are afraid that these expensive products threaten the sustainability and equity of HCSs.

> *"Because paying for innovative therapies requires an allocation of resources from the healthcare/ pharmaceutical budget […], it could necessitate tighter budget constraints for some of the existing healthcare technologies, especially the less effective and cost-effective. ATMPs have the potential to […] drive reallocation of significant resources. […] many stakeholders are concerned about overall affordability and potential negative effects on healthcare budgets." (ARM, 2019b, p. 23; see also Gellad & Kesselheim, 2017)*

6.4. Implications for healthcare systems: Taking risks under uncertainty

Healthcare systems (HCSs) are required nowadays to pursue multiple goals: improving the health of the population, offering high-quality services, controlling expenditure levels, using resources efficiently, and distributing benefits and costs fairly. ATMPs can impact on all these goals. If successful in addressing unmet needs and delivering curative effects, they may improve the health status of the population and benefit patients that have been poorly served so far, while saving resources in the long run. On the other hand, if their success is scanty, they can negatively impact both efficiency—by having health benefits inferior to their health opportunity costs and thus using resources inefficiently—and fairness by inflicting financial burdens on many to benefit only a few. So, whether ATMPs contribute positively or negatively to achieving the goals of HCSs depends on their general effectiveness and their cost-effectiveness.

Thus, HCSs are facing a risk-versus-risk dilemma: the risk of forfeiting promising technologies that can improve health, equity, and long-term efficiency, against the risk of investing prematurely in yet unproven technologies whose costs may outweigh the benefits and worsen equity and efficiency. By confronting HCSs with this choice at an earlier stage, and in the absence of consolidated evidence of the cost-effectiveness and long-term effectiveness of ATMPs, the adaptive regulatory regime for advanced biotherapeutics puts HCSs in the position of having to make decisions under greater uncertainty than in the previous precautionary regime (Woolacott et al., 2017). While this is an unwelcome situation, it should also be acknowledged that, if it is true that a precautionary regulatory regime discourages innovation, then this may have hidden opportunity costs for HCSs too, such as forfeiting the benefits of effective innovations (cf. Eichler et al., 2013). However, our research shows that HCSs are slowly beginning to follow the regulators' lead in supporting innovation and in the gradual adoption and real-world testing of these new technologies. For instance, HCSs use managed access agreements between therapy developers and healthcare providers, as well as other innovative forms of payment, to cautiously and gradually introduce new biotherapeutics on the market, while monitoring their effectiveness post-marketing (Jørgensen et al., 2019). However, these national attempts are also generating further layers of complexity because of national differences and because of the persistent need to be coupled with cost-containment measures (see for

instance the Accelerated Access Collaborative proposed in the United Kingdom by the NHS, or the Performance-Based Risk-Sharing Arrangements developed in Italy by AIFA, the Italian Medicines Agency).

Thus, HCSs, like HTA bodies and payers, must choose whether to adapt to both disruptive technologies and disruptive regulations. If they do not, they will defeat the purpose of adaptive regulations (Gellad & Kesselheim, 2017); if they do, they need to take risks and undertake an effort to build capacity to administer innovative schemes that require considerable technical and administrative resources. They also create administrative burden for developers, who need to master the diversity of these national schemes. Furthermore, such schemes imply a cautious and gradual provision of innovative treatments and hence incomplete patient access. So, we reiterate that we need a clear and evidence-based understanding of how much patient access is broadened even by a full stakeholder adjustment. Whereas this knowledge can only be gained if these new approaches are tried, a genuinely adaptive regulatory regime needs to create feedback mechanisms to monitor its performance (McCray et al., 2010), dynamically learn what processes work to produce the desired effects, be ready to step back if innovation fails to deliver the expected results, and have a viable disinvestment strategy to deal with this possibility.

7. Conclusion: The regulation of biotherapeutics as a test for adaptive regulations

Our case study looking at the rationale, construction, and consequences of the ATMPs regulatory regime shows that EU legislators and regulators responded proactively to the promising benefits of biomedical technologies with the introduction of adaptive regulations. They have attempted to promote not only patient safety and the common market, but also early access to innovative medicines in areas of unmet medical need (ARM, 2019b; Eichler et al., 2008; Faulkner, 2017). Through the adaptive regulatory regime for ATMPs, regulators have managed to keep up with emerging technologies and to signal to developers that they are prepared to listen, adapt their requirements to new products, manufacturing, and testing methods, and to offer advice and help to obtain marketing authorization (Brizmohun, 2019; Corbett et al., 2017; Schuessler-Lenz et al., 2019).

We thus conclude that the EU ATMPs regulatory regime follows the main features of adaptive regulation (see Section 2.1). Through its three pillars—the facilitating pathways, the ATMP Regulation, and the new pharmacovigilance systems—we are seeing a transition from a "binary approach to knowledge" (a medicine is safe or not safe) (Syrett, 2020, p. 259) to institutionalized processes of planned adaptation "to mobilize new factual information for use when re-evaluation [of scientific and risk evidence] takes place" (McCray et al., 2010, p. 952). The "iterative approach to knowledge generation" (Syrett, 2020, p. 275) is also present in this regime through the refinement of technical guidelines by the regulator, the interaction with developers to better understand each product and to identify the appropriate risk–benefit ratio, as well as increased reliance on data collection post-market authorization to ensure the continued safety, efficacy, and quality of biomedical products.

However, our in-depth analysis of the broader implications of the introduction of adaptive approaches in the regulation of biotherapeutics (Sections 5 and 6) demonstrates several shortcomings and tensions in this approach that need to be carefully considered by practitioners and further investigated in the specialist literature. Below, we draw several lessons from our case study about some unintended consequences of the introduction of adaptive regulations.

Our analysis shows that introducing iterative approaches to evidence gathering and knowledge generation to evaluate the safety or efficacy of a product over its lifecycle has disrupted the system of expectations and interdependencies, with several stakeholders facing role adjustments, new responsibilities, and resource constraints. This applies to the regulators themselves who, by engaging in earlier and more frequent communications with industry, face the challenge of maintaining trust for themselves and for their decisions in a context where increased developer-regulator information sharing can prevent regulators from keeping at arm's length from industry (Schuessler-Lenz et al., 2019). Perhaps most critically, and reinforcing Syrett's analysis of the effects of adaptive regulations (2020, pp. 279–281), regulators now need to strengthen their legitimacy for their new stewardship role within innovation systems, while ensuring that they maintain their established reputation for consumer protection, even when taking decisions on risk tolerability that cannot be justified purely on scientific evidence grounds (Eichler et al., 2013).

Beyond the focus on regulators, the adaptive regulations literature needs to further address the effects and consequences of the introduction of such measures on other critical stakeholders. For instance, in their analysis, Syrett mentions that one of the characteristics of adaptive regulation is the potential benefit to developers of innovative products to gain early market access with shorter and less expensive pre-market requirements, "which in

turn should stimulate (or, at least not hinder) innovation" (2020, p. 275). However, our analysis demonstrates that this is not always the case, as tailored marketing authorization processes create uncertainties, require capacity to engage with regulators, and introduce burdensome post-marketing commitments. Challenges especially probing for smaller developers which, in the case of advanced biotherapeutics, are often spin-offs from universities and hospitals (see Section 6.1).

Similar tradeoffs are experienced by other critical stakeholders with implementation responsibilities in an adaptive regulation ecosystem, who now must adapt their resource management and organizational practices. In our analysis, this is most prominent in the case of national HTA bodies who have to make reimbursement decisions and to balance a product's safety and effectiveness with its justifiable use of public resources (see Section 6.3). Adaptive regulations require that all critical stakeholders have the capacity to adjust to the reorganization of regulatory requirements and to procedural changes in evidence gathering, risk management, and information sharing mechanisms. Brass and Sowell (2021) highlight the critical importance of considering the evaluative capabilities and distributed capacities of stakeholders to generate, transform, and internalize knowledge in a planned adaptive regulatory regime. Yet, more research is required to understand the systemic effects of the introduction of adaptive regulations on critical stakeholders and their role in this ecosystem that generally demands a more pluralistic, iterative, and engaging regulatory process.

Lastly, our analysis highlights that more attention needs to be paid to how we evaluate the performance and value of adaptive regulations as a type of regulatory innovation. We address some of these considerations in our case study when we discuss the implications that the introduction of adaptive regulations of biotherapeutics has on patients, taxpayers, and national HCSs (Sections 6.2–6.4). Thus, if the essential goal and value of the adaptive regulation of biotherapeutics is to bring needed medicines to more patients in need, at a faster rate, then the evidence we have so far shows a mixed picture of the success of this reform. This points to another deficiency in our current understanding of adaptive regulations: we do not have sufficient evidence, collected systematically, to evaluate the performance of these new interventions. In fact, we do not even have a baseline that can guide this evaluation beyond established regulatory impact assessment frameworks, which might not be very suitable for capturing the opportunity costs of making an innovation available on the market sooner and the possibility that it might turn out to be harmful in the longer period. Thus, more needs to be done in the specialist literature to critically engage with the performance and public value considerations of these regulatory reforms, in a similar manner to what has been done with initiatives for better or smarter regulation in the past (Alemanno, 2015; Baldwin, 2010; Sarpi, 2015). This is a serious issue in healthcare, but also other policy domains where balancing the promotion of innovation, consumer protection, and the efficient use of limited resources is a thorny issue. Identifying adequate performance indicators and benchmarks for adaptive regulations is surely not easy. The plurality of objectives, the systemic impacts, and the response of multiple stakeholders create a shifting context. Yet, clear criteria and principles for weighing gain and losses, an explicit assessment timeline, as well as evidence capable of withstanding critical scrutiny are needed for the public justification of adaptive regulations.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Endnotes

[1] The path is different in the case of in vivo gene therapies, where the nucleic acid (not necessarily of human origin) is administered directly to the patient through a viral vector or another gene editing technique.

[2] A controversial measure is the hospital exemption that allows the custom-based, non-routine production of an ATMP by hospitals without marketing authorization but following national requirements about traceability, quality, and pharmacovigilance. We do not discuss this particular measure in this article because it has already received considerable attention elsewhere, and does not constitute a feature of adaptive regulations per se.

[3] In the context of medicinal products regulation, the risk-based approach does not refer to how regulatory agencies prioritize their enforcement efforts (Black, 2010), but is rather an instance of proportionality between the product risk and safety documentation required. In practice, instead of following a fixed protocol, the producer has the opportunity to decide which data need to be submitted and provides a justification based on the specific risks and characteristics of their product.

[4] The legal basis for this new system gradually emerged over almost a decade. They were first outlined in Regulation 726/2004, further developed in Regulation 1235/2010 and Directive 2010/84/EU, and finally fully laid out and implemented in Regulation 520/2012.

[5] See the note in the Guidance (EMA, 2018, p. 3): "It needs to be emphasised that both the S&E [safety and efficacy] follow-up activities do not substitute for the adequate data to be provided at the time of marketing authorisation and enable a benefit–risk evaluation." In fact, the rationale for a different model of evidence collection, "from prediction to monitoring" (Eichler et al., 2015, p. 243; Oye et al., 2016, fig. 1) is based on the assumption that increased post-marketing evidence collection lightens the burden of pre-authorization evidence production. "Early approvals, albeit based on robust data, are only possible if a well thought-through post approval commitment plan is put in place" (Schuessler-Lenz et al., 2019, Abstract). Herder (2019, p. 837) comes to the same conclusion in his analysis of lifecycle management by the FDA and quotes a former FDA director saying that: "[t]he fact that the agency can require post marketing commitments has probably allowed the agency to approve more drugs than they would have otherwise."

[6] During our primary research, a workshop participant stressed that HTA advice is much less straightforward than regulatory advice and much more challenging because reimbursement is not a binary decision: "reimbursement decisions are much more complex" (SWG October 2019, Participant 2). Another participant reported: "I've heard from some companies that went through the pilot of the joint assessment and they said afterwards that they regretted it, that there was so much red tape that it took so long that we could have brought up our product much earlier if we hadn't done that" (SWG October 2019, Participant 3).

[7] As an interview participant told us: "Only large pharma at the time had the competence to both develop the product and successfully take it through the regulatory approval process and to organize the supply chain and market access."

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