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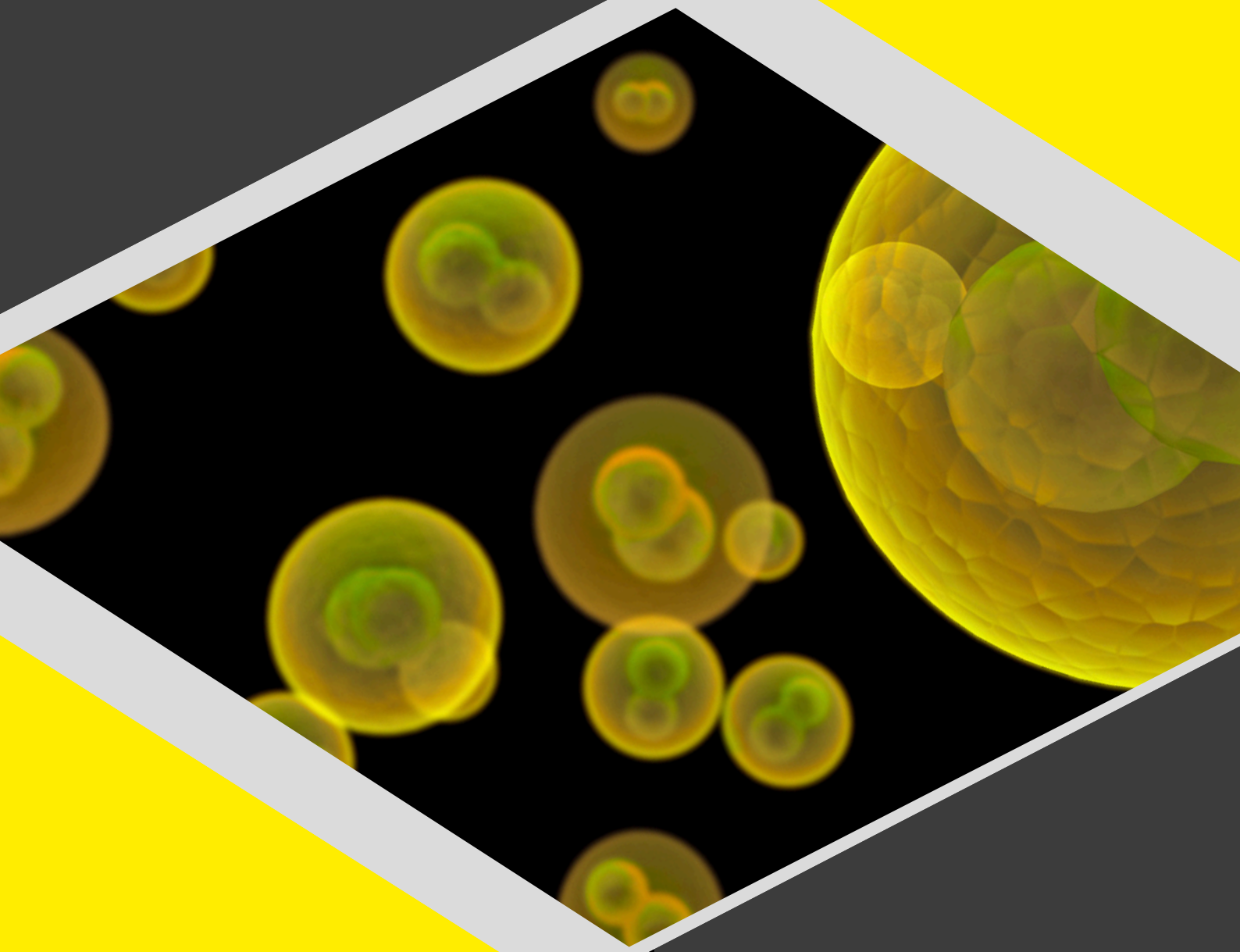

Cell and gene therapy regulation

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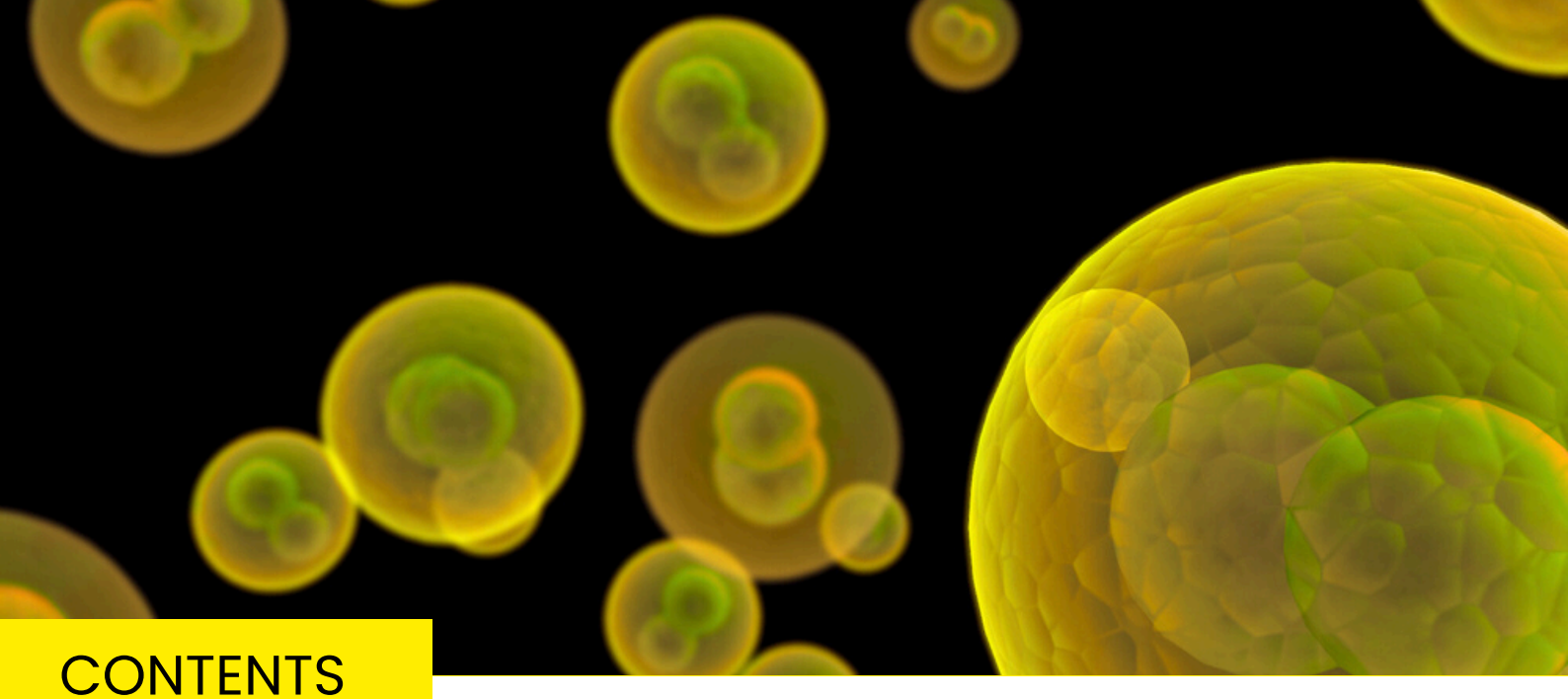


CONTENTS

FOREWORD

We are pleased to present you with this eBook to conclude our **Spotlight feature** on cell and gene therapy regulation.

The regulation of cell and gene therapies is highly complex, with the rapid evolution of these technologies continually reshaping regulatory and operational frameworks. This dynamic environment creates distinct challenges and opportunities for regulators, developers and manufacturers alike.

As we explored throughout our Spotlight feature, navigating this landscape demands innovation, collaboration and adaptability. In our Spotlight survey, industry professionals underscored key regulatory pain points that highlight the magnitude of this challenge. For instance, 25% of respondents cited a lack of expertise from regulatory authorities on new modalities as one of the most significant obstacles during the early development stages. This gap underscores the need for greater alignment between regulators and innovators, ensuring that new therapies are both safe and accessible to patients.

As therapies progress into clinical manufacturing, the hurdles only grow more pronounced. 26% of respondents identified the lack of guidance for efficient scale-up as a major challenge, alongside concerns about raw material quality and defining critical quality attributes. These barriers not only delay progress but also highlight the necessity of co-creating clear, adaptable regulatory frameworks to support cell and gene therapies from bench to bedside.

Our survey revealed that navigating the Biologics License Application preparation process, ensuring GMP compliance, and aligning commercial plans with regulations were among the top concerns during GMP and commercial readiness stages. These challenges underscore the critical need for robust regulatory support systems that can keep pace with rapid scientific advancements.

To address these hurdles, respondents emphasized the importance of tools and resources that simplify compliance. For example, 30% called for comprehensive regulatory guidance and templates, while others highlighted the potential of AI-driven compliance tools and integrated analytics platforms to streamline processes.

This eBook builds on these insights, delving deeper into the shifting regulatory landscape and the challenges encountered at every stage of cell and gene therapy development.

We hope you enjoy reading these expert insights with us.

Megan Giboney
Digital Editor, RegMedNet
Megan.Giboney@tandf.co.uk

Cell and gene therapy commercialization: an interview with Elizabetta Zanon

Elisabetta Zanon is the Director of European Public Affairs and Advocacy at the Alliance for Regenerative Medicine (DC, USA), an international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems and society. The Alliance aims to shape the policy and regulatory environment that supports the development and commercialization of cell and gene therapies representing its 400+ member organizations, including small biotechs, large pharma companies, academic centers and patient organizations.

Here, Elisabetta discusses the regulatory landscape for advanced therapies in Europe, the challenges associated with their commercialization and how innovative new payment models could help improve their uptake.

Elisabetta Zanon

Director of European Public Affairs & Advocacy

Alliance for Regenerative Medicine

1 What are the public and regulatory perceptions of advanced therapies in Europe?

We have now seen a number of regulatory approvals for cell and gene therapies in Europe by the European Medicines Agency. But, these approvals are just the tip of the iceberg. There are many ongoing clinical trials and further candidates in the development pipeline that could reach patients going forward. The potential offered by these therapies is absolutely phenomenal; in the future we could potentially see upwards of ten approvals per year.

Now what is the perception? The perception, I would say, is that these therapies are a disruptive innovation. Our healthcare systems need to adapt to accommodate regenerative medicines, which represent a paradigm shift compared to traditional medicinal products. Currently, healthcare systems are not ready for this; science is moving much faster than our healthcare systems are updating.

For healthcare systems to maximize the impact that cell and gene therapies could have on our society, we need changes from regulatory, health technology assessment and pricing perspectives. We need to help inform pricing and reimbursement bodies on the value of these therapies, because if you compare these transformational therapies with the existing, conventional therapies, they are often far more expensive at the moment of administration, but they offer a durable effect over time and as such they are cost effective in the medium and long term. So the potential is there, but that there is a lot of work required for us to realize it.

2 How can healthcare systems adapt to accommodate advanced therapies?

We need to start with the health technology assessment, which is the way healthcare systems assess the value of a therapy after it has received regulatory approval, ultimately to help them decide if they will pay for it. Most health technology assessments rely on information from randomized controlled trials that essentially test the innovative therapy against a competitor or the current standard of care, or a placebo group, for example, in a randomized controlled trial.

Cell and gene therapy commercialization: an interview with Elizabetta Zanon

Very often, randomized controlled trials are not possible for cell and gene therapies for several reasons. Often the therapy is for a rare disease and the number of patients is so small that you cannot have a control group. Alternatively, it can be unethical to have a placebo group as the treatment requires invasive administration, so you would have to conduct an invasive procedure without giving a patient the option of receiving the transformational therapy.

As a result, regenerative medicines are often assessed in single arm trials. Health technology assessment bodies then claim that we don't have enough evidence to properly estimate the clinical value of this therapy against the standard of care or against the control group and so healthcare systems may refuse to pay for it. There is this level of uncertainty where the evidence, which is considered sufficient by the regulator to give authorization, is later considered to be insufficient by technology assessment bodies or pricing and reimbursement bodies. This is a big challenge.

3 What do you see as the solution to this challenge?

We need more alignment between the regulatory and health technology assessment bodies in terms of the evidence needed for both of them to come to a decision.

4 How else can we adapt to facilitate the adoption of these therapies?

We need to implement more innovative payment models to alleviate the impact of the high cost of these therapies. Instead of paying the full cost of a therapy at the moment of administration, we could split the payment of that therapy over a number of years. You could also link the payment to the outcome: if the outcome is good, then you continue paying as long as the therapeutic effects of the therapy persist; if the outcome is not the one you expected, then you can stop the payment.

These innovative payment models are very important for our sector to ensure a significant take up of these therapies going forward, because the cost of these therapies can be significant at the point of administration. If you have a chronic patient receiving a treatment over the course of their life, the cost of the treatment is split over a long period of time. Transformational therapies like cell and gene therapies are most often only administered once and then they have a very durable effect over a long period of time. Therefore, they can seem more expensive at first, but they lack the hidden cost of continual repeat treatment. For healthcare systems, this can be difficult from a spending perspective.

However, while I think that introducing these innovative payment models can help make costs more manageable, it will, of course, requires healthcare systems to begin more structured follow-up with patients to capture outcomes. As a result we often notice resistance from healthcare systems to adopt these innovative payment models due to the additional work and cost associated with that follow up.

5 Are the companies making these therapies enthusiastic about these payment models?

Mostly, yes. I cannot, of course, speak for individual companies, but we have seen a number of therapies going to market and being commercialized using these innovative approaches and these payment models have eased discussions and negotiations,

ultimately leading to an increased uptake of these innovative therapies.

This is vitally important as in recent years we have seen seven products that received marketing authorization in Europe be withdrawn from the market due to the difficulty in commercializing them. So around one-third of the products approved by the European Medicines Agency have been withdrawn from the market mainly for commercial reasons. We need creative solutions to ensure that the products authorized by the European Medicines Agency are commercially viable in Europe.

6 **If there was one thing that you could ask for to improve outcomes for the regulatory approval and commercialization of these therapies, what would it be?**

This is really challenging because it's the whole ecosystem that matters. We are talking of really disruptive innovation here. These therapies are very, very different compared to traditional medicine but we still rely on the old system for the authorization, assessment and commercialization of these products. We need this system to develop to support these advances, all the way through the development, testing, authorization, clinical assessment, health technology assessment, cost and ultimately, the commercialization of these products.

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of RegMedNet or Taylor & Francis Group.

Navigating accelerated cell and gene therapy pathways

Compared to traditional pharmaceuticals, accelerated clinical trials pathways for advanced therapy medicinal products (ATMPs) allow less time for product development and characterization. However, expectations are still high when it comes to regulatory compliance.

In a recent Aspen Survey, 53% of respondents felt that regulatory submissions are the biggest bottleneck in biopharmaceutical development [1].

Explore the key regulatory challenges at each critical checkpoint in the accelerated pathway for cell and gene therapies.

Preclinical phases

Risk assessments

Create a risk assessment based on all process materials and components and revise at each stage of product development.

Product development

Start product development and characterization with full materials and component traceability. Ensure your supplier can take you from product development to commercialization.

Endpoints

Safety endpoints in disease models, including cytotoxicity and potency tests should be considered.

Clinical phases

Control strategy

Establish Critical Process Parameters and Critical Quality Attributes to set manufacturing specifications. Review your risk assessment ensuring a robust contamination control strategy.

Process design

Design your process with cGMP compliance in mind, thinking ahead on scalability, reproducible performance and increasing compliance requirements through clinical phases.

Testing and control

Extractables and leachables

Perform an extractables and leachables risk assessment with your supplier, noting the enhanced complexity of product contact with single-use-systems in cell therapy. *In silico* modeling may be applied to predict extractables and leachables outcomes.

Microbial quality control

The short shelf life of many ATMPs requires real-time release testing for sterility and mycoplasma.

GMP-compliant raw materials

Ensure all raw materials are suitable for GMP manufacturing.

Product specifications

Product specifications must be set by Phase III with validated analytical methods. Note that limited patient numbers at the time of filing leads to a conservative approach to setting process parameters and specifications.

Process validation

Process validation should be carried out to document that the manufacturing process can consistently produce results within specific parameters.

Supply chain management and qualification

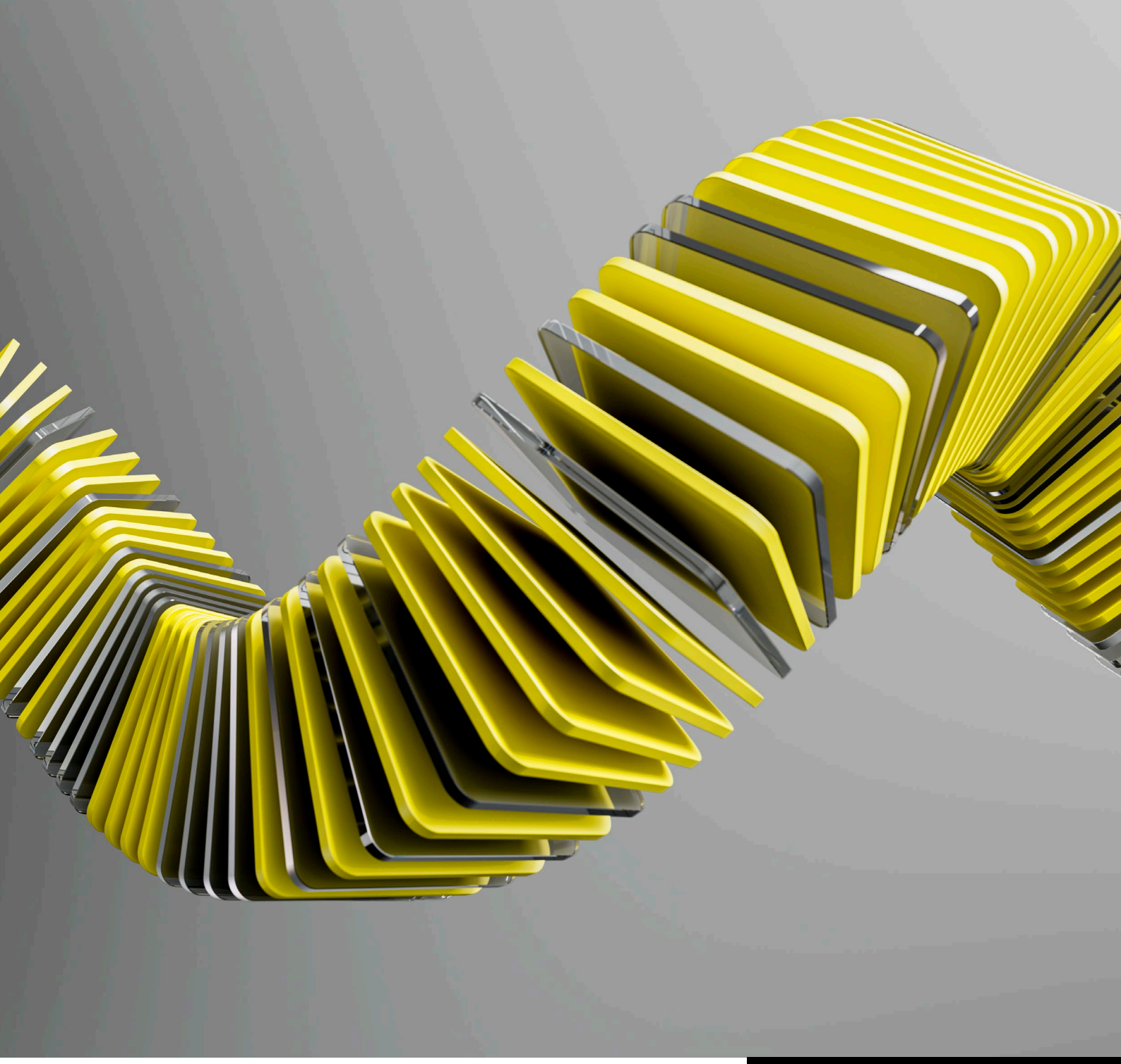
Ensure reliable supply of critical materials supported with appropriate documentation for regulatory filing. Qualify your supplier's quality management systems and enter into a quality agreement.

Biologics License Application/ Market Authorization Application submitted

Sartorius offers comprehensive support from research and development through GMP-grade production, providing phase-appropriate solutions to navigate the complexities of cell and gene therapy development.

Explore more Sartorius cell and gene therapy resources.

1. Aspen Alert. ASQ 818 2022 0114 - Where is the biggest bottleneck in biopharmaceutical development?
https://aspenalert.com/asq-818-2022-0114-of-the-following-where-is-the-biggest-bottleneck-in-biopharmaceutical-development-please-comment-on-your-reasons



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Regenerative Medicine

Regulating advanced therapy medicinal products through the Hospital Exemption: an analysis of regulatory approaches in nine EU countries

Delphi GM Coppens[1], Helga Gardarsdottir[1,2], Marie L De Bruin[1,3], Pauline Meij[4], Hubert GM Leufkens[1] & Jarno Hoekman*[,1,5]

[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[2]Department of Clinical Pharmacy, Division Laboratories, Pharmacy & Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

[3]Copenhagen Centre for Regulatory Science, University of Copenhagen, Copenhagen, Denmark

[4]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands

[5]Innovation Studies Group, Faculty of Geosciences, Utrecht University, Utrecht, The Netherlands

*Author for correspondence: j.hoekman@uu.nl

Aim: To study regulatory approaches for the implementation and utilization of the Hospital Exemption (HE) in nine EU countries. **Materials & methods:** Using public regulatory documentation and interviews with authorities we characterized the national implementation process of the HE, including national implementation characteristics and two outcomes: national licensing provisions and the amount of license holders. **Results:** National licensing provisions vary substantially among selected countries as a result of different regulatory considerations that relate to unmet medical needs, benefit/risk balance, and innovation. The amount of license holders per country is moderate (0–11). **Conclusion:** The HE facilitates HE utilization in clinical practice in some countries, yet safeguarding of public health and incentivizing commercial development is challenging.

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Keywords: advanced therapy medicinal product • clinical practice • commercial development • drug regulatory science • hospital exemption • implementation process • license holders • national licensing provisions

Gene and cell-based therapies (GCTs) represent a challenging class of therapies to appropriately accommodate into the regulatory framework for marketing authorization of pharmaceuticals (i.e., small molecules and biologics). Inherent product characteristics such as the complexities of scaling-up manufacturing and working with and transporting tissues and cells, impose developmental and regulatory challenges on quality aspects and manufacturing procedures [1,2]. Furthermore, as many GCTs originate from academic centers and have close proximity to clinical practice, there are questions about how pre-existing regulatory requirements for ensuring safety and efficacy of the medicinal products produced can be fulfilled in GCT development close to clinical practice [3–5]. Authorities around the world responded by introducing flexibilities for GCTs in existing licensing regimes for medicinal products [6–8]. In the EU and Japan, authorities also exempted some GCTs from medicinal product regulations altogether to accommodate noncommercial activities [9,10].

EU policy makers harmonized GCT regulations across member states by implementing the Advanced Therapy Medicinal Product (ATMP) Regulation (1394/2007) in 2009 after multiple public consultations [11]. Motivated to protect public health and ensure patient safety [1], the ATMP Regulation subjects GCTs to the centralized authorization procedure of the EMA, making it mandatory that GCTs are developed based on stringent evidentiary requirements of evidence-based medicine and multiple stages of clinical trials [12]. Definitions of ATMPs, and therefore medicinal products, include therapies that have been historically used in hospital settings and regulated human tissues and cells [13]. Yet, the ATMP Regulation only applies to ATMPs that are industrially prepared and

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intended for the market [9,14]. The draft proposal for the ATMP Regulation stated that noncommercial activities were exempted from the centralized ATMP regulations [14], and initial statements were redrafted into Article 28 of the final ATMP Regulation, the so-called Hospital Exemption (HE).

The HE allows manufacturing of ATMPs that are "*processed on a non-routine basis according to specific quality standards, and used within the same EU member state in a hospital setting under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient*" (Regulation European Commission [EC] 1394/2007, Article 28). Implementation of the HE was left to individual member states and their national competent authorities [9]. Previous studies reported that difficulties in how to interpret the terminology of Article 28 (e.g., 'non-routine') led to divergent national regulatory approaches for the HE and transposition delays [10,15,16]. For instance, French, Italian, Lithuanian, Polish, Spanish and United Kingdom (UK) provisions lack clear definitions related to 'non-routine' [17,18]. French and UK entry provisions differ due to national existing legislation [17], and provisions for data requirements range from quality (e.g., Finland [FI]) to quality, nonclinical and clinical data (e.g., Spain [ES]) [15]. Furthermore, several factors are reported to be instrumental in how Article 28 was implemented, which include external influence from industry on the implementation process in France (FR), Germany (DE) and the UK [15], existing regulations for tissue products in DE [19] and the availability of other national exemption pathways such as the Specials scheme in the UK [20]. Previous work also shows that HE utilization occurred in DE and the Netherlands (NL), among others [21,22]. Yet, how regulatory licensing provisions and HE utilization compare among various EU countries is largely unclear.

In this study we provide a comparative analysis of how competent authorities across multiple EU countries interpreted Article 28 and implemented the HE nationally. We compare two outcomes of the implementation process; national licensing provisions and the amount of HE license holders across countries. Additionally, we shed light on how characteristics of the implementation process of the HE, including role divisions between competent authorities, discussions on intended purpose for the HE and capacities of developers, are associated with outcomes. The comparative analysis includes nine countries (Austria [AT], Belgium [BE], FI, FR, DE, Italy [IT], NL, ES and UK). It provides clarity on variation in HE implementation, informs the debate on the HE within the wider debate of regulatory change for ATMPs, and facilitates policy learning for HE utilization across EU countries.

Materials & methods

Country selection

We selected European countries with the following attributes: a member state of the EU, implemented provisions by June 2018 and showed indications of ATMP clinical activity, either evident through the conduct of clinical trials [5] and/or ATMP manufacturing under the HE [21]. We ensured to include countries from various European regions. Based on these criteria, we selected AT, BE, FI, FR, DE, IT, NL, ES and the UK.

Analytical framework

Article 28 is listed as an amendment to the overarching Directive 2001/83/EC for medicinal products, and therefore, is required to be transposed into national law by each EU member state [23]. Through transposition into national law, competent authorities of member states are made responsible for drafting specific national licensing provisions and putting these into use on a national level. When national licensing provisions are implemented, the authorization of HE licenses is put under the authority of either the national regulatory authority or the inspectorate.

Based on previous work [23,24], an analytical framework was developed to understand the implementation process in each selected country. The implementation process was separated into a transposition phase defined as the process of translating Article 28 into national provisions for the HE and a utilization phase defined as putting national provisions into practical use. Utilization starts from the moment applications for a HE license can be submitted (Figure 1).

The framework distinguishes between the process of regulatory implementation and outcomes of the transposition phase and utilization phase. We defined the national licensing provisions for the HE as the outcome of the transposition phase and the authorization of HE licenses (yes/no) as the outcome of the HE utilization phase. The latter was further substantiated as the number of license holders per country (Figure 1). Outcomes were captured between May and October 2018.

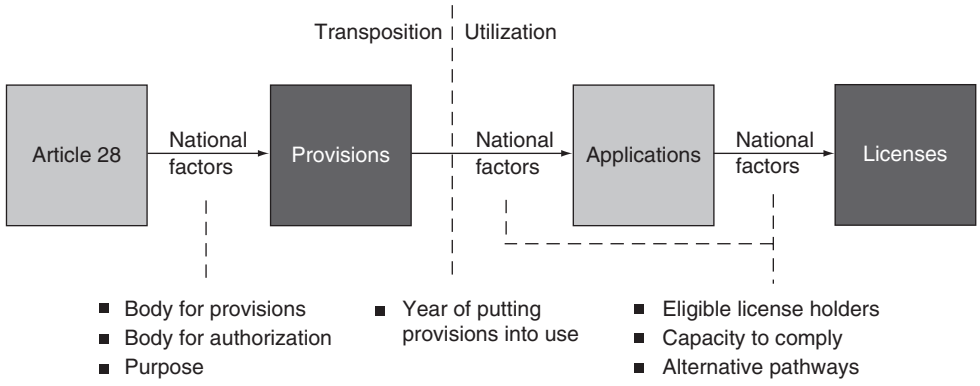

Figure 1. Schematic chronological representation of the Hospital Exemption implementation process.

Data collection

Regulatory documentation

The websites of the competent authorities of the selected countries were used to search for information on national licensing provisions for the HE [25–33]. We defined national licensing provisions as all legislative regulations, guidance documents and procedural forms, including law, royal decrees, regulations, guidelines and application forms. If information on provisions was not available in English or Dutch, Google Translate was used to translate documentation from other languages into English. Documents were investigated in May–August 2018. If multiple versions of documentation (e.g., guidelines and application forms) were available, the most recent version was used for analysis.

Interviews

Invitations for interviews were sent to senior employees of the inspectorate and national regulatory authorities per selected country. The most suitable interviewee for the interview within the main responsible body for the HE was identified through email contact. We conducted nine interviews in total, with one (AT, BE, FI, DE, ES and UK), and three (NL) ATMP experts of the competent authorities, respectively. The competent authorities of FR and IT were unavailable for interviews. All interviewees were senior ATMP experts within their national regulatory agency for medicinal products and had first-hand experience or knowledge on the implementation process and HE authorizations.

A semi-structured interview guide was used (Supplementary Material 1) to discuss and verify national provisions for the HE (outcome of transposition phase) and HE utilization (outcome of utilization phase), as well as to discuss how national characteristics of the implementation process contributed to these outcomes from a regulatory perspective by asking questions on the transposition process, the context in which provisions emerged and on utilization (Supplementary Material 1). Oral consent for recording was sought before interviews were started, and anonymity was ensured to the interviewees. Interviews were conducted between June and October 2018, and fully transcribed. Reported information in this study was verified with the interviewees in July 2019.

Data analysis

National licensing provisions

The national licensing provisions laid out in regulatory documentation were grouped into four main categories: scope, eligibility criteria, data entry requirements and process standards (Supplementary Table 1). Each provision category was assessed on a number of specific aspects that were defined based on previous work [34] and knowledge of the design and functioning of regulatory pathways. Assessment was first done based on regulatory documentation and then verified using information from the interviews. To compare provisions across countries, we distinguished between: provisions that are the same in each country and directly originate from Article 28 (e.g., process standards for manufacturing); provisions that varied among countries, but still originated from Article 28 (e.g., 'preparation on a non-routine basis' and 'preparation of custom-made products for individual patients'); and additional provisions that differed among countries and did not directly originate from Article 28 (e.g., data entry requirements).

Table 1. Article 28 provisions.

Category	Provision
Scope	Nonroutine processing Custom-made product for individual patient
Eligibility	Delivery on individual medical prescription Treatment in hospital No export
Data entry requirements	Nondefined
Process standards	National traceability regulations National pharmacovigilance regulations Manufacturing & quality equivalent to ATMP authorization pathway (regulation 1394/2007)

ATMP: Advanced therapy medicinal product.

HE license holders

Data on regulatory experience with HE licensing were captured in terms of whether applications for HE licenses were filed (yes/no), and amount of authorizations of HE licenses, extracted from the transcripts, tabulated and comparatively analyzed among countries. Additionally, we searched for online regulatory information on HE license holders for all countries to supplement information from the interview transcripts.

National characteristics of the implementation process

National characteristics that played a role in the process of transposition and utilization were qualitatively analyzed in NVivo Pro v11 to shed light on how national variation in implementation contributed to outcomes. We identified national characteristics of the implementation process described in the interview transcripts through an initial round of open coding and grouping of codes (Supplementary Table 2). The coding round revealed the importance of national characteristics on outcomes, and substantial variability among countries. Some characteristics correspond with previously reported characteristics in literature (e.g., existing legislation, external influence, year of implementation and other exemption pathways) [15,16,19], yet, others were grouped entirely in an inductive manner (e.g., intended purpose).

Due to the large variability of identified implementation process characteristics, we performed an axial round of coding to identify characteristics that were commonly described by all competent authorities in relation to the studied outcomes. Three characteristics of the implementation process were frequently mentioned in relation to national provisions: the body for drafting the provisions, the body for HE authorization within the national competent authority and the intended regulatory purpose of the HE. Three characteristics were frequently mentioned in relation to the outcome of HE authorization: the eligible license holders, their capacity to comply with national licensing provisions and the availability and preference to manufacture noncentrally licensed ATMPs under alternative pathways. The characteristics and their values per country were extracted from NVivo in order to perform a comparative analysis of characteristics of the implementation process and their association with studied outcomes among countries.

Results

National licensing provisions for the HE

National licensing provisions for the HE vary among selected EU countries. We distinguish between provisions originating from Article 28 that are the same in each country, provisions originating from Article 28 that vary among countries and additional provisions not originating from Article 28 that vary among countries.

Nonvariable provisions

Article 28 imposes some licensing provisions for the HE that are fully transposed into national provisions and implemented in the same way across the studied countries. These provisions entail ATMP manufacture by delivery on prescription, for treatment of individual patients in hospitals under the responsibility of medical practitioners, no export of manufactured ATMPs, and compliance with quality requirements for ATMPs equivalent to centralized authorization pathways and national regulations for traceability and pharmacovigilance (Table 1). All selected countries fully transposed these Article 28 provisions into national provisions, except for FR. For nonpharmaceutical establishments in FR, adherence to GMP guidance suffices in order for these establishments to meet GMP

requirements over time. In all other selected countries, compliance with GMP regulations is mandatory. Extensive manufacturing and quality data are mandatory in all selected countries to enter the HE pathway (Table 2). Furthermore, all countries incorporated national provisions for traceability and pharmacovigilance that are similar to regulations for pharmaceuticals (not shown).

Variable provisions

Other provisions showed more variability on a national level (Table 2). Some Article 28 provisions were not transposed into clearly defined provisions in all selected countries in particular for 'preparation on a non-routine basis' and 'preparation of custom-made products for individual patients'. Five countries (BE, NL, FI, DE and UK, and not AT, FR, IT and ES) provide guidance in their provisions to what could be considered 'preparation on a non-routine basis'. These revolve around manufacturing on a scale similar to first-in-man trials (BE), small scale manufacturing for few patients (NL), nonindustrial manufacturing (FI), products for which a full benefit/risk evaluation under commercial trajectories is not possible (DE) and scale of manufacturing in comparison with other manufacturing activities (UK). There were no defined limitations on the number of patients that can be treated under a HE license, except in NL (ten patients per year, or a maximum of 50 patients per year for renewed licenses). Yet, all interviewees indicated that 'non-routine' was interpreted as ATMP manufacturing for treatment on a small scale in hospitals, which is evaluated on a case-by-case basis. Whether ATMP manufacturing under a HE license remains within the scope of 'non-routine' is re-evaluated over time based on mandatory annual reporting that includes scale of manufacturing and patient treatment in all selected countries (Table 2). None of the authorities described revoking HE licenses due to large-scale manufacturing.

Additional provisions

Article 28 was supplemented with additional provisions in all countries, except for the UK. Across countries, several provisions in various combinations were described that are part of assessment procedures and relate to: whether clinical evidence is required for a HE license, the type of eligible license holders (hospitals/public, unrestricted), restrictions when alternative treatment for the same indication (licensed pharmaceuticals, including but not limited to ATMPs) is available to prevent competition and whether manufacturing under a HE is required to target an unmet medical need (Figure 2).

BE, DE, NL and ES have stringent clinical data entry provisions for the HE. All available clinical data are required in order for the authorities to perform a preliminary benefit/risk assessment. Assessment for licensing follows similar principles to benefit/risk assessments in other authorization pathways. However, less robust data can suffice to assess benefits and safety for patients, based on case-by-case considerations. In NL, established safety suffices for authorization. On top of these clinical data provisions, the product should target an unmet medical need and restrictions are in place when licensed pharmaceuticals are available in BE and NL. In ES, only hospitals are eligible to apply for a HE license. German provisions have stringent clinical data entry provisions, but do not impose further restrictions (Figure 2).

There are five countries where HE licenses can be granted without clinical evidence: AT, Fl, FR, IT and the UK. Clinical data can be submitted if available. However, other additional provisions were implemented to restrict the use of the HE. In FR, HE license applications without clinical data need to target an unmet medical need and no other licensed pharmaceuticals should be available. Targeting unmet medical need is required for licensing in AT, Fl and IT as well. In Fl and IT, licensing is further restricted when other licensed pharmaceuticals are already available (regardless of clinical data availability). At last, HE licenses are only granted to hospitals and public institutes in AT and IT, respectively. The UK is the only selected country where HE licenses can be granted without clinical evidence and without additional provisions (Figure 2).

HE license holders

Whether HE authorizations were granted and the amount of HE license holders varied between the selected countries as of June 2018. The number of HE license holders was relatively high in FR [35], DE [36] and NL (Table 3). In FR, there are 11 public facilities that hold one or two types of HE licenses (HE authorization under a national product authorization, and/or under a clinical trial framework) to manufacture HE products [35]. There were seven HE license holders in DE, of which most were companies (n = 6). There was one company that holds two HE licenses [36]. In NL, the number of HE license holders was relatively large (n = 11), of which most were academic hospitals and public facilities (n = 7). Dutch license holders may hold several licenses for individual

Table 2. Variable and additional national provisions for the Hospital Exemption, per selected country.

	AT	BE	FI	FR	DE	IT	NL	ES	UK
Scope									
Nonroutine/custom-made product	Nondefined	Guidance	Guidance	Nondefined	Guidance	Nondefined	Guidance	Nondefined	Guidance
Number of patients	Nondefined	Nondefined	Nondefined	Nondefined	Nondefined	Nondefined	10/50 patients	Nondefined	Nondefined
Duration of license	Nondefined	1 year	Nondefined	5 years	Nondefined	Nondefined	1 year	3–5 years	Nondefined
Annual reporting	Required	Required	Required	Required	Required	Required	Required	Required	Required
Eligibility									
Eligible license holders	Hospitals	All	All	All	All	Public institutes	All	Hospitals	All
Restricted when licensed products are available	No	Yes	Yes	Yes[†]	No	Yes	Yes	No	No
Medical need considerations[‡]	Yes	Yes	Yes	Yes[†]	No	Yes	Yes	No	No
Data entry requirements									
Manufacturing & quality	Required	Required	Required	Required	Required	Required	Required	Required	Required
Clinical	Not required	Required	Not required	Not required	Required	Not required	Required	Required	Not required
Process standards									
GMP compliance	Required	Required	Required	Not required[§]	Required	Required	Required	Required	Required

[†]When clinical data are not available.
[‡]Refers to whether the competent authority considers medical need justifications in their decision making for authorization.
[§]Not required for non-pharmaceutical establishments only.
AT: Austria; BE: Belgium; DE: Germany; ES: Spain; FI: Finland; FR: France; IT: Italy; NL: Netherlands; UK: United Kingdom.

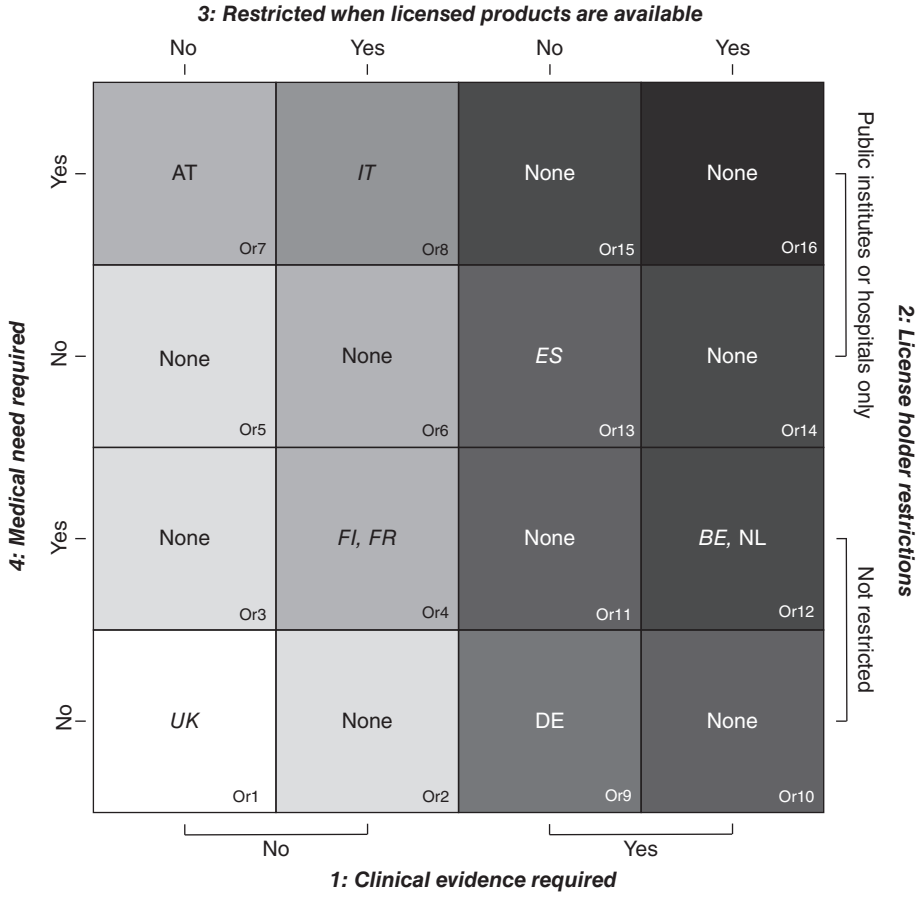

Figure 2. Additional provisions for the Hospital Exemption in selected countries. Shading from white (Or1) to black (Or16) depicts the increasing stringency of the combination of additional provisions. Or1 depicts no clinical data, no additional provisions; Or2,3,5 depicts no clinical data, one additional provision; Or4,6,7 depicts no clinical data, two additional provisions; Or8 depicts no clinical data, three additional provisions; Or9 depicts clinical data, no additional provisions; Or10,11,13 depicts clinical data, one additional provision; Or12,14,15 depicts clinical data, two additional provisions; and Or16 depicts clinical data, three additional provisions. Italic depicts detailed regulations (including decrees), no italic depicts Article 28 transposition into law combined with practical guidance.
AT: Austria; BE: Belgium; DE: Germany; ES: Spain; FI: Finland; FR: France; IT: Italy; NL: Netherlands; UK: United Kingdom.

Table 3. Hospital Exemption authorizations and applications in selected countries.

Country	Authorizations (n license holders)	Applications
Austria	No	No
Belgium	No	No
Finland	Yes (2)	Yes
France	Yes (11)	Yes
Germany	Yes (7)	Yes
Italy	Unknown†	Unknown†
Netherlands	Yes (11)	Yes
Spain	No	Yes
United Kingdom	Yes (1)	Yes

†Authorities were unavailable for interviews.

Table 4. Overview of national characteristics and outcomes of the implementation process.

Country	Transposition national factors			Outcome	Utilization national factors				Outcome
	Body for drafting provisions	Body for authorization	Purpose	Provisions†	Year of putting provisions to use	Eligible license holders	Capacity to comply	Alternative pathways	Amount of license holders‡
Austria	■	•	•	•	2017	•	□	■	○
Finland	◙	◙	•	•	2009	■	□	□	□
UK	■	•	•	○	2010	■	■	■	□
Belgium	□	□	□	■	2017	■	□	□	○
Netherlands	◙	◙	□	■	2010	■	■	□	■
Germany	■	□	■	□	2010	■	■	□	■
Spain	□	□	■	■	2014	•	□	■	○

†Reflects national provisions during May–October 2018.
‡Reflects Hospital Exemption license holders during Jun–Oct 2018.
Transposition: Body for drafting provisions: ◙ = Inspectorate in collaboration with regulatory authority, □ = Regulatory authority, ■ = Ministry in collaboration with regulatory authority and/or inspectorate; Body for authorization: • = Inspectorate, ◙ = Inspectorate in collaboration with regulatory authority, □ = Regulatory authority. Outcome: Purpose: • = Unmet medical needs, □ = Unmet medical needs and benefit and safety, ■ = Benefit and safety and innovation; Provisions: ○ = No clinical evidence required, no additional provisions, • = No clinical evidence required, with additional provisions, □ = Clinical evidence required, without additional provisions, ■ = Clinical evidence required, with additional provisions.
Utilization: Year of putting provisions to use: (year); Eligible license holders: • = Hospitals only, ■ = Not restricted; Capacity to comply (with provisions): □ = Limited capacity, ■ = Capacity by eligible license holders; Alternative pathways (regulatory pathways for noncentrally licensed products): □ = No alternative pathways preferred or available, only other pathway is clinical trial, ■ = Use of alternative pathways; License holders: ○ = None, □ = Limited, ■ = Relatively high.

products per facility, which need to be renewed each year. There were relatively few HE license holders in Fl (n = 2, public) and the UK (n = 1, public). In ES, none of the HE applications had been authorized. In AT and BE no applications had been received by the authorities. Some authorities indicated few applications were under evaluation or expected in the near future. The number of authorizations in IT is unknown (Table 3).

National characteristics of the HE implementation process

The implementation process for the HE differed across countries. Interview respondents described national characteristics related to the process of transposition, alignment with existing national legislation and the perceived need for and capacity to comply with the HE by national manufacturers. Supplementary Table 2 provides a comparative overview of all characteristics described by interview respondents.

Interview respondents also described discussions on the kind of manufacturing activities that were deemed suitable for the HE from a regulatory perspective. Discussions on suitability led to an intended regulatory purpose for the HE in each country as perceived by the interviewees. The purpose was described as playing an imperative role in the drafting of national provisions. Across countries, several purposes were described in various combinations: to fulfill unmet medical needs, to provide treatment of sufficient benefit and safety (i.e., benefit/risk balance) and to collect data for central authorization (innovation pathway) (Table 4). The competent authorities of FR and IT were unavailable for interviews, and therefore, not described below.

Across countries, the intended purposes were different depending on the bodies that were responsible for the transposition and/or granting of licenses. When inspectorates were mainly involved in transposition and responsible for granting licenses, the purpose of the HE was focused on manufacturing for unmet medical needs (AT, FI and UK). In contrast, when regulatory authorities were involved in transposition and the drafting of licensing provisions, and/or when they were responsible for granting licenses, the purpose of the HE was also focused on treatments of sufficient benefit and safety (BE, DE, ES and NL) (Table 4). Furthermore, Article 28 was either transposed into national law with more detailed provisions in guidance documents, or national provisions were transposed into detailed national regulations (Figure 2). These variations illustrate that national political procedures for the transposition of EU legislation differ among countries. Importantly, similar purposes and provisions did not result in the same amount of HE license holders among countries. To allow for a comparative analysis, we group countries with common purposes and provisions, and describe their implementation process characteristics to shed light on differences in the amount of HE license holders among countries (Table 4, & Supplementary Table 2).

Unmet medical needs

In AT, Fl and UK, the HE was intended as a manufacturing license for therapies indicated to treat patients with unmet medical needs (Table 4). Not many additional licensing provisions were implemented (Figure 2), but the amount of license holders is low in all three countries. In AT, implementation occurred relatively late (2017). The lack of applications was further attributed to Austrian drug law, which allows ATMP manufacture in point-of-care settings without centralized oversight. Hospitals were also reported to have limited GMP manufacturing capacity. In Fl, the amount of HE license holders is limited, despite the possibility to manufacture ATMPs for human administration before clinical trial conduct. It was reported that some applications were withdrawn before GMP inspection. Furthermore, in both AT and Fl it was reported that most patients receive ATMP treatment within commercially sponsored clinical trials. In the UK, policy makers had concerns related to the ambiguous terminology in Article 28 and potential competition with licensed pharmaceuticals [37]. This created a general view that the historically used Named Patient Use pathway (i.e., Specials scheme) was better suited to manufacture unlicensed ATMPs for unmet medical needs (Table 4 & Supplementary Table 2). The amount of HE license holders is limited, while there are many public and private facilities that hold a Specials license for ATMP manufacture (~25) [38].

Unmet medical needs & benefit/risk balance

In BE and NL, the HE was intended as a manufacturing license for unmet medical needs when clinical trials or central authorization are not feasible (Table 4). The requirement to demonstrate a preliminary benefit/risk balance means that clinical evidence is required, and other additional provisions are similar (Figure 2). Yet, authorizations were granted in NL, but not in BE. The Dutch inspectorate implemented additional provisions through guidelines and procedures in close consultation with regulators and mostly public stakeholders in 2010. Patients without further treatment options can be treated with ATMPs manufactured under the HE if safety has been established. Capacity to comply with provisions was not considered to be a hurdle for authorization. In BE, regulators drafted a royal decree, which was implemented relatively late in 2017 after a lengthy consultation process. The lack of applications was attributed to stringent clinical data requirements, GMP and quality requirements that are equivalent to the centralized procedure, and a lack of capacity to comply (Table 4).

Benefit/risk balance & innovation

In DE and ES, the HE was intended as a national authorization when clinical trials or central authorization are not, or not yet, feasible, in order to enable patient access to beneficial and safe ATMPs, and stimulate innovation by allowing clinical data collection that can support dossiers for central authorization (Table 4). Provisions are relatively similar, except that license holders are restricted to hospitals in ES (Figure 2). Yet, authorizations were granted in DE, but not in ES. In DE, policy makers extended pharmaceutical regulations to HE provisions, considering that tissues and cells are also regulated as pharmaceuticals. Many applications were filed, but also rejected or withdrawn due to limited capacity to comply with provisions. In DE, HE licenses were granted to companies to manufacture ATMPs that were previously manufactured under tissue licenses, but also for a few new ATMPs. Data collection led to centralized marketing authorization of one HE product [36], which was enabled by German provisions: the HE can be used as a stepping-stone toward centralized authorization, companies are eligible and manufacturing under the HE is not restricted when alternative marketed medicinal products are available. In ES, regulators drafted a royal decree, which was implemented relatively late (2014). Applications were limited and none were authorized due to a lack of capacity to comply with provisions or due to ongoing assessment. Named Patient Use was reported to be used for ATMP manufacture (Table 4 & Supplementary Table 2).

Discussion

In this study we document how the HE has been implemented in various EU countries. Our results show that national licensing provisions vary substantially as a result of discretionary interpretation of Article 28. In some countries, national provisions resemble the basic Article 28 provisions to accommodate ATMP manufacturing for unmet medical needs. In other countries, additional provisions (e.g., clinical data requirements) led to HE pathways that shifted toward procedures for national authorization. Some countries implemented the HE as a stepping-stone for central authorization, while others put restrictions on the HE to prevent competition with licensed pharmaceuticals.

More restrictive provisions are expected to result in fewer HE license holders, but our results indicate otherwise. HE licenses were authorized to accommodate local manufacturing activities in hospital settings [14] in FR and NL,

and to some extent in Fl and the UK, which have varying levels of stringency in their licensing provisions. In DE, mainly companies hold HE licenses to manufacture ATMPs, as well as a few companies in NL. In AT, BE and ES, HE licenses were not granted yet. Limited utilization of the HE was often attributed to limited capacity to comply with provisions (mainly manufacturing, quality and clinical data requirements), implementation delays or to alternative pathways that are preferred over the HE pathway (e.g., UK's Specials scheme).

Transposition of EU legislation is a challenging process; delays are common and national opposition to EU directives may lead to deviations from the original policy [23]. For the HE, the ambiguous terminology and lack of a clearly defined purpose in Article 28 led to discretionary implementation of national provisions among selected countries, which has been a point of critique [10]. Harmonization of national provisions for the HE could provide more regulatory clarity and reduce variety as to how the HE is used among countries in the EU [39,40]. It might also facilitate utilization and availability in some countries that have limited utilization of HE so far. However, harmonization across countries is naturally less aligned with local activities and opportunities [12], and may be beneficial for some countries but not for others. The variety of national provisions of the HE and utilization in clinical practice underline differences in political choices and differences in national innovation system characteristics in terms of, for example, ATMP developers and biomedical knowledge base. From this perspective, national variation can be seen as an outcome of 'boundary work' by national member states to retain competencies and responsibilities at the national level in close alignment with their respective healthcare systems [17].

The regulatory flexibilities that are incorporated in the ATMP Regulation indicate that authorities are searching for justified flexibility from stringent requirements for medicinal product authorization under the centralized pathway, in an attempt to balance the protection of public health and ATMP development and innovation [9,41]. The tension between the need for potentially life-saving treatment and for benefit/risk data is stronger for the HE compared with centralized marketing authorization of ATMPs. Article 28 exempts ATMPs from evidentiary requirements for centralized authorization of ATMPs, with some exceptions such as GMP compliance. These subpar evidentiary requirements have been postulated to put patients at risk [42]. Due to the unmet medical need and scientific uncertainty that is so typical to the ATMP field [1,41], it becomes an ethical question to find the right balance between patient needs versus patient benefits and safety. In clinical practice, patients and healthcare professionals decide whether risks and uncertainties are acceptable considering the prognosis. Yet, authorities have a mandate gatekeeper function to protect patients and society from unacceptable risks [10,42], but also from malicious practices including treatment without benefits [43]. Considering that more comprehensive or confirmatory evidence of a benefit/risk balance, as is required for the centralized pathway, is not required under the HE in all selected countries, it appears justified to safeguard public health and patient safety through the implementation of additional provisions. This regulatory approach particularly suits ATMPs that have close proximity to practices with long clinical history and for which evidentiary support of clinical benefits and safety might already be available such as cultured tissue for severe burn wounds [13,44] or stem cell therapies [8]. Furthermore, it is important to make sure that there is a strong focus on learning while doing in the HE. Further collection of evidence can be achieved through provisions to protect patients and guarantee the monitoring of benefits and risks over a longer period of time (e.g., through registries for long-term follow-up), in particular when larger groups of patients are treated under the HE.

When the ATMP Regulation was implemented, it was feared that its stringent regulations would impair availability of ATMPs in clinical practice, in particular for noncommercial activities by public facilities [8,45,46]. Limited availability may be explained through the notion of institutional readiness to adopt new practices and structures in clinical practice [47,48]. In this study we found limited institutional readiness for the uptake of ATMPs in some countries. Therefore, competent authorities and stakeholders in the field are recommended to collaborate for capacity building for GMP manufacturing, pharmacovigilance, traceability, and quality and clinical data collection in order for eligible license holders to comply with HE provisions and to gear up for compliance with the wider principles of the ATMP Regulation. However, limited institutional readiness to switch from point-of-care settings or manufacturing under national human cells and tissue regulations to HE provisions, is likely dependent on the relative stringency of the HE provisions in comparison with clinical trial regulations and other factors that remain to be confirmed by public facilities. Enabling noncommercial activities in hospitals and access to treatment under the HE, as intended by the EC [9,14], is undermined when stringent data provisions approach requirements for central authorization (e.g., BE).

It has been argued that the HE undermines commercial ATMP development for central authorization, and even impedes patient access in the future if used inappropriately [10,18,39,42,49]. On the contrary, it is questionable whether

it is commercially viable to develop all ATMPs via the central authorization pathway [50]. Not all ATMPs that are administered to humans may be intended for commercial development. The HE could enable manufacturing of particular therapies for which incentives for commercial development are lacking. Our results underline that the distinction between HE manufacturing for noncommercial purposes and commercial innovation has become blurry after national implementation [9], and the tension between noncommercial and commercial activities varies among countries. This tension is most evident in DE where the HE approaches the procedure for national authorization and restrictive provisions are lacking. Together with a relatively large ATMP developer field, the HE facilitates national market entry of ATMPs regardless of centralized ATMP marketing authorizations. Developers that are located in other EU countries cannot use the HE in the same manner. Thus, HE licenses provide a competitive advantage to developers located in DE, compared with developers in other EU countries. ATMP market withdrawals have occurred in the past, and are illustrative of pricing and reimbursement issues in the EU [50,51]. Competition between HE products and marketed ATMPs for reimbursement may lead to future market failures of centrally authorized ATMPs. Thus, even though HE licenses may benefit patients in DE for a short term, it is undesirable to manufacture ATMPs for the national German market under the HE. These practices also seem to conflict with the intended purpose of the EC to regulate ATMP manufacturing within clinical practice that is not intended for the market.

The heterogeneity of ATMPs and the specificity of their modes of action have important implications for how they are best regulated in relation to the commercial value of an individual GCT. GCTs have a 'precision medicines' approach to treat individual patients or subgroups of patients [52]. However, not all ATMPs that target rare diseases are suited for orphan drug designation [15], or they have low commercial value due to limited intellectual property options for example or high risk profiles for development [15,53]. Thus, some may be better regulated within clinical practice settings under the HE. Other GCTs with commercial value are better suited to be transferred to competitive environments in order to facilitate market entry [53,54]. Some central coordinating bodies already provide support to determine the commercial value of GCTs and opportunities for reimbursement, which is best determined in early phases of clinical development [55]. More consideration of commercial aspects in early development, on top of considerations of 'small-scale' manufacturing could facilitate an optimized use of exemption pathways versus pathways for commercial development, in a complementary fashion. However, criteria to determine commercial values are likely to be a moving target because of scientific and technological advance. Although it is reported that certain cell types, including lymphocytes, chondrocytes, dendritic cells and stem cells, have been manufactured under HE licenses [22], transparency on more detailed product characteristics and motivation to manufacture under the HE are lacking. Public registries could increase clarity on HE manufacturing across the EU, and facilitate collaboration and coordination among public facilities and informed decision making for commercial development [39].

Conclusion

In conclusion, this paper showed how the implementation process of the HE and its outcomes in terms of regulatory licensing provisions and the amount of licenses differed substantially among EU countries. The observed differences among countries are closely related to priorities in the implementation process to issues of unmet medical need, benefit and risks, and innovation. It is complex and uncertain to assess what the implications of these prioritizations are for availability, public health and innovation across countries. It is imperative that competent authorities carefully consider and provide clarity for which kind of activities the HE should be used, and monitor how provisions facilitate appropriate use in clinical practice while safeguarding public health and maintaining incentives for commercial GCT development.

Summary points

- The Hospital Exemption (HE) was enacted to accommodate manufacturing of advanced therapy medicinal products (ATMPs) for treatment purposes. However, how its implementation compares among countries of the EU is largely unknown.
- The aim of this study is to compare how the HE has been implemented in nine EU countries focusing on two outcomes: national licensing provisions and the amount of HE license holders. We also document characteristics of the national implementation process, and how characteristics are associated with outcomes.
- National licensing provisions vary for the HE due to discretionary interpretation of Article 28. Authorities considered unmet medical need, benefits and risks, and innovation in various ways for their intended purpose for the HE.
- In some countries, national licensing provisions resemble the basic provisions that were laid down in EU legislation. In other countries, authorities implemented additional provisions that mandate evidence of positive clinical outcomes for HE authorization or provisions that restrict access to therapies under the HE for which licensed alternative treatment is lacking, among others.
- Judged by the amount of public license holders per country, manufacturing of noncommercial ATMPs for treatment purposes is facilitated under the HE in three countries (Finland, France and the Netherlands). For Italy, license holders remain to be investigated.
- Limited national capacity to comply with provisions, implementation delays, and the use of alternative pathways limits utilization of the HE in four countries (Austria, Belgium, Spain and United Kingdom).
- The HE can be used as a stepping-stone toward commercial development in Germany and Spain. Judged by the amount of private license holders and lack of restrictive provisions, the HE has provided a competitive advantage for German developers compared with commercial developers in other EU countries.

Author contributions

Conceptualization of this manuscript was done by DGM Coppens, H Gardarsdottir, P Meij and J Hoekman. Methodology was designed by DGM Coppens, H Gardarsdottir and J Hoekman. Investigation of this study was done by DGM Coppens. The original draft was written by DGM Coppens and J Hoekman. The written draft was reviewed and edited by H Gardarsdottir, ML De Bruin, P Meij, HGM Leufkens and J Hoekman. The supervision of this manuscript was performed by H Gardarsdottir, ML De Bruin, HGM Leufkens and J Hoekman.

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Editorial

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Regenerative Medicine

Technology digest: mitigating cell culture variability with robust screening of raw materials

Freya Leask*,[1]
[1]Future Science Group, London, N3 1QB, UK
*Author for correspondence: editor@regmednet.com

"Monitoring cell culture processes from the earliest stages of process development can generate data and actionable insights. However, cell culture utilizing traditional methods, such as culture flasks or human serum-containing culture media, is limited in scope and utility for future quality control."

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Keywords: advanced therapies • cell culture media • cell therapy manufacturing • good manufacturing practice • process development

Advanced therapies, including cell and gene therapies, are complex biological products that are strongly impacted by the characteristics of the materials and processes involved in their manufacture. These can include biological components, such as allogeneic or autologous cells, ancillary materials, such as culture media and supplements and physical parameters such as mixing rate or culture temperature.

GMP guidelines cover key considerations around manufacturing, including eliminating the risk of cross-contamination and potential presence of disease agents, as terminal sterilization is impossible [1]. Given the inherent variability in biological materials, quality and regulatory requirements for advanced therapies manufacturing necessitate consistency and reliability in documented supply chains and processes. Anyone culturing cells for therapeutic or non therapeutic applications is cautioned "*not to underestimate the 'culture system' as it could impact cell quality and potency*" [2]; therefore, when initially defining a process, and on the occasion of any necessary changes, thorough and verifiable screening must take place to validate a process and the components within it [3].

Optimizing a screening process

Monitoring cell culture processes from the earliest stages of process development can generate data and actionable insights. However, cell culture utilizing traditional methods, such as culture flasks or human serum-containing culture media, is limited in scope and utility for future quality control. In addition, when scaling a process up or out with a view to commercialization, manufacturers will move toward GMP grade materials and methods that can produce advanced therapies of the required quality and at greater volumes and rates.

Speaking to RegMedNet as part of a feature on raw material validation, Patricia Chimot-Marolle, Manager of Regulatory Affairs & Quality Support at Sartorius CellGenix (Freiburg, Germany), explained: "*Slight variations in impurity profiles (e.g., trace elements content), composition or biological activity may lead to unwanted effects like lower expansion rates, or an altered surface marker profile of the cells*" [4]. Therefore, in addition to the usual quality control tests that are performed on the final product to validate quality and identity, any new conditions that enter the production process should be screened to understand the effect they will have on the final product, particularly any risk they may introduce.

Continuing, Chimot-Marolle stated "*it is therefore crucial to establish a production process in which all aspects are controlled, including the quality and source of raw materials, to ensure the desired output*". Understanding and controlling all aspects requires a comprehensive screening methodology, which can be addressed with a framework of acquire, analyze and apply whereby screening data generates actionable insights that can be applied to process

Future Medicine

development. Optimal culture conditions can be devised following comprehensive screening of process components. The most important characteristics to screen for will vary depending on the application of the analyte, in both how it functions and where it features in the production process, but media, reagents and clones should all be characterized.

Multifactor experiments enable large quantities of quantitative and qualitative data to be generated and analyzed to correlate process parameters with critical quality attributes [5]. To complete these studies, high-performance media and reagents that are designed for specific cell types are recommended and can be obtained and validated using vendor provided documents. "*Raw materials should be fit for purpose: therefore, beyond properties like consistency, safety, identity and purity, the functionality also plays a great role in specifications and should be monitored. Release tests that are performed by the supplier should be good indicators of these parameters*", explained Chimot-Marolle.

However, different vendors will use different functionality tests, which are all likely to differ from the specific conditions in an end user's process, so vendor provided testing will serve as an indication of quality rather than confirmation. Use of specific phenotypic and functional characterization is recommended to confirm the identity of the final product, for example a CAR construct that is optimized for a particular marker. Flow cytometry [5] and live-cell analysis, in conjunction with cell-specific kits, have shown promise in characterizing T cells at multiple stages in their manufacturing process [6].

This process and product characterization will therefore give rise to actionable data on the process in question. This knowledge will build the foundation for a clinical translatable protocol that has been developed with the goals of quality and GMP compliance in mind. Using an integrated system, such as the Sartorius Screening Ensemble, seeks to accelerate cell therapy development by: coordinating bioreactor culture with dedicated reagents; incorporating Design of Experiments software to easily design effective and efficient experiments; and facilitating continuous characterization, including the use of live-cell imaging and flow cytometry [7]. By using a closed-loop system, all collected data are easily translated into adjustments to further optimize cell culture and ensure final product quality when scaling into future production [8].

Validated GMP reagents

Controlling sensitive parameters and multiple culture components remains the goal and challenge for fully qualifying raw materials for advanced therapy production. In order to maintain a consistent output, ensuring a consistent source is crucial. According to Chimot-Marolle, "*raw materials of consistent and reliable high quality, sourced from qualified suppliers, are therefore an essential prerequisite for the production of advanced therapy medicinal products (ATMPs)*".

At minimum, the use of xeno- and serum-free medium formulations limits the introduction of additional variability and improves reproducibility, supporting the application of a previously defined process to a large patient population. It also lowers the potential risk from biological disease agents. Media formulations are usually tailored to the needs of specific cell types, increasing fold expansion, transduction efficiency and cell viability [9].

Supporting cell growth with supplements, such as cytokines and growth factors, can further support activation, expansion and differentiation of human cells. By using the appropriately validated grade of cytokines – from preclinical to GMP – qualification and validation can be simplified through vendor provision of purity, potency, consistency and stability documentation [10]. However, Chimot-Marolle cautions, "*. . . raw materials might not be available in the desired quality, or only as research grade materials. In these cases, qualification is more complex and supplier auditing is more critical: therefore, selecting high quality suppliers is a crucial part of raw material qualification*". Nevertheless, using preclinical reagents with GMP grade versions will be beneficial due to lower costs at the preclinical stage as well as a seamless transition to the clinical or commercial phase, lowering overall risk.

A further challenge for cell therapy developers is that the regulatory burden falls more heavily on them to demonstrate consistency, quality and appropriate application of method and raw materials, rather than the raw material vendor [11]. There are also comprehensive guidelines around the manufacturing facility itself. In addition to applying a suitable screening method early on, cell therapy developers can further support their investigational therapy through close dialogue with regulators. A suitable screening method will enable close monitoring of process variables, providing the required evidence of quality strategy to satisfy regulatory bodies [12].

Summary

As therapies become more complex, comprehensive screening is required to fully understand the impact of each variable, and identifying the appropriate quality grade of your materials is even more important. For developers, full

consideration should be given to early process development to avoid variation further down the line. Technological advancements, including turnkey systems and automation [13] along with reliable raw materials inputs, will support closed-loop analytics and in turn reduce contamination and variability risk.

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Review

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Personalized Medicine

State-of-the-art knowledge on the regulation of advanced therapy medicinal products

Patcharaphun Kidpun*,[1], Warit Ruanglertboon[2] & Rapeepun Chalongsuk[1]

[1]Department of Community Pharmacy, Faculty of Pharmacy, Silpakorn University, Sanam Chandra Palace Campus, Nakhon Pathom, Thailand

[2]Discipline of Pharmacology, Division of Health and Applied Sciences, Faculty of Science, Prince of Songkla University, Songkhla, Thailand

*Author for correspondence: patcharaphun_k@yahoo.com

Advanced therapy medicinal products (ATMPs) constitute therapeutic agents based on obtained cells, tissues or genes representing a novel treatment opportunity in medicine. In addition, ATMPs are administered into the cells or tissues of humans from the patient's own cells, donors, or genetically modified cells. Recently, the field of developing ATMPs has become a point of attention due to the clinical efficacy expected in defeating incurable diseases such as cancers and neurodegenerative disorders. Currently, there are two modes regarding the distribution of ATMPs. First, ATMPs that might be legally authorized for marketing. Second, the patients are able to access unapproved ATMPs through the hospital exemption (HE) or clinical practice program or through the compassionate use and expanded access program. The aim of this review is to discuss state-of-the-art knowledge on the regulation of ATMPs and provide regulatory recommendations.

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Keywords: advanced therapy medicinal products • cell therapies • gene therapies • regenerative medicine • tissue engineered products

In the past 2 decades, advances in biomedical and biotechnology research have resulted in novel approaches to addressing numerous health issues. This novel approach combined cutting-edge technologies and innovations such as *in vitro* cellular models, *ex vivo* genome modification and tissue engineering. Due to their complexity, these products can be grouped and categorized as advanced therapy medicinal products (ATMPs). Generally, ATMPs are classified based on the starting material such as genes (gene therapy medical products [GTMPs]), cells (somatic cell therapy medical products [sCTMPs]), tissue-engineered medical products [TEPs]) and the combined ATMPs, which integrate medical devices in adjunct to the cells/genes-based ATMPs. ATMPs have begun to deliver an influential role in public health, particularly in the area of unmet medical needs [1–3]. Various clinical trials have demonstrated significant clinical benefits of specific ATMPs in the treatment of advanced or life-threatening diseases such as cancer, limbal stem cell transplants, neurodegeneration, osteoarthritis and spinal injuries [4–7]. The promising clinical benefits of ATMPs have attracted interest from healthcare providers, both private and government sections. However, some ATMPs showed severe adverse events during the clinical trial and an extraordinary cost, which in turn led to a halt of further development or withdrawal of the product. Currently, there are several authorized ATMPs such as Kymriah®, YESCARTA®, Spherox®, MACI®, TEMCELL HS® and Luxturna™. Depending on the local legal framework, these products may be available only in the selected countries.

However, patients may access the unapproved products through hospital exemption (HE) or clinical practice utilizing a particular medical procedure framework in which the arrangements must be tied in with the certified clinicians. Moreover, it has been observed that many countries provided the access to investigational products to patients in response to the life-threatening situation via well-regulated programs. Such programs were the compassionate use programs and expanded access programs in the EU and the USA, respectively. Notably, the

Future Medicine

aforementioned products/programs were provided only to patients who could not participate in clinical trials or failed to attain the optimal treatment goal [8]. Although patients can access ATMPs through many options, the reported severe adverse events and overpromised medical advertisement have detrimental effects on patients both economically and health-wise. Notably, the area of clinical setting was, potentially, the place where the misuse of the exemption has been seen the most. The clinical setting seemed to be operated with less restrictive accessibility to ATMPs than others where the products must undergo a series of regulatory approval before delivering into the market [9].

The development of ATMPs is, arguably, one of the most perilous journeys in drug development research. As ATMPs are generated using complex technologies, this multifactorial process could intertwine with many challenges during product development or even until post-marketing. Some ATMPs rely strongly on the turnover rate of cell proliferation and differentiation, in which most of them could not be accelerated by any means. Subsequently, once the products are ready to dispatch, a particular logistic arrangement is required. Thus, the total cost from the very start to deliver the ATMP product to patients is likely exceeding a general therapeutic goods benchmark [10–13]. One such example was in the case of Glybera®, an ATMPs product being withdrawn from the EU market due to its exorbitant cost per unit [14]. As a result, ATMPs have not been established in the broad market. Although ATMPs have many challenges and limitations, reports from the Alliance for Regenerative Medicine in 2021 have found more than 1300 clinical trials sites are undergoing the process of testing and development of ATMPs [15]. It is expected that the registration of novel ATMPs will increase in the coming year forward after the end of phase III clinical trials in humans. Thus, ATMPs are at the forefront of medical innovation owing to their complexity and uniqueness. A dedicated regulatory framework for the approval or service of ATMPs is therefore required, which takes into account the risks and benefits for authorizing the product.

Methods

A literature search was conducted to gather published studies/information, mainly from the homepage of the EMA, US FDA and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. The documents available for public access were thoroughly evaluated and collected primarily focused on the licensing, specific licensing schemes and other forms of activity involving using ATMPs as part of the procedure. Additionally, the literature search was also performed via PubMed, Google Scholar and the Web of Science database for other essential articles regarding the development, safety and efficacy of ATMPs.

General information on ATMPs

The interventional process of ATMPs is the primary factor reflecting their uniqueness. Cell-based ATMPs are derived from the cells of human tissues, primarily from patients for constructing 'autologous products', alternatively from healthy donors for allogeneic products [16,17]. Gene therapy is described by the technique of introducing genetically modified genes accompanied by vectors (viral or nonviral) to treat or prevent disease. This technique utilizes the genetic manipulation of the genes of interest combined with patients' cells, then reintroducing them into patients' bodies, a truly personalized treatment. The successful implementation of gene therapy has been observed in hematopoietic stem cells (HSCs), lymphocytes, bone marrow cells and progenitor cells [18,19]. In the last 3 decades, the fast-forwarding advancement of biotechnology has derived multiple improvements in ATMPs research. Such examples have been seen in the refinement of vectorization, enhancement of culture and transduction conditions to accomplish long-lasting and highly consistent effects across patients [20–22]. The nonviral vectors are more favored over the viral ones due to their lower complexity and production cost. Moreover, the nonviral vectors exhibited low pathogenicity, which in turn led to a better safety profile [23,24]. Nevertheless, caution should be made when using this type of product as an immune response secondary to product exposure could occur in each individual.

ATMPs have obtained marketing authorization (MA) in the EU, the USA and Japan. As of April 2021, there are 18, 15 and 9 products available in the US, the EU and Japan, respectively [25–29]. Due to its complexity and marked difference from any other therapeutic goods, ATMPs can be classified broadly into two groups based on the source of the original materials.

Autologous products

Autologous products utilized patients' cells to create remarkably tailor-made ATMPs specific to the patients. This approach provides several advantages, such as minimizing risks from systemic immunological reactions, bioincompatibility and disease transmission associated with grafts or cells from donors [30,31]. Additionally, tissue-

engineered products (TEPs) are also a part of the cell-based ATMPs. A good example of products that fall into this category is Spherox. Spherox is an autologous chondrocyte implantation (ACI) product approved in 2017 in the EU. The product is administered via an intra-articular route to treat and repair cartilage defects of the knees in adults [32–34]. The major components of Spherox are prepared from the patient's chondrocyte extracted by arthroscopy followed by culturing expansion in a GMP facility. Similarly, matrix-induced autologous chondrocyte implantation (MACI) uses the patient's chondrocytes as the major active component to manufacture cell-based ATMPs with indications to regenerate the damaged cartilage in patients. MACI uses a unique matrix membrane derived from porcine sources; thus, it may not be suitable for patients who are allergic to materials derived from pigs or cows. Nevertheless, MACI was being used in the EU and the USA between 2013 and 2016 until its production site was closed due to commercial reasons, not because of its lack of safety and efficacy issues [35].

Another exemplar of a gene therapy product is Kymriah, a lentiviral vector-encoded anti-CD19 chimeric antigen receptor (CAR) agent modified from the patients' T cells, demonstrating sustained efficacy without requiring additional therapy. Pediatrics and young adult patients who suffered from acute lymphoblastic leukemia (ALL) with a history of treatment-refractory and relapse obtained an 83% overall remission rate within 3 months and 66% relapse-free survival during the first 18 months after receiving Kymriah [36]. Thus, the approved indications of Kymriah, are for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic lines of therapy [37–39]. The T cells for producing Kymriah are obtained by leukapheresis technique where the enriched T cells are transduced with a lentiviral vector containing the anti-CD19 CAR transgene. Subsequently, the transduced T cells are expanded using cell culture technique in a GMP facility. Finally, the finished product is finalized as suspension and cryopreserved. Likewise, YESCARTA (axicabtagene ciloleucel) is a CAR-T cell product for treating DLBCL and primary mediastinal large B-cell lymphoma (PMBCL) in adult patients. Eligible patients who received YESCARTA showed an 83% objective response rate (ORR) with a 58% complete remission rate (CR) [40,41]. Although the manufacturing processes are slightly different between autologous products, the shared essence is that the products are made from each individual cell and used for their own treatment. As such, autologous products could be somewhat categorized as 'a truly personalized medicine' [42].

Allogeneic products

Allogeneic products are derived from a single donor or a pool of a small number of donors to provide one large batch for treating multiple patients. Unlike autologous products, allogeneic products are more adjustable to be manufactured on a larger scale, standing as 'off-the-shelf products' [43]. Due to various starting material sources, as the allogeneic product can be derived from many donors. Thus, quality assurance of the materials is the immediate challenge prior to the manufacturing process. Notably, the reaction between the innate immunogenicity of donors to patients is, to a certain degree, the utmost priority during the quality assurance process [44]. An example of allogeneic products derived from stem cells is TEMCELL HS (approved in Canada and New Zealand in 2012 referred to as Prochymal®, and Japan in 2015) [29,45]. The main therapeutic component of the product is derived from human bone marrow-derived mesenchymal stem cells (MSCs). Generally, MSCs are responsible for the tissue repairing process as it possesses high intrinsic capability in proliferation and differentiation. In addition, MSC cells have the characteristics of low immunogenicity, are potent anti-inflammatory modulators, have the capability to accentuate the innate immune response and others, which support their promising role in stem-cell therapy. TEMCELL HS demonstrated the achievement of a 50% complete response within 6 weeks after the first infusion with more than a half reduction of the dose steroid used within 8 weeks. Thus, TEMCELL HS was approved for acute graft-versus-host disease (aGVHD) after hematopoietic stem cell transplant [45–47].

The other type of allogeneic product is in the form of gene therapy. Generally, gene therapy requires a vector, as a carrier to orient to the target cells/organs of patients, by the *ex vivo* or *in vivo* method. *Ex vivo* gene therapy, a technique of adjustable genetic manipulation inserted into patient's own cells the process of which is outside the body. Then, modified cells' genetics are given back to the patient through a vein. On the other hand, *in vivo* gene therapy modifies genes directly and transform abnormal to normal working genes which will be delivered into patients. This medical procedure is not related to the cells of specific patients, therefore, it can be used with any patients regardless of whether they have genes related to certain diseases [20]. Additionally, the viral vectors technique utilized in gene therapy must be initially performed as a pre-treatment process to reduce the immunogenicity. Such techniques include a reduction of vector concentration, capsid modification and optimizing the transgene expression profile. The level of immunogenicity would directly determine the safety, efficacy and efficiency in carrying the transgene when used in patients.

Currently, the availability of *in vivo*, viral vector-based gene therapy that has been authorized in USA, the EU and other countries includes Imlygic®, Zolgensma® and Luxturna. However, an extended monitoring program to observe the immune hypersensitivity is still in place following the administration of the products. Likewise, *ex vivo* gene therapy developments have put the highest caution toward immune hypersensitivity. Research conducted in animal models and, to a lesser extent, in clinical studies have seen numerous grievous adverse events, highly likely to arise from immune-related reactions. Hence, the biggest hindrance of producing gene therapy, notably the vector experiment, is handling the immunogenicity accompanied by the products.

Although the novel biomedical products have been named differently, such as biologic drugs (USA), regenerative medicines (Japan) and ATMPs (EU, Thailand and Brazil), they present new curative possibilities for a range of, so far, untreatable diseases [48–51]. Unquestionably, patients who suffered from a life-threatening disease or poor prognosis in the longer term, such as cancers, genetic disorders, osteoarthritis, particularly in areas of previously untreatable illness, would gain health benefits from accessing ATMPs. On the other hand, it has been observed that some ATMPs showed a lack of efficacy, and some produced serious adverse events following product exposure [52]. As such, the registration scheme of ATMP products should be a well-customized scheme, anticipating atypical product characteristics of ATMPs compared with other standard therapeutic goods. This includes the adaptability of the program to invent a product-specific registration track as each ATMPs behave distinctively. Regulation of ATMPs can be categorized into two main approaches as shown below.

Medicinal products for human use

The regulatory authority in each country/region controls this category, such as the FDA, the EMA and the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act) in Japan. Also, The National Health Brazilian Agency (Anvisa) in Brazil. ATMPs are classified as medicinal products or known as special medicine in Brazil based on legal definitions and therefore require a marketing authorization to reach the market and patients. They need to fulfill the requirements of the medicines legislation in each country/region. For example, the regulation no.1394/2007/EC – 'ATMP Regulation' was specifically formulated to control ATMPs in the EU [53]. In the USA, the regulations that apply to ATMPs are Title 21 of the Code of Federal Regulations (CFR) part 600–680 under the Food, Drug & Cosmetics Act (FDCA) and section 351 of the Public Health Service (PHS) Act [54]. Meanwhile, the PMD Act is the core principle of the current regulatory framework for ATMPs in Japan (ATMPs are called regenerative medicines in Japan) [49,50]. Moreover, classification of ATMPs in Brazil is divided into two main subclass, class I and class II products. Class I product's are described as advanced cellular therapy product's presented to minimal manipulation and are non-homologous that intended to not the same function from the donor to receipt. In comparison, class II product's are described as advanced cellular therapy product presented to extensive manipulation, tissue engineering product and gene therapy product. Noticeably, the definitions used in describing the ATMPs products in Brazil and the documentation regarding safety and efficacy profile are similar to those used by the FDA, the EMA and Japan. The only slight difference between Brazil and the others is that the regulatory agency in Brazil implements more details in classification within the cell-based therapy group [55,56].

Furthermore, developers of ATMPs and sponsors of clinical trials have to adhere to regulatory requirements for the manufacture and demonstration of quality, nonclinical/clinical safety and efficacy. Those requirements are generally aligned with the GMP, GLP, GCP and Good Review Practice (GRP). Subsequently, successful product approval must be continually monitored as part of the post-marketing program using the protocol suggested by Good Pharmacovigilance Practices (GVP). Although not specifically developed for ATMPs, these products have been able to take advantage of dedicated approval schemes for medicinal products providing exceptional clinical benefits, especially in situations of unmet medical needs.

Expedite program

The expedite program was set for a new drug or novel medicine intended to treat a severe condition that has demonstrated the potential to address an unmet medical need. As such, the main objective of the expedite program is to offer early and proactive support to medicine developers to optimize data generation based on the risk and benefit of the product to patients. This type of program has been observed in many countries such as Fast Track Designation and Breakthrough Therapy Designation in USA [57,58], the PRIME program [59,60], Adaptive Pathways in the EU [61] and SAKIGAKE Designation system in Japan [62]. Further acceleration can be provided by accelerated assessment of marketing authorization submissions, priority review or rolling review.

Conditional approval

The conditional approval or accelerated approval can be granted for a product that has demonstrated a positive benefit–risk, in which the further data are mandated to submit afterward [58,60]. The conditional marketing authorization may be withdrawn anytime if the post-marketing obligations are not fulfilled.

Specific licensing scheme for ATMPs or RM

Specific licensing scheme for ATMPs or RM is the scheme developed mainly for a particular circumstance. The scheme considers the importance of the length of time the product would be available for highly vulnerable patients, such as patients in a critical health condition or currently incurable diseases. Thus, the product would be readily approved under this scheme as soon as the safety and efficacy have reached an adequate standard. Notably, the countries that adopted this particular scheme were Japan and the USA. In Japan, the specific licensing scheme was established under the PMD act. The PMDA was promulgated in 2013 due to the preceding Pharmaceutical Affairs Law (PAL) did not include the regulation of regenerative medicines. Under the PMD act, regenerative medicine products will be subject to conditional or time-limited approval after safety and efficacy are confirmed or sufficiently evaluated. Subsequently, post-marketing surveillance is required for products after successful launch into the market. Generally, the criteria for specific licensing approval include:

- It meets the definition of regenerative medicine therapy;
- Significant promising results in the early phase for registration trials in terms of efficacy and safety;
- Sponsors are obliged to conduct post-marketing clinical studies to reassure efficacy and safety. Generally, post-marketing application submission to support the subsequent full license evaluation must be submitted within 7 years after its first launch [49].

Similarly, the USA established the Regenerative Medicine Advanced Therapy Designation (RMAT) in 2016 under the 21st Century Cures Act. The primary task of this designation is to facilitate a more comfortable, fast-forward and reduced cost for the manufacturers to submit their products [63]. The eligibility criteria for RMAT designation as following [58]:

- It meets the definition of regenerative medicine therapy, which requires more than minimal manipulation of human cells or tissues or/and heterologous use and gene therapies. Further details can be found in section 361 of the Public Health Service Act and 21 CFR part 1271 [64];
- It is intended to treat, modify, alleviate or cure serious disease conditions;
- Preliminary clinical evidence indicates that regenerative medicine therapy has the potential to address unmet medical needs.

RMAT has more flexibility than the Fast Track and Breakthrough Therapy Designation as it has no obligation to demonstrate the substantial improvement of the efficacy over the existing therapies. RMAT only requires a demonstration that the product would very likely address the unmet medical needs, which could subsequently be proven in the post-approval stage using real-world evidence. In contrast, Fast Track and Breakthrough Therapy Designation require supporting information regarding the clinical benefit over the current treatment options [58].

Generally, some ATMPs could produce long-lasting biological effects in patients, although the products undergo a single administration. As such, it is possible to encounter adverse events after ATMPs administration; however, the time to events is likely to depend on the type and specific ATMPs. For example, stem cell-based ATMPs may derive delayed events as the cells' proliferation period require a certain amount of time to achieve the process of proliferation and differentiation. Therefore, stem cell-based ATMPs could develop into inappropriate cell types or multiply unexpectedly, resulting in adverse events [65–67]. Furthermore, the traditional approach of predicting pharmacokinetic profiles such as physiologically based pharmacokinetic modeling (PBPK) and population pharmacokinetics (PopPK) is not applicable for ATMPs due to their peculiar nature. Thus, it is of the highest importance in formulating the monitoring scheme for ATMPs products to promote post-marketing efficacy and ensure continued safety. The EMA suggested a 2-year close monitoring program for the cell and gene-based therapy after exposure to the products [66,68]. However, monitoring could increase up to 5 years in the case of gene-based therapy. This moderately long monitoring period was determined to be timely and sensible in response to the probability of long-term adverse effects derived from the novel biologic products. Consequently, the personalized vigilant scheme will be placed after completing the primary monitoring program depending on the characteristics of each product

and patients' conditions. Potentially, the record of ATMPs batch numbers could be integrated into patients' registry or anyone in the household contact for further monitoring programs. In addition, the EMA also suggested that the follow-up period should commence prior to product exposure, followed by 3, 6 and 12 months after the first exposure [69]. For the FDA, the recommendation for the monitoring program is to be extended up to 15 years since the first exposure [65,70]. This long-term monitoring program is divided into initial and continuing periods. Of the two periods, the initial period is focused on regular physical examination, once a year for at least 5 years consecutively. Subsequently, the continuing period would focus on general well-being in which telephone queries and face-to-face questionnaires are implemented until achieving the total of 15 years of the monitoring period. Hence, the extended follow-up scheme is highly likely appropriate for monitoring ATMPs products as it would be useful in the detection and prevention of any delayed adverse reactions.

ATMP exemption from the medical legislation

ATMP exemption from the medical legislation is a component of the treatment intervention with ATMPs such as HE, clinical practice in the dedicated institutions and Compassionate Use and Expanded Access Program. In addition, the intervention has to be conducted by the exclusive, professional responsibility of a medical practitioner as a mandatory requirement to comply with an individual therapeutic prescription for a specialized product for each individual [71]. Further described as:

Hospital exemption

HE has a scope of using ATMPs as 'prepared on a non-routine basis according to specific quality standards and used within the same member state in a hospital under the exclusive, professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient' [53]. Therefore, HE can, relatively, be an exemption for accessing ATMPs under the conditions that the intended-to-use products are restricted only per requested individual, not producing on an industrial scale and restricted distribution around the member countries. Upon the approval of the EMA, the manufacturing of ATMPs registered with HE could proceed on the condition that they are abided by the regulatory framework of the designated country [72]. Although a slightly lenient regulation of HE compared with the other accessibilities of ATMPs, a monitoring program as part of the pharmacovigilance is still required. Such programs must be harmonized across the EU members and aligned with the code of Directive 2001/83/EC and Regulation (EC) no 726/2004. On the other hand, HE has the potential of facilitating innovation and patient access. These differences have created parallel paths to market access as well as diverse approaches that are used between member states for HE authorization. Thus, the approval process of HE to access ATMPs could be very heterogeneous among EU members. Some countries may promptly approve HE based on a few safety and efficacy documents, but some may require multiple data in various paradigms before granting the HE which may prolong the time to fulfil all requirements. As such, it could derive an uncertainty as to the time-to-access ATMPs of patients, which will be highly likely to impede their quality of life.

Clinical practice or medical procedure in dedicated institutions

The other type of exemption of ATMPs is employing ATMPs as part of medical interventions. More importantly, this operation ought to be conducted only in the dedicated institution and qualified practitioners. Such established operation has been observed in Japan under the scope of the Act on the Safety of Regenerative Medicine (ASRM regulation). ASRM was enacted in November 2013 and came into effect the following year. Initially, the idea of designating ASRM was due to a domestic fatal adverse event resulting from cell therapy [73,74]. ASRM enforces regulations to cover any partakers that propose developing stem cell-based interventions (SCBIs) or utilizing the product, including physicians, medical/educational institutes and cell production facilities. On the other hand, although the regulations under ASRM are expansive in covering many essential paradigms of using ATMPs, the application of ATMPs by physicians could be the pitfall of the entire process. As ATMPs are considered a novel product both in their mechanism of medicinal action and manufacturing procedure, products administration required honed medical skills. A GCP framework could be an exemplary protocol to practice ascertaining the consistency of physicians between clinical sites. More importantly, the ATMPs delivered to patients via this option could also involve unapproved ATMPs; the possibility to develop unexpected adverse events should be assessed. Such examples were reported both in fatal consequences and irreversible organ dysfunction.

Compassionate use & expanded access program

Compassionate use program (CUP) and expanded access program (EAP) are the alternative pathways for patients who experience aggravate symptoms, unattainable treatment satisfactory or an exclusion criterion for any clinical trials of ATMPs. A successful CUP has been established in the EU as referred to the Directive 2001/83/EC and Regulation (EC) no 726/2004 in accordance with the article 83 of 726/2004 as 'a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product'. The medicinal product concerned must either be the subject of an application for a marketing authorization or must be undergoing clinical trial. Similarly, the FDA established the EAP, which has the major responsibility resemble CUP of the EMA. These two programs share several common eligibility criteria, such as suffering from an incurable disease, being under a life-threatening situation due to aggravated diseases and certified supporting documents from the medical agency in the country of residence. On the other hand, EAP has no restriction to any form of ATMPs, including medical devices, but CUP allows only the category of pharmaceutical products to be used in the program. Nevertheless, ATMPs used in these two programs are investigational drugs in which the product authorization has not been completely granted. An intensive monitoring program is needed to apply in these two programs as uncertainties are very high, either risk of developing adverse events or loss of efficacy earlier than expected.

Conclusion

ATMPs are the most anticipated group of innovative medicinal products aiming to address life-threatening or incurable diseases. As such, ATMPs have become an excellent candidate as adjunctive therapy in clinical practices which could widely impact prospective treatment strategies. The ability to access ATMPs either in medicinal products or ATMP exemption would derive a better health benefit to patients, and eventually increasing their quality of life. Nevertheless, some ATMPs might lead to severe adverse events, or lack of efficacy leading to treatment failure. The regulatory body of each country that plans to establish ATMPs legislation should consider the uniqueness of the product, safety and appropriate pharmacovigilant program following product exposure as part of the framework. In addition, this new legislation must be well-applicable regarding the context of socioeconomics and ethical perspectives per the designated country.

Future perspective

ATMPs have shown a promising opportunity to personalize medicine for each individual, especially when traditional treatment approaches are insufficient to mitigate the disease progression. However, the burden of the extraordinary cost of ATMPs, particularly autologous products, prohibits accessibility for many patients. Thus, to overcome the difficulty, one of the primary tasks that must be performed quickly is advancing research and technology. Currently, most ATMPs available are the type of autologous product in which the expenditure per person is significantly higher compared with allogeneic products. Ideally, with the advancement of technology in the near future, most ATMPs should be able to be constructed as the type of allogeneic products. Theoretically, this technology transformation would lower the high cost of ATMPs due to less complexity in handling the manufacturing and logistics processes. Notably, addressing immunogenicity is of the utmost importance driving forward in developing allogeneic products. Second, the exemption of accessing ATMPs under dedicated clinical institutions in different registration modules still needs to be appropriately regulated. This is to ensure the monitoring programs are in place for short-term to long-term vigilant programs of patients who receive ATMPs from this approach. On top of those two critical points mentioned above, consideration down to the process of approval timeframe of the products, subsidiary scheme and further support from the government are, besides, needed to be reviewed in parallel. Thus, policymakers in each country must meticulously take into account all of these aspects to develop the most pragmatic use of ATMPs that suits the public health and general wellbeing developmental framework.

Executive summary

General information on advanced therapy medicinal products

- Advanced therapy medicinal products (ATMPs) are classified into four groups according to the EMA as genes (gene therapy medical products) or cells (somatic cell therapy medical products) or tissue-engineered medical products) or Combined ATMPs related to medical devices.
- ATMPs are classified into two groups based on sources of the product as whether autologous or allogeneic product.
- The first is autologous product, from which cells of individuals and specific patients are used. There are numerous benefits of this approach the minimization of risks from immunological reactions and bio-compatibility.
- The second is allogeneic product which come from a single volunteer donor or a group of donors or *in vivo* virus vector with gene therapies that allogeneic product can be largely manufactured scales and less complex logistics. However, an immune reaction and hypersensitivity are still concerned.

Concept of regulation for ATMPs

- Regulation of ATMPs can be categorized into two main approaches as medicinal products and exemption from the medicine legislation.
- First, medicinal products for human use (controlled by the national regulatory authorities) must be approved before launching. Moreover, many countries laid down the approval schemes for ATMPs positive clinical benefits, especially in situations of unmet medical needs, such as Fast Track Designation, Breakthrough Therapy Designation, PRIME program, Adaptive Pathways and SAKIGAKE Designation system for offering early and proactive support for development and the Conditional approval. In addition, some countries have designed specific licensing scheme for ATMPs or RM as time-limited approval, RMAT in Japan and the USA, respectively.
- Second, ATMPs exemption from the medicine legislation. For instance, HE is exceptions from the Regulation (EC) no 1394/2007, when an ATMPs is not purposed to free distribution or produced industrial scale around the EU and clinical practices in medical institutions are controlled by the exclusive clinician. Also, Compassionate Use and Expand Access Program have been provided for life-threatening conditions or unsatisfied treatment to patients who cannot enroll into the clinical trials that two programs are investigational drugs before licensing.

Discussion

- ATMPs have proved their critical value as novel therapeutic goods to address unmet medical needs in recent years. However, serious side effects have remained.
- Therefore, long-term monitoring is needed. Especially within clinical settings, as these often exaggerate the advancements of products and rely on those from other agencies with less stringent approval processes.
- Thus, regulatory bodies shall formulate the requirements to ensure safety and efficacy within medical institutions.

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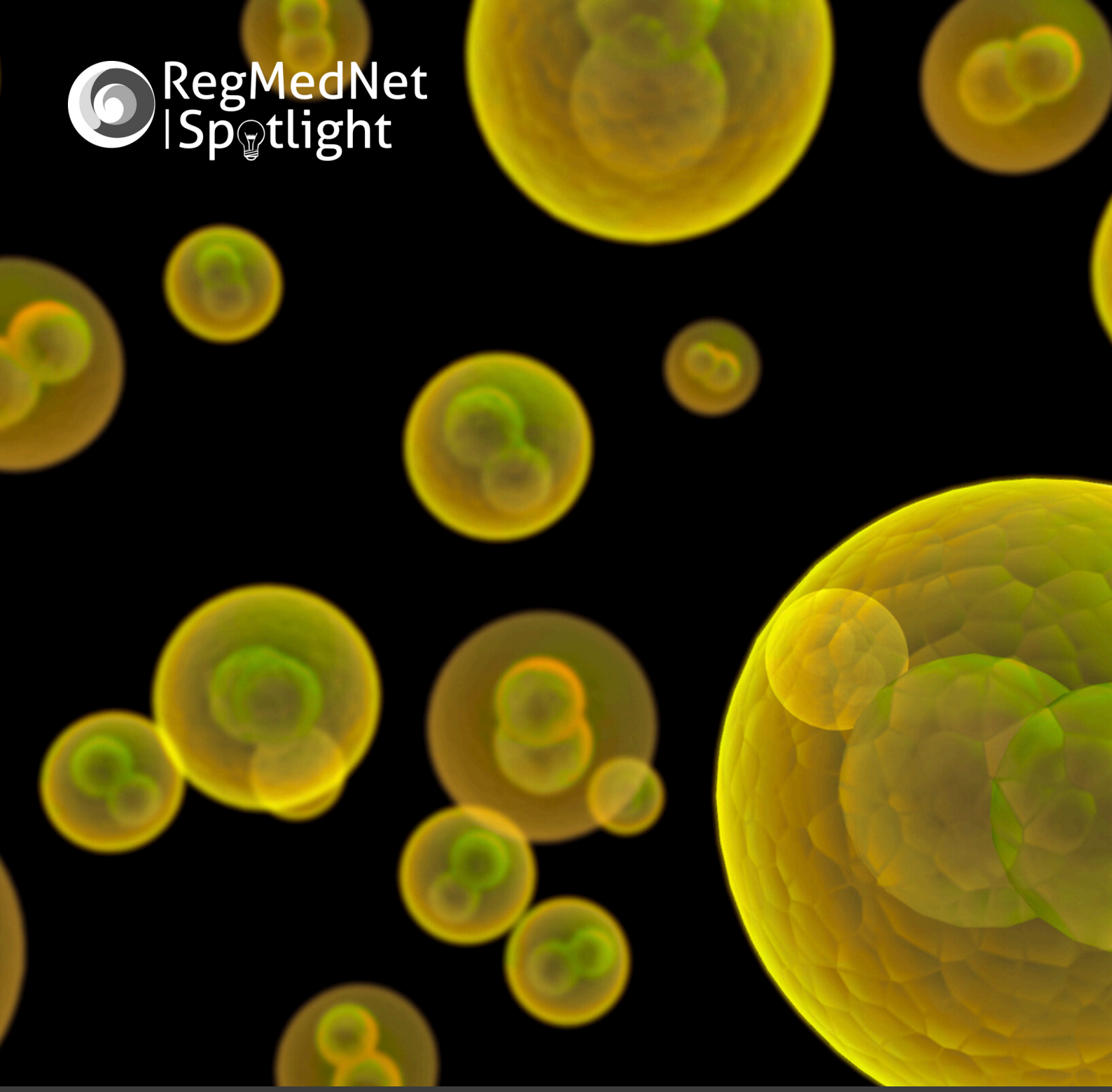

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Editorial Department

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