Global Regulatory Differences for Gene- and Cell-Based Therapies: Consequences and Implications for Patient Access and Therapeutic Innovation

Delphi G.M. Coppens[1], Marie L. De Bruin[1,2], Hubert G.M. Leufkens[1] and Jarno Hoekman[1,3]

Gene- and cell-based therapies (GCTs) offer potential new treatment options for unmet medical needs. However, the use of conventional regulatory requirements for medicinal products to approve GCTs may impede patient access and therapeutic innovation. Furthermore, requirements differ between jurisdictions, complicating the global regulatory landscape. We provide a comparative overview of regulatory requirements for GCT approval in five jurisdictions and hypothesize on the consequences of the observed global differences on patient access and therapeutic innovation.

GCTs represent a new class of medicinal products.[1] These therapies are developed at the frontline of biotechnological innovation and could offer new treatment options in disease areas with limited treatment availability.[2,3] However, the number of GCTs that are currently available to patients remains rather limited, despite substantial advances in this field.[4] The paucity of available GCTs is often attributed to hurdles to translate GCTs from bench to bedside, but the regulatory landscape for marketing approval of medicinal products is also considered a barrier to GCT development, as current regulatory requirements for medicines are not tailored to GCT development.[2,5,6] For instance, randomized-controlled clinical trial (RCT) design is preferred to assess medicinal products for approval,[7] but invasive delivery methods, small patient populations, and a potential lack of comparator treatments and clinical endpoints complicate RCT design for GCTs.[2] Developers also face hurdles to meet manufacturing and quality standards. Lots are often small, with potentially high variability between lots.[8] In addition, GCTs often originate from clinical practice and are largely developed by academic hospitals and small biotechnology companies,[9,10] who often do not have experience with regulatory procedures.[11,12]

The global regulatory environment is also complex because regulatory frameworks for GCTs differ between jurisdictions, including requirements for approval.[13] In 2007, new legislation for GCTs was implemented in the European Union (EU),[2] and more recently, in Japan in 2014.[14,15] The United States (US) and other jurisdictions currently regulate GCTs based on existing laws for biologics and by explicating the specific requirements for GCTs in scientific guidelines.[16–24] However, how these various approaches to regulate approval of GCTs compare and affect patients and therapeutic innovation is unknown. Therefore, we first provide a comparative overview of how GCTs are regulated as medicinal products by comparing 1) legal provisions and guidance for approval of GCTs as medicinal products, 2) entry criteria for medicinal product regulations, and 3) criteria for approval in Canada, the EU, Korea, Japan, and the US. Second, we hypothesize on the consequences and potential implications of the observed regulatory differences between jurisdictions on patient access and therapeutic innovation.

REGULATING GCTS AS MEDICINAL PRODUCTS

Legal provisions and guidance for approval of GCTs

Approval of GCTs as medicinal products is regulated under either specific legal provisions or under existing legislation for medicinal products. Over the last decade, specific laws and other legal provisions for the approval of GCTs as medicinal products were enacted in Japan and the EU,[25] while in Korea, the US, and Canada GCTs are still regulated under legislation for biologics.[26] **Table 1** provides an overview of legislative adaptations specific for GCTs for all jurisdictions, while references to specific legal provisions are included in **Table S1**. **Figure 1** shows that the EU was the first jurisdiction to implement specific legislation for

[1]Utrecht/WHO Collaborating Centre for Pharmaceutical Policy and Regulation, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Copenhagen Centre for Regulatory Science (CORS), Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark; [3]Innovation Studies Group, Copernicus Institute for Sustainable Development, Utrecht University, Utrecht, The Netherlands. Correspondence: J. Hoekman (j.hoekman@uu.nl)

Received 14 August 2017; accepted 1 October 2017; advance online publication 6 October 2017. doi:10.1002/cpt.894

Table 1 Specific legal provisions for approval of GCTs

	Quality, safety, and efficacy requirements[a]	Manufacturing practice standards[a,b]	Clinical trial practice standards[a]
Canada	N	N	N
EU	Y	N	N
Japan	Y	Y	N
Korea	Y	N	N
US	N	N	N

[a]Reflects whether GCT specific elements are included in good practice standards and quality, safety, and efficacy requirements on a legislative level (Y/N). Specific legal provisions are provided in Table S1. [b]Manufacturing practice standards for GCTs are a combination of regulations for GMP and cells and tissue for transplantation purposes. Examples of additional manufacturing practice standards while using cells and tissue as start material for medicinal products are regulations for donor screening and traceability.

GCTs in 2007, the "Advanced Therapy Medicinal Product" (ATMP) Regulation 1394/2007. It amended Directive 2001/83/EC, which now includes a section with quality, safety, and efficacy requirements for approval of ATMPs.[27] In parallel, a scientific committee that evaluates ATMPs was established (Committee for Advanced Therapies). Regulation 1394/2007 also includes incentives to develop ATMPs; fee reductions for scientific advice; an ATMP classification system; and a certification procedure for quality and nonclinical data.[27] More recently, the Japanese Act for Pharmaceuticals, Medical Devices and Other Therapeutic Products was enacted in 2014. It includes a separate section exclusively for GCTs with numerous adaptations for "regenerative medicine" compared to legal provisions for other classes of medicinal products, such as a time-limited conditional approval pathway and specific manufacturing practice. Further details are provided in various ordinances and notifications.[18] In Korea, GCTs have been regulated as a subclass of biologics since 2001, with only a few GCT-specific legal provisions, including a section for the review and approval of GCTs (**Figure 1**).[22] In the US and Canada, there is no specific legislation for GCTs. Instead, GCTs are considered as biologics by law and approved under legal provisions accordingly.

In the US and Canada, interpretation of biologics legislation for GCTs is facilitated by scientific guidelines and communication between developers and regulators (e.g., scientific meetings). The US adopted the first GCT-specific scientific guideline in 1998 and guidance is extensive (**Figure 1**). In contrast, approval requirements for GCTs in Canada are only substantiated in two scientific guidelines and mainly established on a case-by-case basis in communication between developers and regulators. In the EU and Japan, GCT-specific legal provisions are substantiated with various guidelines for good practice standards and interpretation of approval requirements. In Korea, the number of scientific guidelines is relatively limited (**Figure 1**). More details on legislation and scientific guidelines that specify criteria for GCT approval are provided for each jurisdiction in **Tables S1** (legislation) and **S2** (scientific guidelines).

Entry criteria for approval

Each regulatory authority uses specific definitions to distinguish between GCTs that are regulated as medicinal products and those that are regulated as human tissue and cells for use in clinical practice.[26] Gene therapies and GCTs that are combined with a device (combination products) always fall under the definition of medicinal products and need to obtain approval in all jurisdictions. For cell-based therapies (CTs), approval is required for certain subclasses and the exact scope differs between jurisdictions. Across jurisdictions four criteria are used in various combinations to determine whether approval for CTs is needed: 1) the extent of manipulation (e.g., minimal vs. more-than-minimal); 2) whether intended use is homologous or not; 3) whether there is local or systemic effect and the type of action; and 4) whether CTs are developed by an academic center or industry. Different combinations of these four criteria specify 16 CT subtypes that

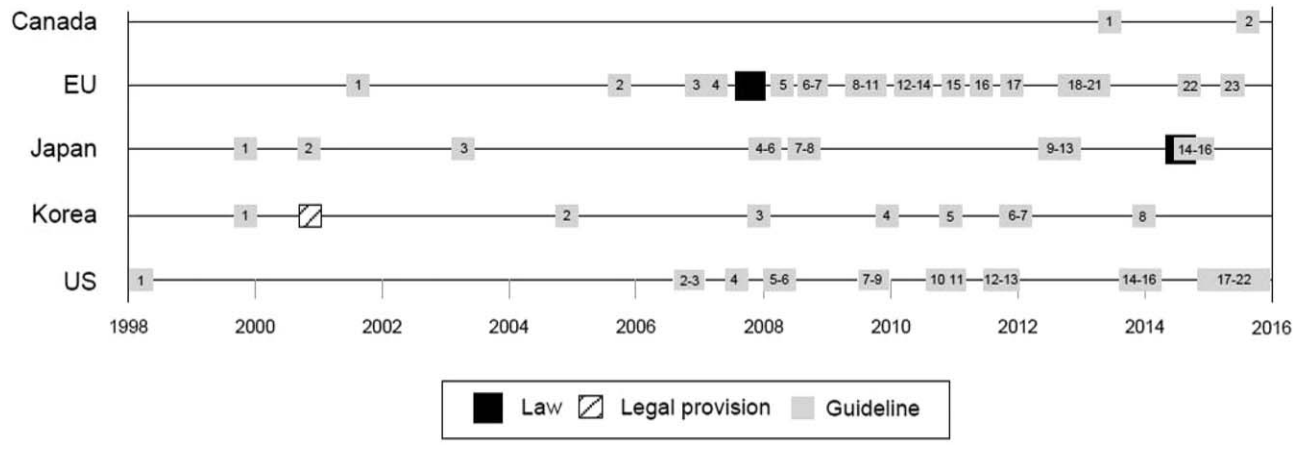

Figure 1 Introduction of GCT legal provisions and scientific guidelines. Timeline represents date of introduction of GCT-specific law, legal provisions and scientific guidelines for five jurisdictions. Guidelines were included if they contained GCT specific elements for good clinical trial practices, good manufacturing practices, or requirements for quality, safety, and efficacy is depicted upon adoption. Numbering of scientific guidelines corresponds to references provided in **Table S2**.

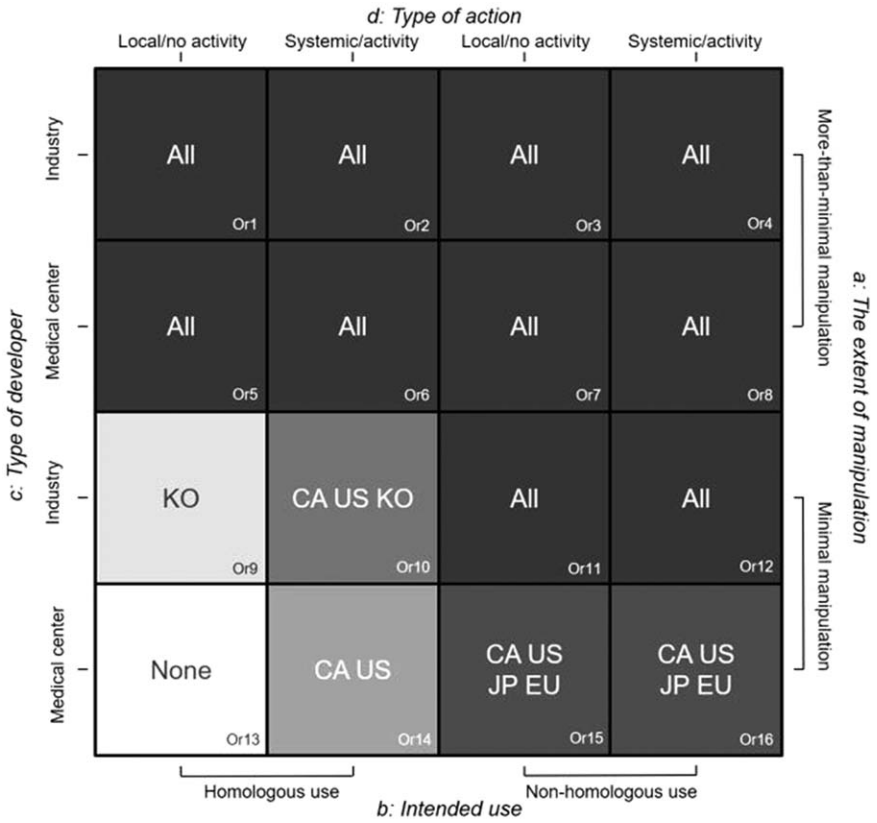

Figure 2 Overview of CT subtypes that require marketing approval in each jurisdiction. Or1-16 represents 16 specific CT subtypes combining four criteria (**a–d**). Text in each orthant (Or) indicates the jurisdictions in which marketing authorization for that particular combination is required. (a) *The extent of manipulation*: More-than-minimal manipulation vs. minimal manipulation. (b) *Intended use*: Nonhomologous use vs. homologous use. (c) *Type of developer*: Processed by industry vs. processed by medical centers. (N.B. criteria are only used in Korea.) (d) *Type of action*: Systemic effects/dependent on biological activity for primary function vs. local effects/not dependent on biological activity for primary function.

may require approval in all, some, or none of the jurisdictions, as depicted by the 16 orthants (Or) in **Figure 2**.

CTs that are engineered, meaning more-than-minimally manipulated and/or for nonhomologous use, generally require approval in all jurisdictions (**Figure 2**; Or1-8,11-12). However, in Korea CTs that are for nonhomologous use, but minimally manipulated in medical centers, do not require approval[23] (**Figure 2**; Or15,16). There is less overlap between jurisdictions for other subtypes, including those that are more related to clinical use of human cells and tissue or those engineered to a less extent (**Figure 2**; Or9-10,13-14). CTs that have a systemic effect and/or depend on their biological activity for their primary function require approval in Canada and the US, but not in Japan and the EU. For example, minimally manipulated, unrelated allogeneic hematopoietic stem/progenitor cell therapies from placental/umbilical cord blood are regulated as biologics in the US due to their systemic effects, although it is not required to submit clinical data to indicate safety and efficacy.[28] These therapies are not regulated as medicinal product in other jurisdictions. In Korea, these CTs only require approval if processed by industry (**Figure 2**; Or10,14). CTs that are minimally manipulated, for homologous use, without systemic effects, and depend on biological activity for their primary function are exempt from approval in all jurisdictions (**Figure 2**; Or13), except those processed by industry in Korea (**Figure 2**; Or9). There are also subtle differences between jurisdiction-specific definitions of criteria (e.g., manipulation) and specific product type exemptions.

Subtypes excluded from approval requirements are generally regulated as cells or tissue for transplantation, which is less stringent compared to approval regulation (e.g., donor screening and testing, quality measures, and traceability).[26]

Entry criteria: Parallel access pathways

GCTs that fall within the scope for approval may under some circumstances be granted an exemption from approval regulations in the EU and Japan. In these two jurisdictions, regulations enable clinical administration parallel to approval trajectories (parallel access pathways). EU regulations specify an exemption for GCTs that are processed "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" (Regulation 1394/2007, Article 28). Under this so-called "hospital exemption" (HE), Member States approve processing of these GCTs and administration to individual patients. Member States must ensure compliance with traceability, pharmacovigilance, and quality standards, but not with all EU

approval requirements. In Japan, the Act on the Safety of Regenerative Medicine (RM Act) was enacted to enhance regulation of GCT clinical research for nonapproval purposes in order to gain scientific knowledge and to investigate medical techniques,[29] including those therapies that resemble characteristics of other GCTs that are regulated as a medicinal product. Administration of GCTs to patients under the RM Act is subject to safety and ethical measures such as facility licenses,[30] adverse event reporting, and informed consent procedures.[19] Parallel access pathways are not available in Canada, Korea, and the US.

Criteria for GCT approval

Legal requirements for quality, safety, and efficacy are the same for GCTs and other medicinal products in Canada, the EU, Korea, and the US. GCT developers need to demonstrate a favorable benefit/risk profile based on *confirmatory* quality, safety, and efficacy outcomes for standard approval. Yet the EU risk-based approach enables flexibility to decide to which extent quality, safety, and efficacy data is necessary to indicate a favorable confirmatory benefit/risk profile, if supported with a scientific rationale (Commission Directive 2009/120/EC). For example, it offers a legal basis to deviate from technical requirements for quality.[8] It can also be used to identify under which conditions a consistent ATMP can be manufactured.[27] However, this approach does not allow deviations from EU GMP regulation.[31]

Japanese legislation has a time-limited, conditional approval pathway that is only eligible for GCTs.[19,32] It enables approval based on a *probability* of efficacy based on surrogate endpoints and heterogeneous patient populations, plus open label and observational study designs to demonstrate safety.[14] To compensate for nonconfirmatory evidence, developers are subject to enhanced postmarketing requirements after conditional approval. During a period of ~7 years, developers are required to conduct confirmatory clinical trials.[30] It is mandatory to submit additional efficacy data after the conditional approval period has ended, which is different from reexamination procedures to confirm earlier established safety and efficacy of other medicinal products.[26] Conditionally approved GCTs can be withdrawn from the market at this point, or granted standard approval.[19]

Expedited regulatory pathways that increase opportunity for communication between developers and regulators and enable approval under lower requirements facilitate early access and shift part of the weight of data collection to the postmarketing phase.[33] These pathways are available to developers of medicinal products in other jurisdictions, provided that an unmet medical need is targeted (e.g., EU conditional approval, US accelerated approval). Eligibility criteria for expedited regulatory pathways are equal for GCTs and other medicinal products in Canada, the EU, and Korea. Since December 2016, eligibility criteria for CTs (defined as "regenerative advanced therapy") to enter US accelerated approval and/or priority review are lowered compared to other medicinal products. Nonconfirmatory clinical evidence suffices to enter accelerated approval, and demonstrating that the product targets an unmet medical need is no longer required for CTs (section 3033, 21st Century Cures Act).[34] For gene therapy, US eligibility criteria for expedited regulatory pathways remain unaltered.

GCTs are regulated under harmonized good practice standards for medicinal products (**Table 1-S1**). Across jurisdictions there is no specific GCP and GMP regulation for GCTs, except for Japanese legislation that specifies good manufacturing standards for GCTs (Good, gene, Cellular and Tissue-based Product manufacturing: GCTP).[30] To be able to interpret the applicable GMP regulations for biologics in other jurisdictions, guidance for manufacturing is provided (**Table S2**). Additional manufacturing and quality regulations are in place when using human cells or tissue as source material. These regulations, such as the US GTP regulations (21 CRF 1271) and EU Directive 2004/23/EC, apply to human cells and tissues for transplantation purposes as well as all GCTs that require approval (**Table S1**).

Ultimately, decision-making for approval is made largely on a case-by-case basis. Interpretation of criteria for approval is facilitated by communication between developers and regulators (e.g., scientific meetings). In all jurisdictions there is ample opportunity to discuss scientific matters with specialized GCT regulatory bodies, of which its importance is consistently stressed by GCT developers and regulators.[26] Opportunities seem most extensive in Japan and the US, with advice meetings being structured around development milestones, such as Investigational New Drug (IND) submission. Compared to developers of other medicinal products, GCT developers in Japan engage in an additional meeting for document maintenance. In the US, GCT developers can choose to engage in a pre-pre-IND meeting.[35] In Korea there are also expanded consultation opportunities for GCT developers, in particular during early-stage development.[26] In Canada and the EU scientific advice opportunities are relatively less structured. In these jurisdictions, developers can request scientific advice at any given point in time. In the EU, GCT developers benefit from a reduced fee for scientific advice.[27] Furthermore, PRIME (EU),[36] Sakigake (Japan),[37] and Breakthrough Therapy Designation (US)[38] all enhance opportunities for interaction between regulators and developers. Many of the designated investigational products under these pathways are GCTs; however, eligibility criteria do not overlap entirely between jurisdictions.[37]

CONSEQUENCES AND POTENTIAL IMPLICATIONS

Emergence of jurisdiction specific legal boundaries

Policy-makers are currently searching for an optimal strategy to embed GCTs into oversight models for medicinal products. Yet GCTs have mainly emerged as hospital innovations[39] within clinical governance systems at the hospital or national level. Their development and use is often also firmly rooted in local clinical practices. In all jurisdictions, there appears to be legitimacy to intervene in local governance systems in an incremental fashion. Oversight models are adapted to the particularities of clinical governance systems and by creating complementarities with already existing governance structures. In addition, regulatory intellectual capacity coevolves with scientific and technological advance that is often gained at the hospital or national level. Science-based standardization for specific subtypes of GCTs may therefore be stronger in particular jurisdictions compared to others. Thus,

Table 2 GCT approvals in the five studied jurisdictions

Canada		EU		Japan		Korea		US	
Product	Year of approval	Product	Year of approval	Product	Year of approval	Product	Year of approval	Product	Year of approval
Prochymal	2012	Chondro Celect	2009	JACE	2007	Chondron	2001	TheraCys	1990
		Glybera	2012	JACC	2012	Holoderm	2002	Carticel	1997
		MACI	2013	Heartsheet	2015	Kaloderm	2005	Provenge	2010
		Provenge	2013	Temcell	2015	Keraheal	2006	Hemacord[a]	2011
		Holoclar	2015			CreaVax-RCC Inj.	2007	Laviv	2011
		Imlygic	2015			Immuncell-LC	2007	Ducord[a]	2012
		Strimvelis	2016			RMS Ossron	2009	Gintuit	2012
		Zalmoxis	2016			Queencell	2010	HPC, Cord Blood[a]	2012
		Spherox	2017			CureSkin	2010	Allocord[a]	2013
						HeartiCellgram	2011	HPC, Cord Blood BLA 125432[a]	2013
						Cupistem	2012	Imlygic	2015
						Cartistem	2012	Clevecord, HPC Cord Blood[a]	2016
						Neuronata-R	2014	HPC, Cord Blood – BLA 125585[a]	2016
						Keraheal-Allo	2015	MACI	2016
								Sterile Cord Blood Collection Unit with Anticoagulant CPD Solution USP[a]	2016
								Kymriah	2017

[a]Minimally manipulated cord blood product. NB: lists approvals until 01-09-2017.

shaping appropriate legal boundaries for GCTs is a highly complex scientific and political effort and it is not surprising that as a result jurisdiction specific approaches to GCTs regulations have emerged.

When innovative biotechnology such as GCTs emerge, legal boundaries of existing frameworks can either be stretched to incorporate new technology or they can be challenged to form a new specific regime.[40] The enactment of the ATMP regulation and the PMD Act installed parallel access pathways and expedited regulatory pathways in the EU and Japan, respectively. Their enactment demonstrates that there is a strong political mandate to advance the GCT field. On one hand, it is likely they will have an effect on the course of the GCT field by facilitating innovation and by providing regulatory clarity to developers.[41] However, insights into the magnitude of development efforts between studied jurisdictions and decision-making by various regulatory authorities are largely lacking. It is also difficult to assess the direct impact of new legislation on product approvals. Judging from product approvals (**Table 2**), there are some indications of a facilitative effect. This is illustrated by nine approvals in the EU and an initial increase of the GCT clinical pipeline[4] since 2007 and two approvals in Japan since 2014 (**Table 2**). Moreover, approvals seem mostly evident in Korea and the US, but half of the approved GCTs in the US would not be considered a medicinal product in the EU (allogeneic cord blood) (**Table 2**). On the other hand, other sociotechnical aspects beyond legislation are also likely to play a substantial role in stimulating innovation. For example, governmental funding of public–private partnerships in Korea[26] may be related to the relatively high number of approvals. Importantly, enactment of legislation early in a technological lifecycle may be accompanied by a loss of flexibility and might disproportionally affect the course of technological trajectories whose potential in the long run is highly uncertain.[42] Authorities in Canada, Korea, and the US put fewer legal constraints on the development of the field and substantiate the interpretation of preexisting legal frameworks in guidelines. This approach facilitates trial-and-error learning and gives more responsibility to implementers; therefore, it may provide a more adaptable tool to keep up with cutting edge therapeutic innovation and to find appropriate solutions for standardization in the long run.

Clinical therapies vs. approved products

Authorities currently regulate the majority of GCTs as medicinal products, including therapies that have been in use in hospital settings for a long time.[43] This may reduce risks for patients and restrict experimenting to regulated environments, but may also affect availability and affordability of GCTs in the clinic.[5,12] One instrument to deal with this trade-off is to enable clinical availability parallel to approval trajectories as used in the Japanese RM Act and European HE. The lower requirements of the RM Act[29] and HE[6] are intended for noncommercial developers to use experimental GCTs in clinical practice, thereby facilitating patient access, clinical experience, and learning, and possibilities for tailor-made hospital innovations. However, public health can also be at risk when oversight is limited, roles and responsibilities are unclear, or when rules are not sufficiently harmonized. For instance, the HE has been critiqued because its implementation varies between Member States,[6,44] which has been said to put patients at risk (e.g., due to nonroutine processing in small batches) and to undermine a level playing field for developers.[6] Nevertheless, it could bridge clinical practice and centralized medicinal product regulation specifically for GCTs, which can facilitate patient access, clinical experience, and act as a catalyzer for innovation. In contrast, the requirements of the RM Act are expected to be higher than prior decentralized oversight at research institutions, likely enhancing patient safety within Japan.[29]

Parallel access pathways can also have a countereffect on commercial development of GCTs,[45] particularly when hospitals disproportionally use this route for products that compete for the same market as already authorized products. It is important that academic developers share their knowledge and know-how gained through parallel access, as otherwise therapeutic innovations may only be available within an academic center or therapeutic knowledge may be lost over time.

Justified flexibility

Legislative adaptations for GCT approval indicate that regulatory authorities are searching for justified flexibility to accommodate innovative techniques within the GCT field, while maintaining stringency to protect public health. The balance between flexibility and stringency differs between jurisdictions, but the overall trend is moving towards the direction of more flexibility. It is well known that GCT developers face specific challenges,[2,6,7,9,10,35] and even when traditional development trajectories would be followed, considerable uncertainties are likely to remain during assessment due to limited (experiential) knowledge about these products. These uncertainties may be impossible to resolve within reasonable timeframes, given the characteristics inherent to the technology, such as long duration periods to reach clinical endpoints (e.g., tissue regeneration) or latent adverse events (e.g., insertional mutagenesis). Some jurisdictions therefore choose to grant approvals based on less complete data and are combined with requirements to conduct confirmatory postmarketing studies. This approval can be granted by either using an expedited regulatory pathway open for a range of medicinal products or a dedicated GCT pathway, as has recently been implemented in Japan.[29]

Japanese conditional approval is the only pathway that was specifically designed for GCTs without criteria for unmet medical need. Moreover, the substantially lower requirements to gain approval may result in more and earlier access in Japan than elsewhere. Foreign developers may be attracted by the new legislation and Japanese product development may be facilitated by scientific research conducted under the RM Act. Although studies are currently lacking, it seems that individual GCTs are approved on less robust scientific evidence in Japan and the EU compared to the US, which is consistent with reports that the US authorities prefer stringent criteria for approval.[46] The 21st Century Act now facilitates access to expedited regulatory pathways for CTs,[34] and it seems, therefore, likely that more GCTs will be approved based on less comprehensive data across jurisdictions, embedded within an expedited regulatory pathway. Criteria to enter expedited regulatory pathways and requirements for approval may prove to become critical factors influencing development and patient access.

Market access is a second challenge for developers after regulatory approval. The one approved GCT in Canada was never marketed, and the developer did not reach approval in other jurisdictions.[47] Currently, four EU-marketed GCTs have been withdrawn after approval due to market failure. None of these products were reimbursed in a majority of EU Member States. Interestingly, these products were not necessary approved through an expedited regulatory pathway, indicating that EU Member States' reimbursement decisions are more stringent in general compared to centralized decision-making by the EMA. In contrast, Japanese GCTs are eligible for national health insurance.[49]

Mitigating uncertainties

While early access through expedited regulatory pathways is an obvious regulatory solution for development challenges with GCTs, it exposes patients to more risks and uncertainties. This calls for enhanced postmarketing surveillance and strict enforcement measures. Such measures vary considerably between jurisdictions. Japanese authorities implemented enhanced postmarketing requirements for conditionally approved products, including safety and quality measures,[19,30] plus mandatory conduct of clinical studies to collect confirmatory efficacy data.[26] Conditionally approved GCTs can be withdrawn from the market at this point, or granted standard approval.[29] In other jurisdictions postmarketing studies can be part of regulatory risk management strategies, in particular in combination with expedited regulatory pathways. However, these may not always be completed or are delayed to enable proper reassessments.[50] It is unclear to which extent medicinal products are withdrawn based on postmarketing experience in other jurisdictions, in particular when preliminary efficacy outcomes are not confirmed.

It is suggested that conditional approval in Japan could facilitate early access for patients in need while protecting public health to a larger extent than expedited regulatory pathways in other jurisdictions.[51] However, the extent of risks and uncertainties upon conditional approval in Japan are likely to be of a larger magnitude compared to expedited regulatory pathways elsewhere, which

could also endanger public health regardless of risk management strategies. Thus, in attempts to foster innovation in the GCT field, the traditional gatekeeper role of regulatory authorities to protect public health may come under pressure. It is vital that regulatory authorities enhance postmarketing surveillance and implement stringent enforcement measures together with expedited pathways to safeguard public health.

THE WAY FORWARD

The majority of R&D activities in the GCT field are still undertaken locally by academic developers and small and medium-sized enterprises.[4,52] Local development is often associated with a regulatory strategy of obtaining initial approval in one particular jurisdiction only. These development efforts likely benefit most from regulatory strategies that are optimized within one particular regulatory framework. In addition, these organizations need substantial guidance and support from regulators and other stakeholders, but necessary expertise and knowledge is often geographically fragmented.[52] Building platforms for knowledge sharing, collaboration, and learning among academia, developers, and regulatory authorities[45] is therefore an area that warrants increased attention. New models of precompetitive collaboration can be utilized to increase R&D efficiency and innovation in the GCT field.[53] At the same time, ongoing collaborations between regulatory agencies and interactions with developers need to be further strengthened.[54] To facilitate global development by larger companies, existing opportunities for parallel scientific advice could be increasingly utilized and extended to other agencies. Regulatory agencies could also explore opportunities to streamline procedures for parallel advice and dossier submission in order to facilitate global development strategies. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a platform to discuss harmonization of scientific, technical, and procedural aspects of GCT development.

With ongoing maturation and increasing clinical development,[4] it is time to consider whether illustrated regulatory differences between jurisdictions reduce incentives for commercial and noncommercial developers to develop and market GCTs in some jurisdictions. For commercial developers, the illustrated diverse regulatory requirements for approval, ranging from manufacturing standards to accepted clinical trial designs, may complicate the conduct of multinational clinical trials[13] and marketing strategies. For noncommercial developers that use parallel-access routes, there might be limited incentive to scale their innovations and make them more widely available in the clinic. It is therefore imperative that regulatory authorities share knowledge and collaborate to continuously coevolve regulatory frameworks with developments in the GCT field, both to safeguard public health as well as to facilitate global patient access.

Additional Supporting Information may be found online in the supporting information tab for this article.

ACKNOWLEDGMENT

We thank Junhee Pyo for contributions on the list of approved GCTs in Korea.

AUTHOR CONTRIBUTIONS

Wrote article (D.C., J.H.); designed research (D.C., M.B., H.L., J.H.); performed research (D.C.); analyzed data (D.C.); review and editing (M.B., H.L., J.H.).

CONFLICT OF INTEREST

This article came about as a result of prior work that has been funded by the European Commission under contract no 20147306 RfS Chafea/2014/Health/24. All authors declare no conflicts of interest: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; or other relationships or activities that could appear to have influenced the submitted work.

1. Fischbach, M.A., Bluestone, J.A. & Lim, W.A. Cell-based therapeutics: the next pillar of medicine. *Sci. Transl. Med.* **5**, 179ps7 (2013).
2. Schneider, C.K. *et al*. Challenges with advanced therapy medicinal products and how to meet them. *Nat. Rev. Drug Discov.* **9**, 195–201 (2010).
3. Kumar, S.R., Markusic, D.M., Biswas, M., High, K.A. & Herzog, R.W. Clinical development of gene therapy: results and lessons from recent successes. *Mol. Ther. Methods Clin. Dev.* **3**, 16034 (2016).
4. Boráò, T. *et al*. Clinical development and commercialization of Advanced Therapy Medicinal Products (ATMPs) in the EU: how are the product pipeline and regulatory framework evolving? *Hum. Gene Ther. Clin. Dev.* (2017) doi:10.1089/humc.2016.193 [Epub ahead of print].
5. Pirnay, J.-P. *et al*. Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems. *Cell Tissue Bank.* **14**, 525–560 (2013).
6. Mansnérus, J. Encountering challenges with the EU regulation on Advance Therapy Medical Products. *Eur. J. Health Law* **22**, 426–461 (2015).
7. Pignatti, F. *et al*. The review of drug applications submitted to the European Medicines Evaluation Agency: frequently raised objections, and outcome. *Eur. J. Clin. Pharmacol.* **58**, 573–580 (2002).
8. Salmikangas, P. *et al*. Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use. *Regen. Med.* **10**, 65–78 (2015).
9. Maciulaitis, R., D'Apote, L., Buchanan, A., Pioppo, L. & Schneider, C.K. Clinical development of advanced therapy medicinal products in Europe: evidence that regulators must be proactive. *Mol. Ther.* **20**, 479–482 (2012).
10. de Wilde, S., Guchelaar, H.-J., Zandvliet, M.L. & Meij, P. Clinical development of gene- and cell-based therapies: overview of the European landscape. *Mol. Ther. Methods Clin. Dev.* **3**, 16073 (2016).
11. de Wilde, S. *et al*. Hurdles in clinical implementation of academic advanced therapy medicinal products: a national evaluation. *Cytotherapy* **18**, 797–805 (2016).
12. Pearce, K.F. *et al*. Regulation of advanced therapy medicinal products in Europe and the role of academia. *Cytotherapy* **16**, 289–297 (2014).
13. Rosemann, A., Bortz, G., Vasen, F. & Sleeboom-Faulkner, M. Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations. *Regen. Med.* **11**, 647–657 (2016).
14. Okada, K., Koike, K. & Sawa, Y. Consideration of and expectations for the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act in Japan. *Regen. Ther.* **1**, 80–83 (2015).
15. Konomi, K., Tobita, M., Kimura, K. & Sato, D. New Japanese initiatives on stem cell therapies. *Cell Stem Cell* **16**, 350–352 (2015).
16. Au, P. *et al*. FDA oversight of cell therapy clinical trials. *Sci. Transl. Med.* **4**, 149fs31–149fs31 (2012).
17. Lee, M.H. *et al*. Considerations for tissue-engineered and regenerative medicine product development prior to clinical trials in the United States. *Tissue Eng. Part B Rev.* **16**, 41–54 (2010).
18. Bailey, A.M., Arcidiacono, J., Benton, K.A., Taraporewala, Z. & Winitsky, S. United States Food and Drug Administration regulation of gene and cell therapies. In *Regulatory Aspects of Gene Therapy and Cell Therapy Products* (eds. Galli, M.C. & Serabian, M.) 1–29 (Springer International Publishing, Heidleberg; 2015).

19. Maeda, D. *et al*. Regulatory frameworks for gene and cell therapies in Japan. In *Regulatory Aspects of Gene Therapy and Cell Therapy Products* (eds. Galli, M.C. & Serabian, M.) 147–162 (Springer International Publishing, Heidelberg; 2015).
20. Ridgway, A.A.G. The regulation of cell therapy products in Canada. *Biologicals* **43**, 406–409 (2015).
21. Viswanathan, S. & Bubela, T. Current practices and reform proposals for the regulation of advanced medicinal products in Canada. *Regen. Med.* **10**, 647–663 (2015).
22. Choi, M., Han, E., Lee, S., Kim, T. & Shin, W. Regulatory oversight of gene therapy and cell therapy products in Korea. In *Regulatory Aspects of Gene Therapy and Cell Therapy Products* (eds. Galli, M.C. & Serabian, M.) 163–179 (Springer International Publishing, Heidelberg; 2015).
23. Lim, J.O. Regulation policy on cell- and tissue-based therapy products in Korea. *Tissue Eng. Part A* **21**, 2791–2796 (2015).
24. Han, E. & Shin, W. Regulation of cell therapy products in Korea. *ISBT Sci. Ser.* **10**, 129–133 (2015).
25. Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004. *Off. J. Eur. Union* **L 324**, 121–131 (2007).
26. van Schothorst, M. *et al*. Study on the regulation of advanced therapies in selected jurisdictions. 20147306 RfS Chafea/2014/Health/24 — Final Report. (2016). Available at: <http://ec.europa.eu/health/human-use/docs/20147306_rfs_chafea_2014_health_24_060516.pdf> (Accessed: 1 September 2017).
27. Salmikangas, P. *et al*. Marketing regulatory oversight of Advanced Therapy Medicinal Products (ATMPs) in Europe: the EMA/CAT perspective. In *Regulatory Aspects of Gene Therapy and Cell Therapy Products* (eds. Galli, M.C. & Serabian, M.) 103–130 (Springer International Publishing, Heidelberg; 2015).
28. Food and Drug Administration. Biologics License Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System — Guidance for Industry. (2014). Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM357135.pdf> (Accessed: 1 September 2017).
29. Hara, A., Sato, D. & Sahara, Y. New governmental regulatory system for stem cell-based therapies in Japan. *Ther. Innov. Regul. Sci.* **48**, 681–688 (2014).
30. Azuma, K. Regulatory landscape of regenerative medicine in Japan. *Curr. Stem Cell Rep.* **1**, 118–128 (2015).
31. European Commission. Consultation Document — Good Manufacturing Practice for Advanced Therapy Medicinal Products. (2015). Available at: <http://ec.europa.eu/health/files/advtherapies/2015_pc/publ_cons_doc_2015.pdf> (Accessed: 1 September 2017).
32. Kusakabe, T. Regulatory perspectives of Japan. *Biologicals* **43**, 422–424 (2015).
33. Liberti, L. *et al*. Adaptive licensing and facilitated regulatory pathways: A survey of stakeholder perceptions. *Clin. Pharmacol. Ther.* **98**, 477–479 (2015).
34. Kesselheim, A.S. & Avorn, J. New '21st Century Cures' legislation: Speed and ease vs science. *JAMA* **317**, 581–582 (2017).
35. Whittlesey, K.J. & Witten, C. US FDA outreach to the regenerative medicine community: challenges and opportunities. *Regen. Med.* **7**, 595–603 (2012).
36. Mullard, A. PRIME time at the EMA. *Nat. Rev. Drug Discov.* **16**, 226–228 (2017).
37. Kondo, H., Hata, T., Ito, K., Koike, H. & Kono, N. The current status of Sakigake designation in Japan, PRIME in the European Union, and breakthrough therapy designation in the United States. *Ther. Innov. Regul. Sci.* **51**, 51–54 (2017).
38. Sherman, R.E., Li, J., Shapley, S., Robb, M. & Woodcock, J. Expediting drug development — The FDA's new 'Breakthrough Therapy' designation. *N. Engl. J. Med.* **369**, 1877–1880 (2013).
39. Gulbrandsen, M., Hopkins, M., Thune, T. & Valentin, F. Hospitals and innovation: Introduction to the special section. *Res. Policy* **45**, 1493–1498 (2016).
40. Faulkner, A. & Poort, L. Stretching and challenging the boundaries of law: varieties of knowledge in biotechnologies regulation. *Minerva* **55**, 209–228 (2017).
41. Brunner, M. & Jilma, B. Development of advanced therapy medicinal products: a case for early scientific advice. In *Clinical Pharmacology: Current Topics and Case Studies* (ed. Müller, M.) 293–303 (Springer International Publishing, Heidleberg; 2016).
42. Faulkner, A. Regulatory policy as innovation: Constructing rules of engagement for a technological zone of tissue engineering in the European Union. *Res. Policy* **38**, 637–646 (2009).
43. Hildebrandt, M. & Sebastian, S. Caught in the gap: ATMP manufacture in academia. *Telegraph* **19**, 1–10 (2012).
44. Van Wilder, P. Advanced therapy medicinal products and exemptions to the regulation 1394/2007: how confident can we be? An exploratory analysis. *Front. Pharmacol.* **3**, (2012).
45. Corbett, M.S., Woolacott, N.F., Webster, A.J. & Hawkins, R. Innovative regenerative medicines in the EU. *BMC Med.* **15**, 49 (2017).
46. Califf, R.M. Benefit-risk assessments at the US Food and Drug Administration: finding the balance. *JAMA* **317**, 693–694 (2017).
47. Dodson, B.P. & Levine, A.D. Challenges in the translation and commercialization of cell therapies. *BMC Biotechnol.* **15**, (2015).
48. Abou-El-Enein, M., Elsanhoury, A. & Reinke, P. Overcoming challenges facing advanced therapies in the EU market. *Cell Stem Cell* **19**, 293–297 (2016).
49. Okada, K., Miyata, T. & Sawa, Y. Insurance systems and reimbursement concerning research and development of regenerative medicine in Japan. *Regen. Med.* **12**, 179–186 (2017).
50. Pease, A.M. *et al*. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. *BMJ* **357**, j1680 (2017).
51. Jokura, Y., Yano, K. & Yamato, M. A comparison of the new Japanese expedited approval legislation for regenerative medicine product with the existing systems of the United States and European Union. *J. Tissue Eng. Regen. Med.* (2017). doi:10.1002/term.2428 [Epub ahead of print].
52. de Wilde, S. *et al*. Development of cell therapy medicinal products by academic institutes. *Drug Discov. Today* **21**, 1206–1212 (2016).
53. Altshuler, J.S. *et al*. Opening up to precompetitive collaboration. *Sci. Transl. Med.* **2**, 52cm26–52cm26 (2010).
54. Milne, C.-P. *et al*. Prospects for harmonizing regulatory science programs in Europe, Japan, and the United States to advance regenerative medicine. *Ther. Innov. Regul. Sci.* **50**, 724–733 (2016).