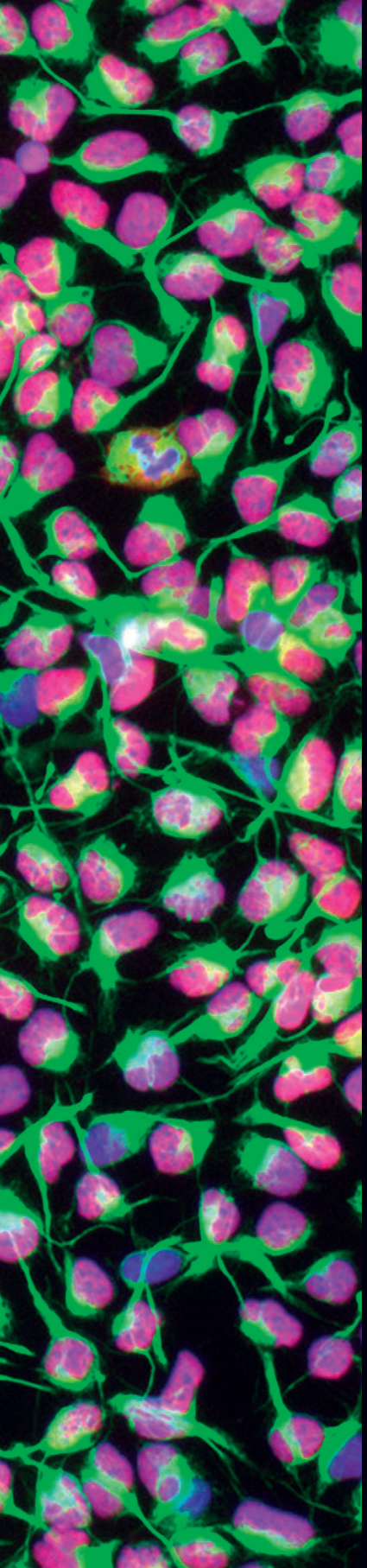

Regulating gene and cell-based therapies as medicinal products

D.G.M. Coppens

Regulating gene and cell-based therapies as medicinal products

Doctoral thesis

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Regulating gene and cell-based therapies as medicinal products

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(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1:
INTRODUCTION

In the early 2000s, hopes for new medical breakthroughs from biomedical research were high. The Human Genome Project had just been finalized by using new methods that allowed rapid DNA sequencing. Unlocking the human genome raised hopes to improve our understanding of human pathology.[1] Around the same time, another modality to treat patients emerged from the field of regenerative medicine, in which new research lines were sparked by the discovery of how to induce pluripotent stem cells from somatic cells in Japan in 2006.[2,3] Immunotherapy was regarded as another field with potential for medical breakthroughs. Scientists had been unraveling signaling pathways of the human immune system for decades, molecule by molecule.[4] Nowadays, researchers are investigating how to use a patient's own immune system to target both hematologic and solid tumors.[5]

Therapies based on gene modification and cells that are engineered to intervene with human biology, have the potential to revolutionize health care.[6,7] Given their new modes of action in comparison with pharmaceuticals (small molecules and biological medicinal products), they offer new modalities for treatment. In particular, they could provide breakthrough therapies in those therapeutic areas with high unmet medical; where there is no treatment available, or where currently available treatment is unsatisfactory.[8] Cell-based therapies can be engineered to target specific biological processes or human bodily functions, with a potential to treat a wide range of diseases including metabolic diseases, autoimmune diseases and cancers, and to replace or regenerate damaged or lost tissue.[6] For example, two chimeric antigen receptor (CAR) T cell products now offer treatment for relapsed or refractory B cell malignancies. Response rates to other treatments are typically very low for relapsed or refractory B cell malignancies, and of short duration. A remarkable complete response rate of 81% and overall survival rate of 76% was demonstrated in pediatric patients after one year of treatment (pediatric B cell acute lymphoblastic leukemia), and a complete response rate of 58% of adult patients after two years of treatment (aggressive B cell non-Hodgkin lymphoma) with CAR T cell products.[9,10] Cellular immunotherapy is even regarded as the future of oncology treatment now.[11] Most gene therapies target a variety of cancers, monogenetic disorders and cardiovascular diseases, and hold great potential to improve health care.[7] For example, infants that suffer from a lethal rare genetic disorder that leads to severe immunodeficiency (deaminase-severe combined immunodeficiency), can now be cured with a marketed gene therapy in the European Union (EU) since 2016, and survive well beyond their first or second year of life.[12,13]

The concerns and challenges to translate gene and cell-based therapies (GCTs) from the laboratory to the clinic (bench-to-bedside) have received a lot attention over the last decade. Great efforts have been put in bridging the gap between basic science and the use of GCTs in the clinic.[14,15] Translation challenges appear to be mitigated to some extent, as GCTs are currently reaching patients through clinical trials across the world.[16,17] However, the availability of GCTs in the clinic and on the market is still limited.[18] Thus, despite high expectations for improved health care, there is also a discourse of concern about implementation challenges to accommodate GCTs in existing regulatory and health care delivery systems.[19]

Over the last two decades, various jurisdictions including the EU have issued regulations to accommodate GCTs within regulatory frameworks that govern pharmaceuticals.[8] As a consequence, a wide variety of GCTs are now regulated as medicinal products. However, these regulatory frameworks co-evolved with scientific and technological advance for pharmaceuticals and may be poorly suited to regulate GCTs. Considering the differences in product characteristics and innovation context between GCT and traditional pharmaceutical development, there is a need to investigate how legal frameworks and regulatory decision-making is changing in order to accommodate and regulate GCTs as medicinal products.

Gene and cell-based therapy characteristics

GCTs are a heterogenous group of therapies, which are fundamentally different from pharmaceuticals with regard to source material, modes of action, and intended function. These therapy characteristics do not fit well with traditional medicinal product regulations for quality, preclinical studies, and clinical studies, which impose various regulatory challenges. First, GCTs are mostly based on cellular source material. Cell-based therapies can be manipulated *ex-vivo* in the laboratory, combined with a medical device, or even genetically modified, to exhibit particular characteristics for pathology intervention. Due to inherit complex GCT characteristics, developers need expertise and technological know-how for GCT manufacturing and quality.[20] Working with cellular starting material leads to challenges such as contamination, production of small batches, incorrect differentiation after manipulation, and inconsistency between batches due to differences between patient (autologous) or donor (allogeneic) material.[21] Furthermore, when delivering genetic material, quality control of the vectors to ensure correct gene transfer is very important to mitigate risks of insertional mutagenesis and tumorigenicity.[22] Thus, the source material used for GCTs is an important cause of regulatory

challenges, because it simply does not fit within the pharmaceutical paradigm of large scale batch production, which are produced according to very strict quality specifications.

Second, GCTs interact differently with the human body compared to pharmaceuticals. Pharmacokinetic clinical studies typically do not apply to GCTs because cells are not metabolized by the human body. Consequently, preclinical pharmacokinetic studies are replaced with biodistribution studies in animals, which makes dosing for human administration highly uncertain. Furthermore, GCTs are more complex than pharmaceuticals. The sheer difference in size between a molecule and a whole cell gives a first impression of the complexity of GCTs. Pharmaceuticals such as monoclonal antibodies typically target one ligand, while cells are vivid and interact with its microenvironment through multiple cellular signaling pathways.[6] Gene therapy essentially revolves around the introduction of genetic material into the human body for treatment. *In-vivo* transfer of genetic material can be accomplished by engineering vectors for gene delivery, or by introducing *ex-vivo* genetically modified cells.[7]

New treatment modalities through highly complex, novel modes of action introduce scientific uncertainties. Animal studies may not be feasible, because modes of action rely on species specific signaling pathways.[8] Furthermore, relations between GCT product characteristics and modes of action are not always well understood,[23] which creates uncertainty on the clinical efficacy of novel GCT modes of action in humans.[6,7,24] GCTs are also accompanied with specific risks compared to pharmaceuticals, such as undesired cell proliferation, tumorigenicity[6] and insertional mutagenesis.[7] These scientific uncertainties and risks are challenging developers in their product development efforts, and regulatory authorities in their assessments and decisions to regulate GCTs.

Third, GCTs have different intended functions compared to pharmaceuticals. As a result of their novel modes of action they differ from the traditional pharmaceutical model of single drug-target interaction, which offers ‘one-size-fits-many’ therapeutics to target disease. Nowadays, there is a general shift away from pharmaceutical therapeutics towards system therapeutics, as a consequence of a deeper understanding of molecular pathways and functioning of biological systems. For instance, there may be multiple defects in molecular pathways that all lead to the same disease, with identical phenotypes.[25] This means that patient groups with the same disease and phenotype can be divided into subgroups of patients according to the underlying molecular defect. Such subgroups of patients exist for diabetes and Parkinson’s disease for

example.[26,27] Systems therapeutics are typically designed to target molecular defects underlying disease, and offer a 'precision medicines' approach for patient subgroups or even individual patients.[25] GCTs are a typical example of a system therapeutics and precision medicine approach. GCTs are often based on autologous cells that are delivered back to an individual patient.[6] These may be engineered to target a molecular pathway that is specific for a subgroup of patients. For example, patient or subgroup specific mutations that underlie hematologic but also solid tumors can be used to engineer cell-based immunotherapy.[5]

The systems therapeutics and precision medicine approaches for GCTs may lead to regulatory challenges, which is largely a result of their specificity and anticipated indication. The majority of GCTs currently in development target various subtypes of cancers, autoimmune diseases[6,16,28] and monogenic disorders.[7,29] These include numerous rare diseases, and typically affect small patient populations. Monogenic disorders that can be targeted with gene therapy are often pediatric indications, and require careful evaluation.[8] Furthermore, the novel modes of action may enable to target diseases or conditions for which no treatment is currently available. Comparator treatment and/or validated clinical endpoints are often not available for indications without alternative treatment, which impedes randomized clinical trial (RCT) design.

Overall, GCTs originate from scientific and technological advance from various disciplines, including but not limited to, molecular and cell biology, genetics, biotechnology, medical device engineering, and pharmacology, and demand an interdisciplinary approach. The complexity and novelty of the field lead to scientific uncertainties and risks, which are challenging existing regulatory requirements and frameworks.[25]

Innovation context for GCT development

Scientific and technological challenges are not the only developmental challenges in the GCT field. Traditionally, the pharmaceutical industry and biotechnology companies bring new pharmaceuticals to the market under a molecular biology paradigm.[30] This paradigm heavily relies on identifying or engineering pharmaceuticals that intervene in human pathology by single drug-target interactions.[25] These pharmaceutical discoveries depend on scientific observations in laboratories,[30] and typically follow a linear development trajectory. The development of GCTs follows another innovation pathway of learning in clinical practice.[31] Thus, learning is non-linear and requires constant interaction and feedback between observations in

clinical practice and scientific and technological advance, to a much larger extent than observed in traditional pharmaceutical development by large industry.[25]

Many GCTs have been historically used in clinical practice as human cells and tissue for transplantation purposes or other therapeutic purposes, such as cultured skin tissue for severe burn wounds and stem cell therapy. This demonstrates that many GCTs emerged in clinical practice, and were developed based on experiential learning in clinical practice to large extent.[32] Public facilities have access to human derived materials, and GCTs are often stored and manufactured in-house by public institutions, which mitigates quality issues that arise quickly as a result of logistical challenges and limited shelf-lives.[33] Over time, GCTs are becoming increasingly complex as a result of experimental learning and scientific and technological advance, and academic developers are heavily involved in self-initiated clinical development of GCTs,[16,17,28] in particular for early stage clinical trials.[16,28] Therefore, it is not surprising that early GCT clinical research currently largely takes place in academic hospitals, which have clinical, scientific, and technological expertise from various disciplines under one roof.[34]

Clinical practice is associated with different perspectives and goals compared to commercial pharmaceutical development.[34,35] Academic hospitals primarily respond to a demand to provide and improve patient care, instead of commercial development. Yet, given the risks that are associated with GCTs administration to patients, regulatory authorities around the world chose to regulate them as medicinal products.[36] However, the switch from regulations for human cells and tissue for transplantation to medicinal product regulation imposes substantial challenges for academic hospitals and other public institutes with historic use of GCTs in clinical practice.[33] Furthermore, academic developers struggle to move from early phase clinical trials to commercial production and marketing authorization.[20,33,37,38] Thus, alongside the scientific and technological challenges, the innovation context of GCT development also imposes development and regulatory challenges. How academic hospitals and other public institutes navigate through the regulatory space for human cells and tissue and medicinal products, and utilize GCTs in routine health care deserves further investigation.[39,40]

Regulatory change to accommodate GCTs as medicinal products

As a consequence of the emergence of GCTs in the clinic, the potential benefits, but also severe adverse risks for patients,[8] and the unique innovation context in which GCTs are developed, policy makers are under pressure for regulatory change for GCTs. The standard regulations for medicinal products do not fit well with the specific characteristics of GCTs,[8,33,41] and create challenges to commercially develop GCTs.[8,40,42–44] Regulatory change from existing medicinal product regulations, specifically implemented for GCTs, deserves further attention.

Throughout the last century, regulatory frameworks for medicinal products evolved together with the development of pharmaceuticals.[45] Medicinal product regulatory frameworks are one of the strongest institutional pressures that structure the development trajectories of pharmaceuticals. Elements for marketing authorization of medicinal products are regulated on two levels; a legislative level as specified in laws, statutes, and regulations, and an implementation level consisting of scientific and procedural guidelines as well as regulatory assessment and decision-making in practice. The elements include substantive elements that entail requirements for authorization (e.g. evidentiary support for authorization, standards for good practices), and procedural elements that specify procedures for decision-making based on the requirements (e.g. procedures for scientific evaluation). Regulatory frameworks guide applications to follow stringent requirements for product development to reach marketing authorization for commercial purposes. As a general rule, authorities only grant authorization to new medicinal products if developers provide evidence that their products have a positive benefit/risk balance and are of sufficient quality.[45] In essence, regulatory frameworks are in place to ensure evidence-based medicine throughout the development process.[36]

Traditional pharmaceutical development typically progresses along a linear trajectory, in which the pharmaceutical industry relies on identifying compounds or designing molecules with a potential to bind to biological targets in the human body.[6] After obtaining proof-of-concept in preclinical research, testing in humans traditionally occurs in randomized clinical trials or other interventional studies, a process that is heavily regulated according to stringent requirements.[46] In addition, there are harmonized standards to ensure that developers follow good practices to ensure evidentiary support of high quality. For example, Good Manufacturing Practice (GMP) is aimed at consistent, quality controlled manufacturing,[47] whereas Good Clinical Practice (GCP) is aimed to collect clinical data of

high quality.[48] Regulators assess evidentiary support for their decision-making on a benefit/risk balance, which under traditional development trajectories, translates into a binary decision-making model for marketing authorization with limited follow up during the post-marketing phase.[49]

Standard processes under the binary decision-making model for marketing authorization can be quite lengthy, and the stringent regulatory requirements may delay access for patients in need of innovative medicines.[50] In order to facilitate early access to patients in need of innovative medicines, regulatory authorities around the world have implemented facilitated regulated pathways;[51] 1) regulatory pathways with different procedures, including shortened regulatory procedures for submission and review, and/or procedures for more interaction between regulators and developers (referred to as expedited pathways from hereon), and 2) regulatory pathways with different evidentiary requirements, including the use of surrogate endpoints in clinical trial design and authorization based on non-confirmatory evidence that needs to be confirmed during the post-marketing phase (referred to as adaptive pathways from hereon).[52] These regulatory pathways are available to developers of all classes of medicines if they adhere to the eligibility criteria. Early access and continued monitoring of patients during the post-marketing, which may be embedded within adaptive regulatory pathways, is also referred to as an adaptive approach to licensing, or life-cycle approach (in contrast to the traditional model of binary licensing).[49,51] Furthermore, other regulatory pathways offer advantages to accommodate development challenges for rare diseases (orphan drug designation (ODD)). They also mitigate market failure as ODD typically includes financial incentives, such as beneficial intellectual property rights of market exclusivity for an extended period.[53]

Considering the ‘precision medicine’ approach of GCTs,[25] many GCTs may be developed for small patient populations and designated as an orphan medicinal product. Furthermore, GCT development may be embedded within expedited and/or adaptive pathways for which all medicinal products are eligible, including PRIME (EU),[54] Sakigake (Japan),[55] and Breakthrough Therapy Designation (United States).[56] However, using existing regulatory strategies to deviate from standard requirements and procedures may not be the only strategy for GCT regulation. Policy makers can also change regulatory structures to facilitate progression of new innovations.[57] There are two strategies that can be used to accommodate GCTs as medicinal products; stretching the boundaries of existing requirements and processes of medicinal product regulation, or designing and implementing new GCT regulations that are separate from existing systems.[58]

In the process of policy reform and regulatory change for GCTs, regulatory authorities face the difficult task to maintain their gatekeeping function when accommodating GCTs into medicinal product regulations, while simultaneously facilitating GCT development and implementation in clinical practice.[59,60] Various actors are involved in the process of policy reform and regulatory change, including policy makers, regulatory authorities, both public and private developers, and patients. Incentives and goals from various actors may not always coincide, and even contradict at times. Developers and patients may push for early market access that is associated with scientific uncertainties and risks, whereas regulators aim to protect public health and guarantee patient safety in their gatekeeping function to ensure evidence-based medicine through more confirmatory benefit/risk data. Thus, uncertain clinical outcomes may be a result of a push for life-saving treatments and innovation incentives, but uncertainties also undermine patient safety.[50] Thus, pressure for policy reform and regulatory change that deviate from standard regulations and the evidence-based medicine paradigm may not always be in patient' interests.[60]

Authorities of the EU implemented regulatory change by introducing European legislation for GCTs in 2007. Due to the complex nature of GCTs, and overlap with biotechnology and medical devices it was deemed appropriate to regulate them on a central, European level, instead of on a national level. In the 2000s, improved clinical outcomes as a result of GCT treatment became more and more evident. However, reports of fatalities as a result of inherit GCT severe safety risks were also reported in the literature and lay press.[8] For example, trials of gene therapy for severe combined immune deficiency were put to a halt after reports came out that children had developed leukemia after treatment. This demonstrated the risk of using retroviral vectors and the inherit risk of insertional mutagenesis.[61] Furthermore, skin cell substitutes and cartilage products were used for more than ten years in clinical practice, but oversight was limited because these were not regulated as medicinal products.[8] To ensure expertise assessment of data and protection of public health, the Committee for Advanced Therapies was established as a central committee of the European Medicines Agency for scientific evaluation and advice.[62] In addition, by adopting EU legislation for GCTs, oversight for marketing authorization became centralized and regulations were harmonized across EU Member States. By harmonizing regulations for commercial GCT development, policy makers intended to stimulate innovation and patient access by facilitating access to the EU market and ensuring free movement of GCTs within the EU, while safeguarding public health.[63]

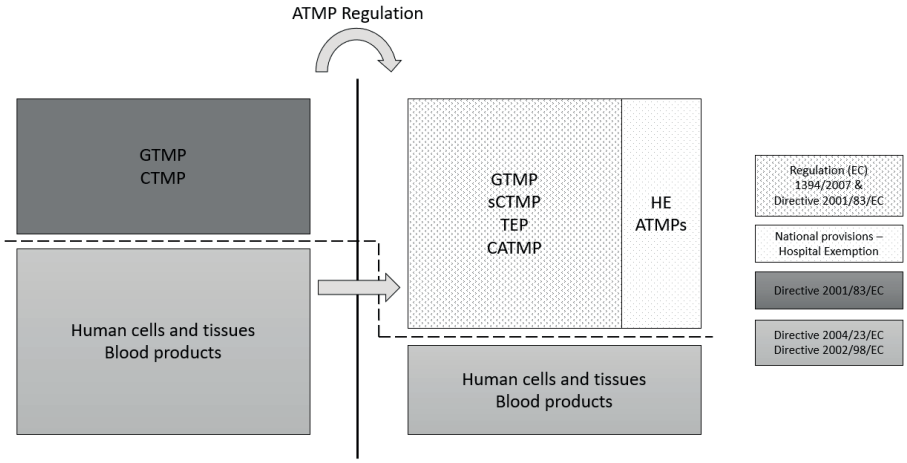
The European regulatory framework for medicinal products consists of two separate systems; European legislation and national legislation of the individual Member States. In European legislation, Regulations are legally binding acts that need to be adhered to in all Member States. Directives are acts that set out goals that need to be achieved in all Member States. However, the competent authorities of the Member States can decide how they implement the goals set out in Directives.[64] Initially, gene and cell therapy medicinal products were introduced into European legislation through the adoption of Directive 2003/63/EC,[65] which amended the overarching Directive for medicinal products (Directive 2011/83/EC). Later in 2009, GCTs were introduced as Advanced Therapy Medicinal Products (ATMPs) as a separate class of medicinal products with the adoption of Regulation (EC) 1394/2007 (ATMP Regulation).[66] Currently, these are four subclasses of ATMPs; gene therapy medicinal product (GTMP), somatic cell therapy medicinal product (sCTMP), tissue engineered product (TEP), and combined advanced therapy medicinal product (CATMP) (Regulation 1394/2007, Chapter I, Article 2). Centralized marketing authorization is granted by the EMA and European Commission (Regulation 726/2004), while clinical trial authorization is granted by the competent authorities of the Member States.[67] The ATMP Regulation and its definitions for the four subclasses had consequences for which type of GCTs were defined as ATMP and regulated as medicinal product, versus human cells and tissue (Figure 1). The enactment of the ATMP Regulation, and the implications for development and availability in clinical practice, is a key rationale to investigate regulatory change for GCTs in the EU and beyond in this thesis.

In summary, GCTs are a group of complex, heterogeneous therapies that originate from academic clinical practice settings to large extent.[37] The scientific uncertainties and close proximity to clinical practice impose a wide array of questions as to how to implement regulatory change that accommodates GCTs in regulatory frameworks, in such a way that it promotes public health, facilitates innovation, and ensures patient safety.[8,68,69]

Thesis objective

This thesis aimed to investigate regulatory change to accommodate gene and cell-based therapies for human administration as medicinal products, regulatory decision-making under the current frameworks, and the implications of regulatory change for GCT development and their availability in clinical practice.

Figure 1: Schematic representation of legislative changes due to the adoption of the ATMP Regulation in the EU



GTMP = gene therapy medicinal product, CTMP = cell therapy medicinal product, sCTMP = somatic cell therapy medicinal product, TEP = tissue engineered product, CATMP = combined advanced therapy medicinal product (with device), HE ATMPs = ATMPs that are manufactured under the Hospital Exemption. Orange arrow indicate transition ATMPs. Above the dotted line therapies are considered medicinal products.

Regulatory change, specifically implemented for GCTs, is the focus of Chapter **2**. We investigate two strategies for regulatory change; regulatory change for GCTs that is embedded within existing regulatory systems for the marketing authorization of medicinal products, and regulatory change through new GCT regulations that deviate from existing regulatory systems for medicinal products.

The ATMP Regulation was implemented to regulate development trajectories that lead up to the marketing authorization of GCTs as medicinal products. Yet, regulatory change in response to the emergence of GCTs also occurred outside of Europe, including in Asia and the Americas.[36] Regulatory change for the marketing authorization of GCTs by several regulatory authorities around the world indicates an attempt for international integration and access to global markets. However, it has been postulated that GCT regulatory change led to diversifications among jurisdictions, and to deviations from evidentiary requirements belonging to the evidence-based medicine paradigm.[60] How regulatory change for marketing authorization of GCTs as medicinal products was implemented, and how this compares among jurisdictions, is the focus of Chapter **2.1**.

In Chapter **2.2**, we investigate regulatory change for GCTs in the EU that deviates from existing medicinal product regulation. EU policy makers considered to exempt small scale manufacturing activities in clinical practice from the regulations of the ATMP Regulation. Throughout the political process of review and approval of the proposal by the European Parliament and Council of Ministers, the initial definition of what would be exempt from the ATMP Regulation was re-drafted into Article 28, which is known as the Hospital Exemption.[63] Transposition of Article 28 into national provisions for the Hospital Exemption is the responsibility of the competent authorities of EU Member States,[70,71] as well as oversight and granting authorizations for manufacturing. How regulatory change for the Hospital Exemption was implemented, and how this compares among EU Member States, is the focus of Chapter **2.2**.

Alongside regulatory change for the marketing authorization of GCTs, we investigate decision-making for marketing authorization of GCTs in Chapter **3.** The complex science and heterogeneity of GCTs, together with limited clinical experience, very often result in scientific uncertainties and technological challenges for developers. Regulatory authorities likely also face considerable uncertainties in their evaluations for centralized marketing authorization and decision-making for benefit/risk balances.[8] How regulators deal with these scientific uncertainties and the extent to which they are flexible in decision-making, potentially in consideration of hope for medical innovation and meeting unmet medical needs, is unclear. How regulatory authorities consider evidentiary support and other factors in their decision-making for GCT marketing authorization, and use available regulatory pathways, is the focus of Chapter **3**. We compare decision-making between regions in Chapter **3.1**, and investigate major scientific issues and regulatory considerations that determine the fate of GCT development in Chapter **3.2**.

Throughout Chapters **2** and **3**, we pay attention to the implications of regulatory change and decision-making on GCT development and availability. In Chapter **4**, we investigate two specific cases of regulatory implications on GCT development, and GCT availability in clinical practice. First, the relatively limited clinical experience and heterogeneity of different GCT technologies impose challenges to standardize regulatory requirements for GCT subtypes that are tailored to particular product characteristics. Regulatory authorities may provide regulatory guidance through scientific guidelines or through interactions with developers.[72] Yet, limited regulatory standardization raises the importance for developers to share scientific knowledge and technical expertise amongst each other. One means to achieve

knowledge sharing is through scientific publication of clinical trial results. Underreporting of pharmaceutical trial results caused much debate over the last few years, in particular for privately sponsored trials.[73] For emerging fields such as the GCT field, publication rates and other features of clinical trial publication are not yet available, and are the focus of Chapter **4.1**.

Second, we investigate the implications of the implementation of the Hospital Exemption on GCT development and availability among EU Member States in Chapter **4.2**. The enactment of the ATMP Regulation and its definitions altered which GCTs were considered a medicinal product. Consequently, some treatments that were previously regulated as human tissues and cells (Directive 2004/23/EC), were now regulated as medicinal products (from here on referred to as transition ATMPs) (Figure 1). It was feared that stringent medicinal product regulations for transition ATMPs would impose barriers for their availability and affordability in the clinic.[33,74,75] The Hospital Exemption could act as a regulatory tool to mitigate barriers for GCT availability in clinical practice. However, the implementation of the Hospital Exemption has stirred substantial debate in the GCT field due to the apparent regulatory diversity among EU Member States and the potential exposure of patients to risks. Furthermore, it is postulated that the Hospital Exemption provides a competitive advantage in comparison to development trajectories for commercialization of GCTs.[40,76–78] This debate is largely anecdotal, while comprehensive overviews of manufacturing activities under the Hospital Exemption are not available. In Chapter **4.2**, we provide insights into manufacturing activities under the Hospital Exemption among several EU Member States, and the implications on GCT availability in clinical practice and commercial development.

Chapter 5 entails a general discussion. The general findings and the implications of the findings for GCT development and their availability in clinical practice are described. Furthermore, we provide perspectives on the way forward and recommendations for future regulatory and innovation studies, and finalize with a general conclusion.

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CHAPTER 2:
REGULATORY CHANGE FOR GENE AND CELL-BASED THERAPIES

Chapter 2.1:
Global regulatory differences for gene and cell-based therapies: consequences and implications for patient access and therapeutic innovation

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Abstract

Gene and cell-based therapies (GCTs) offer potential new treatment options for unmet medical needs. However, 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 consequences of the observed global differences on patient access and therapeutic innovation.

Introduction

Gene and cell-based therapies (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] 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 for GCT development as current regulatory requirements for medicines are not tailored to GCT development.[2,5,6] For instance, randomized controlled clinical trial design (RCTs) 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, EU, Korea, Japan and US. Second, we hypothesize on the consequences and potential implications of the observed regulatory differences between jurisdictions on patient access and therapeutic innovation.

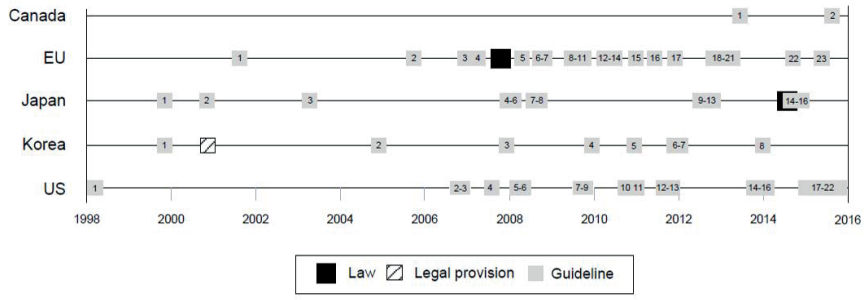
Regulating GCTs as medicinal products

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 product were enacted in Japan and the EU,[25] while in Korea, US, and Canada GCTs are still regulated under legislation for biologics.[26] Table 1 provided 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 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 non-clinical 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 are 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.

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.

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 detail 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

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.

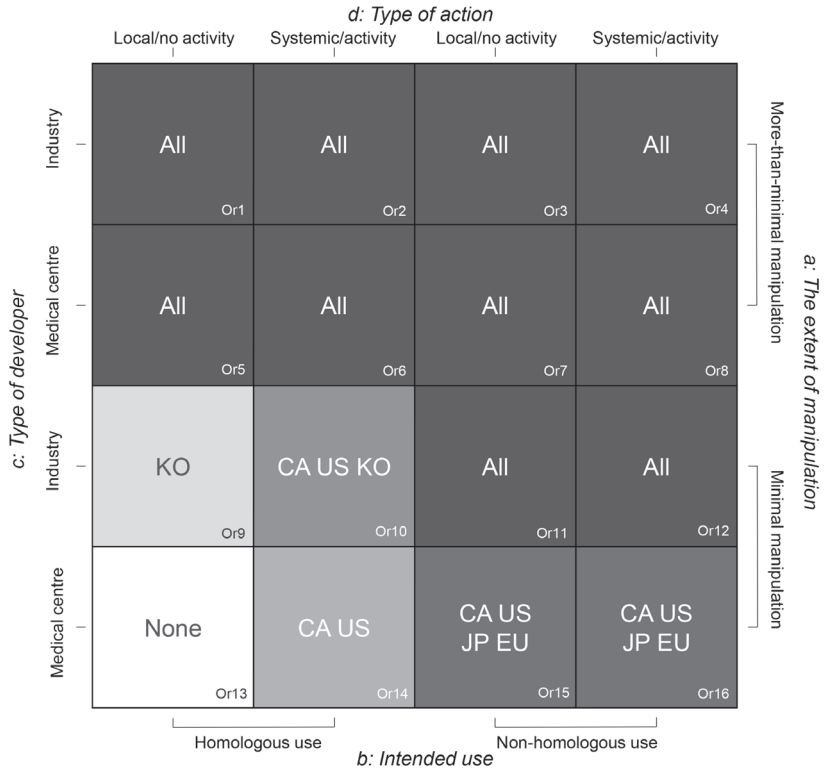
(b) Manufacturing practice standards for GCTs are a combination of regulations for GMP and cells and tissue for transplantation purposes. Examples of additional manufacturing practice standards while using cells and tissue as start material for medicinal products are regulations for donor screening and traceability.

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 non-homologous use, generally require approval in all jurisdictions (Figure 2; Or1-8,11-12). However, in Korea, CTs that are for non-homologous 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 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 US, but not in Japan and 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]

Figure 2: Overview of CT subtypes that require marketing approval in each jurisdiction



Or1-16 Represent 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 versus minimal manipulation.

(b) *Intended use*: Non-homologous use versus homologous use.

(c) *Type of developer*: Processed by industry versus processed by medical centers. (N.B. criteria is only used in Korea).

(d) *Type of action*: Systemic effects/dependent on biological activity for primary function versus local effects/not dependent on biological activity for primary function.

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 non-approval 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 US.

Criteria for GCT approval

Legal requirements for quality, safety and efficacy are the same for GCTs and other medicinal products in Canada, EU, Korea and 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 *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 non-confirmatory evidence, developers are subject to enhanced post-marketing requirements after conditional approval. During a period of approximately seven 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 re-examination 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 post-marketing phase.[33] These pathways are available to developers of medicinal products in other jurisdictions, provided that 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. Non-confirmatory 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 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-Investigation New Drug 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 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 co-evolves with scientific and technological advance that is often gained at hospital or national level. Science-based standardization for specific subtypes of GCTs may therefore be stronger in particular jurisdictions compared to others. Thus, 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 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 life-cycle may be accompanied by 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 pre-existing 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 versus 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 non-commercial 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 danger 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 non-routine 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 de-centralized oversight at research institutions, likely enhancing patient safety within Japan.[29]

Parallel access pathways can also have a counter effect 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 time-frames given 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 combined with requirements to conduct confirmatory post-marketing 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]

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	ChondroCelect®	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 [Δ]	2011
		Holoclar®	2015			CreaVax-RCC Inj.	2007	Laviv®	2011
		Imlygic®	2015			Immuncell-LC®	2007	Ducord [Δ]	2012
		Strimvelis®	2016			RMS Ossron®	2009	Gintuit	2012
		Zalmoxis®	2016			Queencell®	2010	HPC, Cord Blood [Δ]	2012
		Spherox®	2017			CureSkin®	2010	Allocord [Δ]	2013
						HeartiCellgram®	2011	HPC, Cord Blood BLA 125432 [Δ]	2013
						Cupistem®	2012	Imlygic™	2015
						Cartistem®	2012	Clevecord, HPC Cord Blood [Δ]	
						Neuronata-R®	2014	HPC, Cord Blood – BLA 125585 [Δ]	2016
						Keraheal-Allo®	2015	MACI®	2016
								Sterile Cord Blood Collection Unit with Anticoagulant CPD Solution USP [Δ]	2016
								Kymriah™	2017

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

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 post-marketing surveillance and strict enforcement measures. Such measures vary considerably between jurisdictions. Japanese authorities implemented enhanced post-marketing 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 post-marketing 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 re-assessments.[50] It is unclear to which extent medicinal products are withdrawn based on post-marketing 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 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 post-marketing surveillance and implement stringent enforcement measures together with expedited pathways to safeguard public health.

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 jurisdictions 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 pre-competitive 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 non-commercial 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 non-commercial 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 co-evolve regulatory frameworks with developments in the GCT field, both to safeguard public health as well as to facilitate global patient access.

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Table S1: Legal provisions for approval of GCTs

Jurisdiction	Law	Quality, safety and efficacy requirements	Manufacturing standards	Clinical trial standards
Canada	Food and Drugs Act	Food and Drug Regulations, Division 8	FDR Part C – Division 2 & 4; CTO Regulations (starting materials)	Food and Drug Regulations Part C - Division 5
EU	Regulation (EC) No 1394/2007 Regulation (EC) No 726/2004	Directive 2001/83/EC, Annex I, Part I (standards requirements) & Part IV (ATMP requirements)	Directive 2003/94/EC (GMP for medicinal products); Directive 2002/98/EC (human blood); Directive 2004/23/EC (human cells and tissues); Commission Directive 2006/17/EC (technical requirements human cells and tissues); Commission Directive 2006/86/EC (technical requirements human cells and tissues); Commission Directive 2001/18/EC (genetically modified organisms); Commission Directive 2005/61/EC (traceability and SAE reporting)	Directive 2001/20/EC (Regulation 536/2014); Commission Directive 2005/28/EC
Japan	Regenerative Medicine sections of Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act	Article 23-25 Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (standard approval) Article 23-26 Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act	Good, gene, Cellular and Tissue-based product manufacturing Practice (GCTP) (Ministerial Ordinance No. 93, 2014; PFSB Director Notice 0812 No. 11; August 12, 2014; Compliance Division Director Notice 1009 No. 4 (October 9, 2014)); Standards for Biological Materials (2003 Ministerial Notification No. 210 revised by 2014 MN No. 375 (September 26, 2014) and PFSB Director Notice 1002 No. 27 (October 2, 2014); Regulations for buildings and facilities (Ministerial ordinance No. 87, 2014; PFSB Director Notice 0812 No. 1; August 12, 2014)	Good clinical practice (GCP) (Ministerial ordinance No. 89, 2014; PFSB Director Notice 0812 No. 16; August 12, 2014; MRED Director Notice 1121 No. 3 (November 21, 2014))

Korea	Pharmaceutical Affairs Act	Regulation on Review and Authorization of Biological Products (Article 25 Annex II, III; Article 30, 31)	Korean Good Manufacturing Practice	Korean Good Clinical Practice
US	Food, Drug and Cosmetics Act Public Health Services Act	Food, Drug & Cosmetics Act (21 U.S.C. 321); 21 CFR 600, 601, 610	21 CFR 210-211; 600, 606 (cGMP for biologic products); 21 CFR 1271 (GTP: HCT/Ps)	21 CFR 50, 56, 210, 312, 314, 320, 812, 814

Table S2: Scientific guidelines that address assessment criteria for approval of GCTs

Jurisdiction	Scientific guideline
Canada	Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation (18 Jun 2013) Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans (21 Aug 2015)
EU	1. Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (Oct 2001); 2. Development and Manufacture of Lentiviral Vectors (Nov 2005); 3. Guideline on Human Cell-based Medicinal Products (11 Jan 2007); 4. Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors (1 May 2007); 5. Potency testing of cell-based immunotherapy medicinal products for the treatment of cancer (15 May 2008); 6. Guideline on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products (Nov 2008); 7. Non-clinical studies required before first clinical use of gene therapy medicinal products (Nov 2008); 8. ICH Considerations General Principles to Address Virus and Vector Shedding (Jul 2009); 9. ICH Considerations - Oncolytic Viruses (Oct 2009); 10. Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (3 Dec 2009); 11. Questions and answers on gene therapy (17 Dec 2009); 12. Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (16 Apr 2010); 13. Guideline on follow-up of patients administered with gene therapy medicinal products (1 May 2010); 14. Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors (8 Jul 2010); 15. Reflection paper on stem cell-based medicinal products (14 Jan 2011); 16. CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products (23 Jun 2011); 17. Reflection paper on design modifications of gene therapy medicinal products during development (14 Dec 2011); 18. Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (1 Nov 2012); 19. EU guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use (31 Jan 2013); 20. Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products (12 Feb 2013); 21. Reflection paper on management of clinical risks deriving from insertional mutagenesis (19 Apr 2013); 22. Clinical aspects related to tissue engineered products (19 Sep 2014); 23. Quality, non-clinical and clinical aspects of gene therapy medicinal products (23 May 2015);

Japan	1. General Principles for the Handling and Use of Cells/Tissue-Based Products (PFSB/MHLW Notification No. 1314 Appendix 1 – 2000); 2. Quality and Safety Assurance of Pharmaceuticals Manufactured Using Human or Animal derived Components as Raw Materials (Notification of Pharmaceutical and Medical Safety Bureau, the Ministry of Health and Welfare; Iyaku-hatsu No. 1314; 26 Dec, 2000); 3. Considerations in Standards for Biological Materials Notification of Evaluation and Licensing Division, Safety Division, Compliance and Narcotics Division and Blood and Blood Products Division, Pharmaceutical and Medical Safety Bureau, MHLW; Iyakushin-hatsu No. 0520001, Iyakuan-hatsu No. 0520001, Iyakukanma-hatsu No. 0520001 & iyakuketsu-hatsu No. 0520001; 20 May 2003); 4. Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Autologous Cells or Tissue (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushokuhatsu No. 0208003; 8 Feb 2008); 5. Q&A on Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Autologous Cells or Tissues (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; 12 Mar 2008); 6. Concepts for Manufacturing Control and Quality Control of Pharmaceuticals and Medical Devices Based on Human Autologous Cells or Tissues (Notification of Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, MHLW; Yakushokukanma-hatsu No. 0327025; 27 Mar 2008); 7. Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Allogeneic Cells or Tissues (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0912006; 12 Sep 2008); 8. Q&A on Guideline for Quality and Safety Assurance of Pharmaceuticals and Medical Devices Based on Human Allogeneic Cells or Tissues (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; 3 Oct 2008); 9. Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Autologous Human Somatic Stem Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-2; 7 Sep 2012); 10. Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Allogeneic Human Somatic Stem Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-3; 7 Sep 2012); 11. Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Human (Autologous) Induced Pluripotent Stem-Like Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-4; 7 Sep 2012); 12. Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Human (Allogeneic) Induced Pluripotent Stem-Like Cell (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-5; 7 Sep 2012); 13. Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Other Products Derived from Processed Human Embryonic Stem (ES) Cells (Notification of Pharmaceutical and Food Safety Bureau, MHLW; Yakushoku-hatsu No. 0907-6; 7 Sep 2012); 14. Guidance on application for marketing authorization (PFSB Director Notice 0812 No. 30 and MRED Director Notice 0812 No. 5 (August 12, 2014); 15. Guidance on GCTP/GQP/regulations for buildings and facilities Compliance Division Director Notice 1009 No. 1 (October 9, 2014); 16. Guidance on drug master file (ELD Director Notice 1117 No. 3 and MRED Director Notice 1117 No. 1 (November 17, 2014)

Korea	1. Guidelines on Cell Therapy and Gene Therapy Products (2004); 2. Guideline on Replication Competent Virus Test for Gene Therapy Products (2005); 3. Guideline on Mycoplasma Test Suitable for Cell Therapy Products (2008); 4. Guideline on Potency Testing of Cell Therapy Products (2010); 5. Guideline on Stem Cell Products (draft) (2011); 6. Guideline on Manufacture and Quality Control of Cell Therapy Products (2012); 7. Guideline on GMP for Cell Therapy Products (2012); 8. Guideline on Tumorigenicity Study of Stem Cell Products (draft) (2014)

US	1. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (Mar 1998); 2. Guidance for industry: Supplemental guidance on testing for replication competent retrovirus in retroviral vector based gene therapy products and during follow-up of patients in clinical trials using retroviral vectors (Oct 2006); 3. Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (Nov 2006); 4. Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products; guidance for industry (Aug 2007); 5. Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (Apr 2008); 6. Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (Apr 2008); 7. Guidance for industry - Considerations for allogeneic pancreatic islet cell products (Sep 2009); 8. Guidance for industry - Minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution for specified indications (Oct 2009); 9. Guidance for industry - Investigational New Drug Applications for Minimally manipulated, unrelated allogeneic placental/umbilical cord blood intended for hematopoietic reconstitution for specified indications (Oct 2009); 10. Guidance for industry: Cellular therapy for cardiac disease (Oct 2010); 11. Guidance for Industry - Potency Tests for Cellular and Gene Therapy Products (Jan 2011); 12. Guidance for industry: Clinical considerations for therapeutic cancer vaccines (Oct 2011); 13. Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (Dec 2011); 14. Guidance for Industry - Preclinical Assessment of Investigational Cellular and Gene Therapy Products (Nov 2013); 15. 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 (Mar 2014); 16. IND 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 (Mar 2014); 17. Current Good Manufacturing Practice Requirements for Combination Products - Draft Guidance for Industry and FDA Staff (Jan 2015); 18. Determining the need for and content of environmental assessments for gene therapies, vectored vaccines, and related recombinant viral or microbial products; Guidance for industry (18 Mar 2015); 19. Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products - Guidance for Industry (Jun 2015); 20. Design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products; guidance for industry (Aug 2015); 21. Recommendations for microbial vectors used for gene therapy; draft guidance for industry (Oct 2015); 22. Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-based Products Regulated Solely Under 361 of the Public Health Service Act and 21 CFR Part 1271; Draft Guidance for Industry (Dec 2015)

Chapter 2.2:
Regulating ATMPs through exemptions: an analysis of diverging national regulatory approaches for the Hospital Exemption in nine EU countries

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Under consideration for publication

Abstract

The Hospital Exemption was enacted to accommodate manufacturing of Advanced Therapy Medicinal Products (ATMPs) for treatment purposes. However, how its implementation compares among countries of the European Union (EU) is largely unknown. Using public regulatory documentation and information from interviews with competent authorities, we studied the implementation process of the Hospital Exemption in nine EU countries. Results show varying national regulatory provisions for the Hospital Exemption. In some countries, national 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 Hospital Exemption authorization or provisions that restrict potential competitive advantages with licensed alternative treatment, among others. Judged on the amount of Hospital Exemption license holders, manufacturing of non-commercial ATMPs for treatment purposes is facilitated in some countries only. Limited capacity to comply with provisions, implementation delays, and the use of alternative pathways hinder utilization of the Hospital Exemption in clinical practice. In contrast, the Hospital Exemption is used as a stepping stone towards commercial development in other countries. Multi-stakeholder engagement is needed to facilitate non-commercial ATMP manufacturing within clinical practice, without impeding commercial developments.

Introduction

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 working with, scaling-up manufacturing 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 fundamental questions about how pre-existing regulatory requirements for ensuring safety and efficacy of industry-sponsored pharmaceutical trials can be adjusted to fit GCT development close to clinical practice.[3-5]

In the European Union (EU), policy makers have dealt with these challenges by implementing the Advanced Therapy Medicinal Product (ATMP) Regulation (1394/2007) in 2009 after multiple public consultations.[6] The ATMP Regulation subjects ATMPs to the centralized authorization procedure of the European Medicines Agency (EMA), making it mandatory that ATMPs are developed based on stringent evidentiary requirements of evidence-based medicine (EBM) and multiple stages of clinical trials.[7] At the same time, the ATMP Regulation also allows EU countries to implement national provisions that exempt some ATMPs from centralized authorization. Known as the Hospital Exemption (HE), Article 28 of the ATMP Regulation 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 EC 1394/2007, Article 28).

The implementation of the HE has been received with mixed responses in the field. On the one hand, it has been pointed out that the HE has a potential of facilitating innovation and patient access. It can incentivize hospital innovation and serve as a protective space for those therapies that would be difficult or even impossible to develop according to the requirements of the centralized authorization pathway.[8,9] On the other hand, the HE has been criticized for apparent national variation in implementation,[10–12] a lack of clarity about the exact national provisions and requirements, and for potential misuse as an instrument to create competitive advantage compared to commercial ATMP development.[13–16]

So far, these debates are largely based on anecdotal evidence. There is very limited knowledge on how national provisions for the HE have been implemented, and how the HE has been subsequently utilized in multiple EU countries. Therefore, the aim of this study is to compare how the HE has been implemented focusing on two outcomes; national regulatory provisions, and the amount of HE license holders. We also document the implementation process in multiple countries, and associate differences in this process with outcomes. The comparative analysis includes nine countries (Austria (AT), Belgium (BE), Finland (FI), France (FR), Germany (DE), Italy (IT), Netherlands (NL), Spain (ES), and United Kingdom (UK)). It provides clarity on variation in HE implementation, to inform the debate on the HE, and to facilitate policy learning for HE utilization for all EU countries.

Methods

Country selection

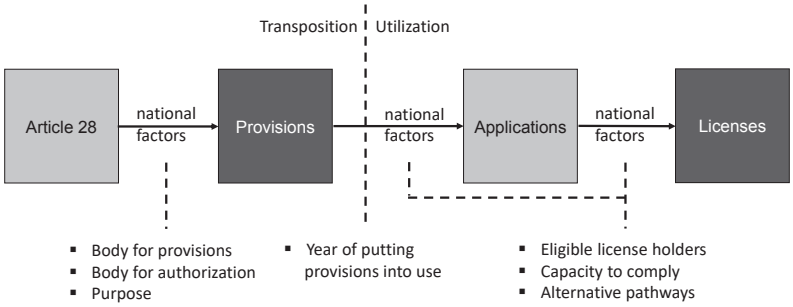
We selected European countries that 1) were a Member State of the EU, 2) implemented provisions by June 2018, and 3) showed indications of ATMP clinical activity, either evident through the conduct of clinical trials[5] and/or ATMP manufacturing under the HE.[17] We ensured to include countries from various European regions. Based on these criteria, we selected Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Spain 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.[18] Through transposition into national law, competent authorities of Member States are made responsible for drafting specific national regulatory provisions and putting these into use on a national level. When national provisions are implemented, the authorization of HE licenses are put under the authority of either the national regulatory authority or the inspectorate.

Based on previous work,[18,19] 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 use in

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



practice. Utilization starts from the moment applications for a HE license can be submitted (Figure 1).

The framework allows to separate outcome measures of transposition and utilization and to examine factors that contributed to how transposition and utilization resulted in the defined outcomes. We defined the intermediate outcome of the transposition phase as the national provisions for the HE. The final outcome of HE utilization was defined as authorization of HE licenses (yes/no), which was further quantified according to the number of license holders per country (Figure 1). Outcomes were captured between May-October 2018.

Data collection

Regulatory documentation

The websites of the competent authorities of the selected countries were used to search for information on national provisions for the HE.[20–28] We defined national 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 employees of the inspectorate and national regulatory authorities per selected country, and a snowball approach was used to identify the most suitable interviewee for the interview. A semi-structured interview guide was used to verify national provisions for the HE, and to discuss regulatory experience with HE authorizations, and national factors that influenced these outcomes. Oral consent for recording was sought before interviews were started. Interviews were conducted between June-October 2018, and fully transcribed. All interviewees were ATMP experts within their national regulatory agency for medicinal products. Reported factual information in this study was verified with the interviewees in July 2019.

Data analysis

We used a mixed methods approach for data analysis. Regulatory documentation served as a starting point for the analysis of national provisions. These informed interviews with competent authorities. The transcribed interviews served to qualitatively analyze the implementation process and outcome measures using a mixed deductive-inductive approach in NVivo Pro v11. First, transcripts were coded using a general coding tree that followed the structure and elements of the interview guide distinguishing between national provisions, authorization of licenses, and national factors. Second, information on the outcome measures of national provisions and authorization of licenses was extracted and tabulated, and an analysis was performed to identify national factors in relation to the studied outcomes, as explained below.

National provisions

The national provisions laid out in regulatory documentation were grouped into four main categories; scope, eligibility criteria, data entry requirements and process standards. For each category a number of specific assessment criteria were developed based on previous work[29] and knowledge of the design and functioning of regulatory pathways. Regulatory documentation was then read in full to assess and code provisions per assessment criterion (Table S1). We conducted interviews with competent authorities to verify information from regulatory documentation.

An overview of national provisions was created distinguishing between three layers. The first layer was defined as provisions that are the same in each country and directly originate from Article 28 (e.g. process standards for manufacturing). The second layer was defined as 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”). The third layer was defined as additional provisions that differed among countries and did not directly originate from Article 28 (e.g. data entry requirements).

Hospital Exemption license holders
Data on regulatory experience with HE authorization was captured in terms of the amount of applications for HE licenses, and authorizations of HE licenses over time, 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 factors
National factors that played a role in the process of transposition and utilization were qualitatively analyzed to explain variation between the studied outcomes among countries. Using an inductive approach, we coded national factors described in the interview transcripts as part of the implementation process. During open coding, the coding tree was adapted and expanded. We grouped open codes into national factors and attributed nation specific values for comparative analysis. The open round of coding revealed the importance of national factors on outcomes, and substantial variability among countries.

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

Results

National provisions for the Hospital Exemption

National provisions for the HE were variable among selected EU countries during the period of analysis. To allow a comprehensive comparison, we distinguish between non-variable and variable provisions that originate from Article 28, and additional provisions that are specific for each country.

Non-variable provisions

Article 28 imposes some provisions for the HE that led to non-variable national provisions across 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, 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 France. For non-pharmaceutical establishments in France, adherence to Good Manufacturing Practices (GMP) guidance suffices in order for these establishments to meet GMP requirements over time. In all other selected countries, compliance with full GMP regulations is mandatory. Extensive manufacturing and quality data is 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”. A few countries 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), non-industrial 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 the Netherlands (10 patients per year, or a maximum of 50 patients per

Table 1: Article 28 provisions

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

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 most countries. Across countries, several provisions in various combinations were described that relate to: 1) whether clinical evidence is required for a HE license, 2) the type of eligible license holders (hospitals/public, unrestricted), 3) restrictions when alternative treatment for the same indication (licensed pharmaceuticals, including but not limited to ATMPs) is available to prevent competition, and 4) whether manufacturing under a HE is intended to treat patients for which there is an unmet medical need (Figure 2).

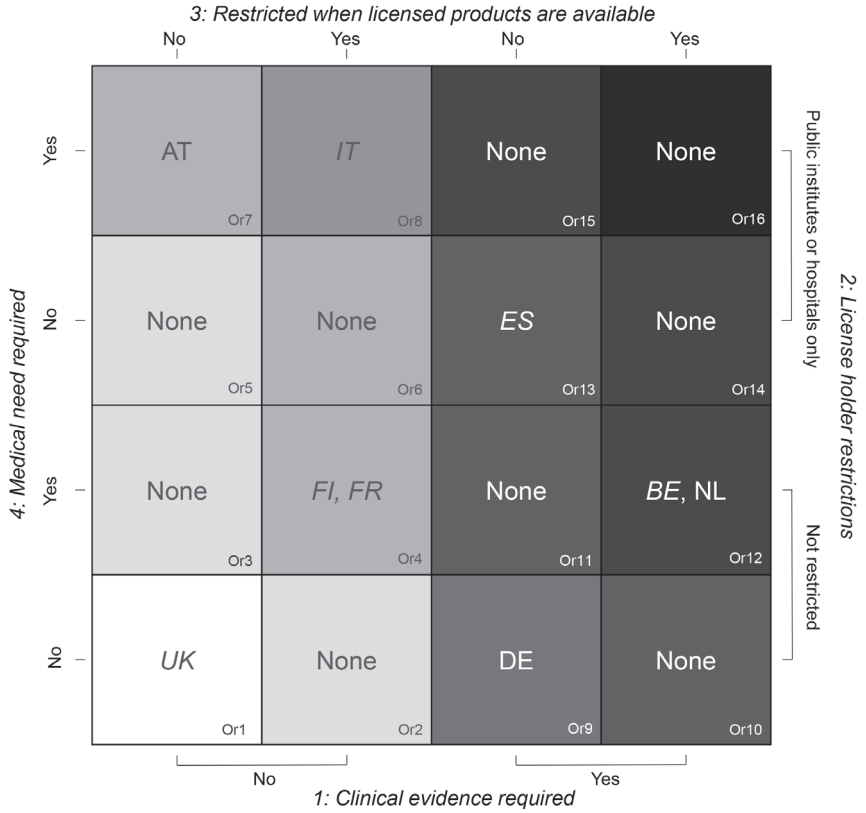
Belgium, Germany, Netherlands, and Spain have stringent clinical data entry provisions for the HE. All available clinical data is required in order for the authorities to perform a preliminary benefit/risk assessment. Yet, in the Netherlands only there is a focus on safety. This assessment follows similar principles to benefit/risk assessments in commercial pathways. However, less robust data can suffice to assess benefits and safety for patients, based on case-by-case considerations. 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 Belgium and the Netherlands. In Spain, only hospitals are eligible to apply for a HE license. German provisions do not impose further restrictions (Figure 2).

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

	AT	BE	FI	FR	DE	IT	NL	ES	UK
Scope									
Non-routine/Custom made product	Non-defined	Guidance	Guidance	Non-defined	Guidance	Non-defined	Guidance	Non-defined	Guidance
Number of patients	Non-defined	Non-defined	Non-defined	Non-defined	Non-defined	Non-defined	10 / 50 patients	Non-defined	Non-defined
Duration of license	Non-defined	1 year	Non-defined	5 years	Non-defined	Non-defined	1 year	3 to 5 years	Non-defined
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 [a]	No	Yes	Yes	No	No
Medical need considerations [b]	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[c]	Required	Required	Required	Required	Required

AT = Austria, BE = Belgium, FI = Finland, FR = France, DE = Germany, IT = Italy, NL = Netherlands, ES = Spain, UK = United Kingdom, a = when clinical data is not available, b = refers to whether the competent authority considers medical need justifications in their decision-making for authorization, c = when clinical data is lacking, d = not required for non-pharmaceutical establishments. NB: Reflects national provisions during May-October 2018.

Figure 2: Additional provisions for the Hospital Exemption in selected countries



AT = Austria, BE = Belgium, FI = Finland, FR = France, DE = Germany, IT = Italy, NL = Netherlands, ES = Spain, UK = United Kingdom. *Italic* = detailed regulations (including royal decrees), no italic = Article 28 transposition into law combined with practical guidance. Shading from white (Or1) to black (Or16) depict the increasing stringency of the combination of additional provisions. Or1 = no clinical data, no additional provisions, Or2,3,5 = no clinical data, 1 additional provision, Or4,6,7 = no clinical data, 2 additional provisions, Or8 = no clinical data, 3 additional provisions, Or9 = clinical data, no additional provisions, Or10,11,13 = clinical data, 1 additional provision, Or 12,14,15 = clinical data, 2 additional provisions, Or16 = clinical data, 3 additional provisions.

There are five countries where HE licenses can be granted without clinical evidence: Austria, Finland, France, Italy, and the UK. Clinical data can be submitted if available, yet, other additional provisions were implemented to restrict the use of the HE. In France, HE license applications without clinical data need to target an unmet medical need and no other licensed

pharmaceuticals should be available. Unmet medical need is also considered for authorization in Austria, Finland, and Italy. In Finland and Italy, authorization is further restricted when licensed pharmaceuticals are available (regardless of clinical data availability).

Lastly, HE licenses are only granted to hospitals and public institutes in Austria and Italy, respectively. The UK is the only selected country without additional provisions (Figure 2).

Hospital Exemption license holders

Whether HE authorizations were granted, and the amount of HE license holders, varied between the selected countries as of June 2018. In comparison with other selected countries, the number of HE license holders was relatively high in France,[30] Germany,[31] and the Netherlands (Table 3). In France, 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.[30] There were seven HE license holders in Germany, of which most were companies (n=6). There was one company that holds two HE licenses.[31] In the Netherlands, 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 products per facility, which need to be renewed each year. There were relatively few HE license holders in Finland (n=2, public) and the UK (n=1, public). In Spain, none of the HE applications had been authorized. In Austria and Belgium 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 Italy is unknown (Table 3).

National factors that influenced HE implementation outcomes

Although Article 28 stipulates a clear requirement for compliance with process standards for quality, traceability and pharmacovigilance, it lacks clarity on for which activities the HE should be used (i.e. the intended regulatory purpose). This played an imperative role in the drafting of national provisions. Across countries, several purposes were described in various combinations: 1) to fulfill unmet medical needs, 2) to provide treatment of sufficient benefit and safety (i.e. benefit/risk balance), and 3) to collect data for central authorization (innovation pathway) (Table 4). We interviewed one (AT, BE, FI, DE, ES, UK), or three (NL) ATMP experts of the competent authorities. The competent authorities of France

Table 3: Hospital Exemption authorizations and applications in selected countries

	Authorizations (number of license holders)	Applications
Austria	No	No
Belgium	No	No
Finland	Yes (2)	Yes
France	Yes (11)	Yes
Germany	Yes (7)	Yes
Italy	Unknown[a]	Unknown[a]
Netherlands	Yes (11)	Yes
Spain	No	Yes
UK	Yes (1)	Yes

NB: Reflects regulatory experience with applications and authorizations of HE licenses during Jun-Oct 2018. (a) authorities were unavailable for interviews.

and Italy were unavailable for interviews, and therefore, not described below.

Across countries, different bodies were responsible for the drafting of provisions and/or granting licenses. When inspectorates are mainly responsible for granting licenses, the purpose of the HE is focused on manufacturing for unmet medical needs (AT, FI, UK). In contrast, when regulators were involved in drafting provisions, and/or when they are responsible for granting licenses, the purpose of the HE is also focused on treatment of sufficient benefit and safety (BE, DE, ES, NL). 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 (Table 4). These variations illustrate that national political procedures for the transposition of EU legislation differ among countries. However, 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 discrepancies in national factors to explain differences in the amount of HE license holders among countries (Table 4).

Table 4: Overview of national factors and implementation outcomes

	Transposition national factors			Outcome	Utilization national factors				Outcome
	Body for drafting provisions	Body for authorization	Purpose	Provisions[a]	Year of putting provisions to use	Eligible license holders	Capacity to comply	Alternative pathways	Amount of license holders[b]
Austria	■	●	●	●	2017	●	□	■	○
Finland	◀	◀	●	●	2009	■	□	□	□
UK	■	●	●	○	2010	■	■	■	□
Belgium	□	□	□	■	2017	■	□	□	○
Netherlands	◀	◀	□	■	2010	■	■	□	■
Germany	■	□	■	□	2010	■	■	□	■
Spain	□	□	■	■	2014	●	□	■	○

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. Purpose: ● = unmet medical needs, □ = unmet medical needs & benefit and safety, ■ = benefit and safety & 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 non-centrally licensed products): □ = no alternative pathways preferred or available, only other pathway is clinical trial, ■ = use of alternative pathways; License holders: ○ = none, □ = limited, ■ = relatively high.

a = reflects national provisions during May-October 2018, b = reflects HE license holders during Jun-Oct 2018.

Unmet medical needs

In Austria, Finland, and the UK, the HE was intended as a manufacturing license for therapies indicated to treat patients with unmet medical needs (Table 4). Not many additional provisions were implemented, but the amount of license holders is low in all three countries. In Austria, 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 Finland, the amount of HE license holders is limited, despite the possibility to manufacture for human administration before clinical trial conduct. It was reported that some applications were withdrawn before GMP inspection. Furthermore, in both Austria and Finland 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.[32] 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. The amount of HE license holders is limited (Table 4), while there are many public and private facilities that hold a Specials license for ATMP manufacture (approximately 25).[33]

Unmet medical needs and benefit/risk balance

In Belgium and the Netherlands, 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 the Netherlands, but not in Belgium. 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 Belgium, 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 and a lack of capacity to comply with full GMP, leading facilities to manufacture under the framework of clinical trials (Table 4).

Benefit/risk balance and innovation

In Germany and Spain, 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 for central authorization (Table 4). Provisions are relatively similar, except that license holders are restricted to hospitals in Spain (Figure 2). Yet, authorizations were granted in Germany, but not in Spain. In Germany, 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. 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.[31] In Spain, 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 on-going assessment. Named Patient Use was reported to be used for ATMP manufacture (Table 4).

Discussion

In this study we document how the HE has been implemented in various EU countries. Our results show that national 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) lead to HE pathways that shifted towards the central authorization procedure. Other provisions put restrictions on the HE to prevent competitive advantage with licensed pharmaceuticals. In contrast, some countries implemented the HE as a stepping stone for central authorization. More restrictive provisions are expected to result in less HE license holders, but our results indicate otherwise. HE licenses were authorized to accommodate local manufacturing activities in hospital settings[34] in France and the Netherlands only, and to some extent in Finland and the UK. In Germany, mostly companies hold HE licenses to manufacture ATMPs, as well as a few companies in the Netherlands. In Austria, Belgium, and Spain, 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.

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.[18] 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. The variety between national provisions, HE utilization, and implementation processes reflect political and legislative differences, and differences of the ATMP development landscape among countries. The variation between national provisions has been critiqued,[35] and the subpar requirements compared to medicinal product requirements is postulated to put patients at risks.[36] Others also suggest that quality manufacturing is at stake when manufacturing only a few batches by individual facilities.[37] Harmonization could be a solution for less regulatory variety across the EU.[38,39] However, harmonization typically does not facilitate local activities and opportunities.[7]

When national provisions are aligned with local activities and opportunities, utilization is expected.[40] Our results indicate otherwise, as lacking capacity to comply with provisions was reported to be a hurdle for authorization. One explanation comes from the notion of institutional readiness to adapt to new practices and structures.[41,42] Suggestions of limited institutional readiness for the HE by public facilities, which is more evident in some countries than others, indicates limited institutional readiness for principles of pharmaceutical regulations at large.[43,44] Competent authorities and stakeholders in the field need to collaborate for capacity building for GMP manufacturing, pharmacovigilance, traceability and clinical data collection, in order for eligible license holders to comply with HE provisions. 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 in comparison with clinical trial regulations, and needs to be investigated further and confirmed by public facilities.

Three principles played an important role in defining the purpose for the HE in each country; clinical principles (e.g. unmet medical needs), evidentiary principles of EBM (e.g. benefit/risk assessments), and innovation principles. To which extent these principles were considered during transposition varies among countries, and reflects differences in national provisions. Article 28 exempts ATMPs from EBM principles in which the ATMP Regulation is embedded, with some exceptions such as GMP manufacturing. Yet, clinical data requirements demonstrate that the HE pathway shifted more towards the central authorization procedure in some countries. Although confirmatory evidence of a positive benefit/risk

balance is not required under the HE, limited capacity to comply illustrates tension between the clinical and EBM paradigm, in particular for public facilities. Due to the unmet medical need and scientific uncertainty that is so typical to the ATMP field,[1,45] it becomes an ethical question to find the right balance between patient needs versus patient benefits and safety. In clinical practice, patients and health care professionals decide whether risks and uncertainties are acceptable considering the prognosis. Yet, authorities have a mandate to protect patients and society from unacceptable risks,[35,36] but also from malicious practices including treatment without benefits.[46] Safeguarding public health and enforcement against malicious practices justifies the implementation of additional provisions for the HE. However, access to potentially life-saving treatment is impeded if manufacturers cannot comply with provisions.

The relatively lenient provisions of Article 28 in comparison to pharmaceutical regulations could facilitate ATMP treatment and innovation in hospital settings,[8,47] away from the pressure of existing frameworks.[48] This regulatory approach particularly suits ATMPs that have close proximity to practices with long clinical history, including ATMPs that are based on cultured tissue for severe burn wounds,[49,50] or stem cell therapies.[51] Furthermore, exemption structures may be vital to treat patients with ATMPs that suffer from rare or ultra-rare conditions or diseases.[9] ATMP market withdrawals, for example for Glybera,[52] indicate that it is currently uncertain whether orphan ATMPs are commercially viable. The HE could enable manufacturing of particular therapies for which incentives for commercial development are lacking. However, it is largely unknown how manufacturing under the HE is incentivized and used in clinical practice. It is reported that particular cell types, including lymphocytes, chondrocytes, dendritic cells, and stem cells, were manufactured under HE licenses.[12] Yet, more detailed information on targeted indications, scale of manufacturing and treatment, and the clinical implications is lacking.

It has been argued that the HE undermines ATMP development for central authorization, and even impedes patient access in the future if used inappropriately.[16,35,36,38,53] On the contrary, it is questionable whether it is commercially viable to develop all ATMPs via the central authorization pathway.[43] Tensions between HE manufacturing and commercial innovation also vary among countries. For instance, the HE creates a competitive advantage for German companies compared to other EU commercial developers, while other authorities limit commercial competition of the HE with provisions. Furthermore, HE licenses are restricted to small scale manufacturing. Research, guidance and definitions to distinguish between commercially and

non-commercially viable ATMPs could improve utilization of the HE for non-commercial treatment versus utilization of clinical trial pathways for commercial innovation.[10] It requires a continuous, inclusive and open dialogue between the competent authorities and other stakeholders, as commercial viability is likely to be a moving target due to scientific and technological advance. 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.[38]

In conclusion, the implementation process of the HE varied substantially among selected countries as a result of different regulatory considerations that relate to unmet medical needs, benefit and risks, and innovation. In some countries, the HE is facilitating ATMP treatment and hospital innovation, whereas in others it is used as a stepping stone towards commercial development. In countries with more restrictive provisions the HE pathway shifted towards the central authorization procedure. Yet, capacity to comply with provisions, implementation delays, and the use of alternative pathways mediate the effect of provisions on HE utilization. Multi-stakeholder engagement is needed to facilitate appropriate use of both the HE pathway and centralized commercial development trajectories.

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Supplementary Material

Table S1: Final assessment instrument for national Hospital Exemption provisions

Class	Provisions	Codes
Scope	Definition of “non-routine” and “custom-made product”	Not defined, Guidance
	Number of patients	Not defined, 10 to 50 patients
	Duration of license	Not defined, 1 year , 3 year, 5 year
	Annual reporting	Not required, Required
Eligibility criteria	Delivery	Delivery on individual medical prescription
	Treatment	Treatment in hospital
	Export	No export
	Eligible license holders	No restriction, Hospitals only, Public institutes only
	Restricted when licensed products are available	No restriction, Restriction when clinical data is not available and competing products are available, Restriction when competing products are available
	Medical need considerations for authorization (e.g. last resort treatment, urgency to treat)	Not considered, Medical need considered when clinical data is lacking, Medical need considered
Data entry requirements	Manufacturing & Quality	Not required, Required
	Clinical	Not required, Required
Process standards	Manufacturing & Quality equivalent to ATMP authorization pathway	GMP not required for hospitals, GMP compliance required
	National traceability regulations	National traceability regulations required
	National pharmacovigilance regulations	National pharmacovigilance reporting required
Legislation	Legislative ground of provisions	Article 28 transposition into law combined with practical guidance, Detailed regulations (including royal decrees)

CHAPTER 3:
DECISION-MAKING FOR MARKETING AUTHORIZATION OF GENE AND CELL-BASED THERAPIES

Chapter 3.1:
A decade of marketing approval of gene and cell-based therapies in the United States, European Union, and Japan: a regulatory decision-making evaluation

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Abstract

There is a widely-held expectation of clinical advance with the development of gene and cell-based therapies (GCTs). Yet, establishing benefits and risks is highly uncertain. We examine differences in decision-making for GCT approval between jurisdictions by comparing regulatory assessment procedures in the United States (US), European Union (EU), and Japan. A cohort of 18 assessment procedures was analyzed by comparing product characteristics, evidentiary and non-evidentiary factors considered for approval, and post-marketing risk management. Product characteristics are very heterogeneous and only three products are marketed in multiple jurisdictions. Almost half of all approved GCTs were designated an orphan drug. Overall, confirmatory evidence or indications of clinical benefit were evident in US and EU applications, whereas in Japan approval was solely granted based on non-confirmatory evidence. Due to scientific uncertainties and safety risks, substantial post-marketing risk management activities were requested in the EU and Japan. EU and Japanese authorities often took unmet medical needs into consideration in decision-making for approval. These observations underline the effects of implemented legislation in these two jurisdictions that facilitate an adaptive approach to licensing. In the US, the recent assessments of two CAR-T cell products are suggestive of a trend towards a more permissive approach for GCT approval under recent reforms, in contrast to a more binary decision-making approach for previous approvals. It indicates that all three regulatory agencies are currently willing to take risk by approving GCTs with scientific uncertainties and safety risks, urging them to pay accurate attention to post-marketing risk management.

Introduction

Gene and cell-based therapies (GCTs) represent a heterogeneous class of medicines[1–4] with potential for clinical benefit in a wide range of therapeutic areas, including areas with limited treatment availability.[5] Regulatory authorities face considerably uncertainties when deciding on the marketing approval of these products. Quality control and methodologies to demonstrate benefits and risks tend to be suboptimal or not available at all due to the complex and idiosyncratic nature of therapies and often small target populations.[5–7] Furthermore, efficacy of novel modes of action and associated potential safety risks (e.g. insertional mutagenesis, tumorigenicity) are uncertain.[1,2,4]

Worldwide, regulatory authorities aim to consider benefits and risks in a structured assessment for approval of medicines.[8] However, authorities differ in how they balance the need for robust scientific evidence and timely access for patients,[9] as well as to which degree they consider non-evidentiary factors in assessments.[10–12] Due to the novelty of the GCT field, regulators also face scientific issues that have not been discussed in previous regulatory procedures. Consequently, detailed regulatory requirements for GCT approval are not standardized or harmonized yet.[13]

So far, insights into regulatory assessment and decision-making for GCT approval is limited, but we observed that the European Union (EU) authorities are currently exploring an adaptive regulatory approach. Furthermore, the regulatory assessment of the first approved gene therapy in the EU showed to be a challenging process due to many scientific uncertainties.[14] However, it is unknown how this approach compares to decision-making for GCT approval in other regions.

This study aims to compare decision-making for GCT approval by the United States (US), Japanese, and EU regulatory authorities during the last ten years. First, we compare product profiles, evidentiary support, and regulatory procedures between jurisdictions. Second, we provide insight into benefit/risk assessments by analyzing how different authorities consider scientific evidence and related uncertainties, plus other non-evidentiary factors to grant approval. Finally, we examine how uncertainties and safety risks are managed post-marketing.

Methods

This is a cohort study of approved GCTs by the Food and Drug Administration (FDA), Pharmaceuticals and Medical Device Agency (PMDA), and European Medicines Agency (EMA). Data on assessment and decision-making for approval was extracted from public assessment reports.[15–17] Assessment procedures were included if 1) GCTs were assessed as a medicine and approved in the last ten years (2008-2017), and 2) quality, preclinical and clinical evidence was required for application and available for analysis.

Characteristics of regulatory assessments

We constructed variables to unpack assessment procedures into factors that were part of decision-making, such as scientific evidence, medical context, and available regulatory processes.[11,12] We first defined a preliminary set of variables, building on previous studies.[18–20] We subsequently added other relevant variables to tailor the classification scheme to GCT technological aspects, and to adequately capture quality and preclinical aspects. Variables were organized under four main categories; 1) product profile, 2) scientific evidence, 3) regulatory processes, and 4) outcome. Two researchers (DC, SdW) independently extracted data from assessment reports and assigned pre-determined categorical or numerical values per variable (Table S1). Data extraction and value assignment were compared between researchers, discrepancies were discussed until consensus.

We first conducted a quantitative descriptive cohort analysis (analysis 1) based on the assigned values. IBM SPSS Statistics 24 was used to stratify and tabulate data by jurisdiction (Table S2). To reveal commonalities between jurisdictions, data was also stratified by orphan drug designation (yes/no) and regulatory pathway for approval (standard/non-standard). Given small numbers, statistical analysis was not performed.

Benefit/risk assessments & post-marketing risk management

We subsequently conducted a qualitative analysis to understand evidentiary considerations and other non-evidentiary factors that were decisive for approval (analysis 2), and how uncertainties and safety risks were managed post-marketing (analysis 3). We extracted sections on benefit/risk balances and post-marketing obligations from assessment reports. No major discrepancies between specificity, the level of detail and format of EU, Japanese, and US assessment reports were identified.

The extracted text was qualitatively analyzed in NVivo Pro 11 for each assessment separately. Evidentiary certainties and uncertainties, plus non-evidentiary factors were identified and grouped using the variables. If available, corresponding regulatory interpretation (e.g. satisfactory, unacceptable) and/or post-marketing obligations were identified. Independent data extraction and organization were compared between researchers (DC, SdW). Discrepancies were discussed until consensus.

Four subcategories were frequently part of benefit/risk assessments: clinical study design, benefits, risks, and unmet medical needs (Table 3). Per subcategory, evidentiary certainties and uncertainties, plus regulatory interpretation were captured to illustrate considerations for approval and their relative weight. In addition, post-marketing study obligations demonstrate how uncertainty on clinical outcomes and safety risks are managed post-marketing. Results were pooled per jurisdiction to reveal patterns per regulatory authority.

Results

Characteristics of regulatory assessments

In total, 18 assessment procedures were included, seven in the US, nine in the EU, and two in Japan (Table 1). Most products were cell-based therapies (CTs - including device-combined therapies, n=12/18). *In-vivo* and *ex-vivo* gene therapies (GTs) were exclusively approved in the US and EU. Provenge, Imlygic, and MACI were approved in both the US and EU. Other GCTs were exclusively marketed in the US, Japan or EU.

Most CTs originate from autologous starting material (n=12/18,Table 2). More detailed product characteristics vary substantially, for example, cellular starting material consists of either antigen presenting cells, differentiated tissue cells, lymphocytes or stem cells. GTs include both *ex-vivo* and *in-vivo* products with specific vectors (not shown.

A large proportion of approvals were granted for oncology (n=7/18) and cartilage defects products (n=4/18). A substantial amount (n=7/9) of EU products target indications that were considered severely debilitating or life-threatening. Multiple US (n=3/7) and EU products (n=4/9) were designated as orphan drugs, but lack of available alternative treatment for these products was mostly evident in the EU (n=4/9). Targeted indications were also considered life-threatening in Japan (n=2/2), yet alternative

Table 1: Overview of included products

	Product	Year of approval	Approval pathway	Product description	Therapeutic area[a]	Orphan drug
US	Provenge	2010	Fast track	Autologous peripheral blood mononuclear cells	Prostate cancer	N
	Laviv	2011	Standard	Autologous cultured fibroblasts	Moderate to severe nasolabial fold wrinkles	N
	Gintuit	2012	Standard	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen	Mucogingival conditions	N
	Imlygic	2015	Fast track	Genetically modified oncolytic viral therapy	Lesions in patients with melanoma	Y
	MACI	2016	Standard	Autologous cultured chondrocytes on a porcine collagen membrane	Cartilage defects of the knee	N
	Kymriah	2017	Standard (BTD)	Genetically modified autologous T cell immunotherapy	B cell precursor acute lymphoblastic leukemia (ALL)	Y
	Yescarta	2017	Standard (BTD)	Genetically modified autologous T cell immunotherapy	Relapsed or refractory large B cell lymphoma	Y
EU	Chondro-Celect	2009	Standard	Autologous cartilage cells	Cartilage defects of the knee	N
	Glybera	2012	Approval under exceptional circumstances	Adeno-associated viral vector for gene delivery	Familial lipoprotein lipase deficiency	Y
	MACI	2013	Standard	Matrix applied characterized autologous cultured chondrocytes	Cartilage defects of the knee	N
	Provenge	2013	Standard	Autologous peripheral blood mononuclear cells	Prostate cancer	N
	Imlygic	2015	Standard	Genetically modified oncolytic viral therapy	Melanoma	N
	Holoclar	2015	Conditional	Autologous human corneal epithelial cells containing stem cells	Corneal lesions	Y
	Strimvelis	2016	Standard	Autologous CD34+ transduced cells with retroviral vector	Adenosine deaminase deficiency (ADA-SCID)	Y
	Zalmoxis	2016	Conditional	Allogeneic T cells genetically modified with retroviral vector	Adjunctive treatment in haploidentical hematopoietic stem cell transplantation of adult patients with high-risk hematological malignancies	Y

	Spherox	2017	Standard	Spheroids of human autologous matrix-associated chondrocytes	Cartilage defects of the knee	N
JP	Temcell	2015	Standard	Allogeneic bone marrow-derived mesenchymal stem cells	GvHD	Y
	Heartsheet	2015	Conditional	Autologous skeletal myoblast-derived cell sheet	Severe heart failure (ischemic heart disease)	N

BTD = Breakthrough Therapy Designation, [a] = based on indication of approved label, GvHD = Graft versus Host Disease.

treatment was not lacking (n=0/2). One GCT was designated an orphan drug, (Table 2).

The level of scientific evidence is comparable between the US and EU (Table 2). A significant efficacy outcome on primary endpoint was demonstrated for all US (n=7/7) and most EU (n=7/9) assessments, whereas in Japan non-significant trends of efficacy were sufficient for approval. An added clinical benefit over standard treatment was demonstrated in pivotal trials for only two products (MACI (EU/US), Gintuit (US)), but most trial designs lacked an active comparator or other standard therapy arm (US n=5/7, EU: n=6/9, JP: n=2/2). Yet, all EU and one US orphan GCT were considered to have added clinical benefit because alternative treatment is lacking (n=5/8). Pivotal trial design was most robust in the US for products approved before 2017, illustrated by exclusive approval based on randomized controlled trial (RCT) design (US n=5/7), compared to the EU (n=5/9) and Japan (n=0/2). Other non-randomized single arm trial designs were accepted for two recent approvals in the US, three EU orphan drugs and all Japanese GCTs. Observational study design was used for one EU orphan GCT that was already previously available in some EU Member States. Furthermore, more patients were included in pivotal trials in the US (μ=255, range 68-512) compared to the EU (μ=179, range 12-512) and Japan (μ=16, range 7-25).

Approximately half of all products gained standard approval without expedited designations (n=10/18), while others were approved under various expedited pathways and adaptive pathways (US n=4/7, JP: n=1/2, EU: n=3/8) (Table 1-2, for definition see Table S1). Overall, we observed less robust evidence for orphan drugs and approval under expedited or adaptive pathways, indicated by less RCTs, less significant efficacy outcomes, and lower number of patients. Results indicated no differences between evidentiary support for gene versus cell-based products (not shown).

Table 2: Summary of characteristics of regulatory assessment procedures per jurisdiction (n)

Variable	US (n=7)	EU (n=9)	Japan (n=2)	Total (n=18)
Product type				
Product profile				
Gene therapy	3	3	0	6
Cell therapy	2	4	2	8
Combination therapies	2	2	0	4
Starting material cell-based therapy				
Autologous	5	6	1	12
Allogeneic	1	1	1	3
Target population				
Lack of alternative therapy	1	4	0	5
Orphan designation	3	4	1	8
Severe disease	5	7	2	14
Scientific evidence				
Randomized clinical trial/Ph3/comparator	5	5	0	10
Blinded pivotal trials	2	1	0	3
Clinically relevant primary endpoint(s)	7	9	1	17
Clinically relevant secondary endpoint(s)	5	5	1	11
Total number of patients in pivotal trial(s)[a]	255	179	16	na
Significant outcome primary endpoint	7	7	0	14
Significant outcome secondary endpoint	2	4	0	6
Added clinical benefit	4	4	0	8
Regulatory process				
Expedited/adaptive pathway	4	3	1	8

[a] Mean number of patients included in pivotal trial, including all study arms, [b] Mean number of days between application and final outcome.

Benefit/risk assessments

Regulatory assessment of scientific evidence was associated with considerable uncertainty in all jurisdictions. Uncertainties were often a result of suboptimal study design characteristics, including open label or single arm design, change of primary endpoints, uncertain clinical relevance of endpoints, cross-study comparisons, retrospective data collection, use of historical controls and a lack of biomarkers. Together with scarce technological and clinical experience these suboptimal study designs lead

to limitations in the interpretation of efficacy and safety outcomes. Results indicate that regulatory authorities accept varying levels of uncertainty and safety risks for approval, taking different combinations of non-evidentiary factors into consideration. For many products, unmet medical need was considered to accept uncertainties and safety risks (n=9/18), which was mostly evident in the EU and Japan (Table 3).

The PMDA accepted limited evidence of efficacy and uncertain risks of severe adverse events for approval, considering the severity of targeted diseases and poor prognosis of patients with exhausted treatment options. Heartsheet was conditionally approved as a last resort treatment option, despite the highly uncertain clinical benefit. Temcell was approved as second line treatment due to the observed trend of clinical benefit and otherwise poor prognosis (Table 3). Furthermore, post-marketing pharmaceutical product development (i.e. acknowledging sterility issues and allowing to verify in-process specifications based on cumulative clinical data) was accepted under Japanese legislation for GCTs.[21,22]

Compared to Japan, submitted evidence in the EU was more robust. Nevertheless, many uncertainties were unresolved at approval. Non-significant indications of clinical benefit from non-randomized trials were accepted for approval of orphan GCTs that target severe indications without available alternative treatment, under adaptive pathways (Table 3). For standard approvals significant efficacy outcomes were demonstrated, which weighed heavily to reach positive opinions. However, suboptimal study characteristics (e.g. non-validated endpoints, no active comparator arm) and subsequent uncertainties on benefits were evident but considered acceptable, taking into account a balanced safety profile, or substantial benefits for indications with an unmet medical need. Safety profiles were considered manageable despite uncertainty around severe adverse events, or adverse events were deemed to be relatively well-tolerated compared to alternative treatment (oncology) (Table 3).

In contrast to a focus on benefits and unmet medical needs in the EU, discussions for standard US approvals without expedited designations (Laviv, Gintuit) revolved more around uncertainty of safety risks because of the non-severe indications. Relatively robust study design and benefits were interpreted as uncertain by the FDA, however, these were ultimately accepted (Laviv) or resolved by Advisory Committee input (Gintuit). The study design and benefit/risk profile of MACI did not raise any concerns (Table 3).

Imlygic and Provenge were approved in the US based on the same scientific evidence that was later submitted to the EMA. Regulatory assessments and outcome for Imlygic differed between the FDA and EMA, and other factors were considered to accept uncertainties. The invalidated primary endpoint and subsequent uncertain benefits were considered insufficient for approval by the FDA. However, clinical relevance was considered established due to patient reports of cosmetic and psychological benefits. To reflect this benefit, the FDA changed the label to treatment of lesions. In contrast, the EMA considered clinical benefit for melanoma established for a subgroup of patients, based on the same evidence. For Provenge, the benefit/risk assessment was comparable between the FDA and EMA (Table 3), after consistent manufacturing was demonstrated in the EU. Substantially improved survival for a fatal disease outweighed the risk of severe adverse events for Provenge. For MACI benefits and risks were deemed satisfactory upon approval by both EMA and FDA.

The recent approval of two Chimeric Antigen Receptor (CAR)-T cell products (Kymriah, Yescarta) indicate different considerations in FDA decision-making compared to earlier approvals. Considering the substantial clinical benefit demonstrated for Kymriah, the FDA accepted severe safety risks (e.g. cytokine release syndrome and neurotoxicity) under conditions of enhanced risk management (Risk Evaluation and Mitigation Strategies - REMS). The uncertainties related to the clinical benefit due to trial design and similar safety concerns for Yescarta were accepted considering the unmet medical need, together with REMS.

Post-marketing risk management and collection of confirmatory evidence

A wide range of post-marketing strategies to manage uncertainties and safety risks were observed in all jurisdictions, including safety risk surveillance, restricted labelling, risk minimization measures (e.g. boxed warnings, training material), obligations to further develop quality and to conduct studies to confirm clinical outcomes and/or to manage long-term uncertainties. All regulatory authorities chose to restrict the label to specific patient groups as a result of uncertainties around clinical benefit (n=12/18). However, in Japan and the EU post-marketing study obligations spread across quality, efficacy and safety aspects, while there is a general focus on safety in the US (Table 3).

In Japan, follow up is required for all patients, either via a survey after standard approval or an all-case surveillance evaluation during time-limited conditional approval. For the latter, in-process specifications also need to be confirmed based on cumulative clinical experience. In the EU, approvals are accompanied with substantial post-marketing study obligations compared to Japan and the US. Registries are required for products with uncertain risks of severe adverse events (e.g. tumorigenicity) (n=6/9), including requests to collect long-term or confirmatory data in observational studies. Clinical trials to provide confirmatory evidence were requested for all but one product. Release specifications need to be further developed for four products in the EU. In the US, study obligations mainly focused on management of safety risks through clinical studies and registries. Few clinical trials were requested to confirm efficacy. The FDA allowed further quality development for three products (Table 3).

Discussion

In this paper we compared regulatory assessment and decision-making for GCT approval in the US, EU, and Japan. Despite a limited cohort size, our results suggest that willingness to accept GCT associated uncertainties and safety risks is highest in Japan, followed by the EU and US. Considerations of the target population and unmet medical needs are more prominent in Japanese and EU benefit/risk assessments, as well as post-marketing management of uncertainties. In the US, considerations for two recent approvals of CAR-T cell products suggests a shift towards a more permissive approach by the FDA, since previous approvals revealed a relatively low willingness to accept uncertainty and safety risks upon approval in the US. However, there is less emphasis on post-marketing collection of confirmatory evidence in the US compared to the EU and Japan.

The results from our study underline the effects of implemented legislation for GCTs in the EU and Japan over the last ten years.[13] Moreover, the substantial use of adaptive pathways and subsequent approval based on non-confirmatory evidence, combined with a relatively large emphasis on unmet medical needs and post-marketing data collection indicates a trend towards an adaptive approach to licensing or a life cycle approach.[23,24] In Japan, regulations moved towards a legislative model of adaptive licensing, enabling conditional approval based on early development data since 2014.[21,25,26] These regulatory standards facilitate the development of innovative GCT technologies and early access, while many quality, efficacy and safety uncertainties may be unresolved at approval. Although findings are limited

in numbers here, they are in line with the legislative approach for GCT approval in Japan. If this trend continues, it is critical to prevent off-label use and ensure correct administration methods when more GCTs reach the Japanese market, particularly because global GCT development may become skewed towards Japan due to regulatory advantages.[13] The Japanese approach for approval of GCTs is in stark contrast with stringent decision-making for approval of other medicines in Japan.[27] Therefore, it is recommended to carefully monitor and evaluate the impact of GCT legislation to optimize its effects on public health in due time.

In the EU, half of the approved GCTs represent niche products, marked by their orphan drug designation and exclusive approval in Europe. Lack of available treatment and small patient populations explains observations of regulatory willingness to accept uncertainty and non-confirmatory evidence for orphan GCT approval.[28,29] However, our findings confirm earlier observations that EU regulators are prepared to have an adaptive approach for GCT approval in general. Early indications of clinical benefit and unmet medical need considerations currently outweigh uncertainties and safety risks across therapeutic areas,[1,3,5] under conditions of substantial post-marketing risk management and data collection. This approach extends to non-orphan GCTs, thereby creating space to facilitate GCT innovation. However, it is important that authorities deliberately consider adaptive pathways for GCTs in early development phases to avoid becoming a 'rescue option' for substandard applications,[20] and prevent inappropriate use of orphan drug designation.[30] An inclusive approach to adaptive licensing is also warranted in order to take patient needs into account and to prevent market access issues and negative reimbursement evaluations.[31,32] Early multilateral scientific advice with regulatory agencies and payers is one possible solution to ensure patient access to innovative medicines for which adaptive licensing is considered necessary.[33]

For approvals before 2017, US regulators appear to have had a relatively risk averse approach for GCT approval compared to their Japanese and EU counterparts, which is in line with an earlier report.[34] Three of the marketed products in the US are also marketed in the EU, while the other US approvals are relatively less innovative compared to products exclusively marketed in Japan and the EU: GCTs that were developed for cosmetic and periodontal purposes. However, the recent approval of two CAR-T cell products could indicate a tipping point in regulatory decision-making in the US. This observation is in line with recent reforms in the US.[23] Newly implemented regulatory designations that facilitate the development of GCTs and other medicines (i.e. Breakthrough Therapy Designations) were evident in the CAR-T

assessments and may also impact future applications with the potential of substantially improved clinical outcomes.[23] In addition, the implementation of the 21st Century act provides another designation to expedite GCT approval specifically; the Regenerative Medicine Advanced Therapy (RMAT) Designation.[35] RMAT Designation provides similar benefits for developers as Breakthrough Therapy Designation, including to discuss possibilities to use surrogate endpoints. In contrast to Breakthrough Therapy Designation, RMAT Designation supports eligibility for accelerate approval. Furthermore, eligibility for RMAT Designation does not require preliminary clinical evidence that indicates a substantial improvement on clinically relevant endpoints. Instead, clinical evidence needs to indicate the potential to address unmet medical needs.[36] This facilitated approach is indicative of regulatory convergence for GCT licensing across regions and an increasingly leveled playing field for GCT regulatory evaluation.

Despite a converging trend towards expedited and adaptive licensing in the GCT field, eligibility criteria for jurisdiction-specific pathways and the corresponding requirements for approval are different. These differences are a natural consequence of the still small-scale nature of GCT development and the corresponding emergence of regulatory oversight in different governance structures and clinical practice.[13] However, applications and approvals of breakthrough GCT technologies and other innovative GCTs are likely to increase in the near future considering the vast GCT clinical pipeline[37–41] More global development and registration strategies are likely to emerge in the future with a high probability of using expedited and adaptive pathways across jurisdictions, including other pathways not discussed here, such as the EU PRIME scheme and the Japanese Sakigake strategy.[23,42] Parallel scientific advice meetings with multiple regulatory agencies could clarify which evidentiary requirements are needed for global registration strategies. Furthermore, regulatory agencies are holding joint meetings and other forums to harmonize regulatory strategies for GCT approval.[43] However, early access to GCTs is ultimately dependent on payment structures, such as national reimbursement schemes, rather than adaptive approaches to licensing. Future approaches to the integration of post-marketing risk management and regional payment structures may differ substantially between jurisdictions.[23]

Accepting substantial uncertainties and safety risks for GCT approval calls for long-term post-marketing surveillance and enforcement measures.[13] Not just to monitor uncertainties that are noted at point of approval but also new uncertainties that arise after approval.[44] The success of the Japanese legislation for GCTs may depend on appropriate post-marketing surveillance and data collection,[45] a role in which the PMDA has limited experience.[46]

Table 3: Representation of regulatory considerations for approval

		Considerations for approval				Outcomes	Post-marketing study obligations		
	Product	**Study design**	**Clinical benefit**	**Safety profile**	**Unmet medical need**	**Restricted labeling**	**Quality**	**Efficacy**	**Safety**
US	Laviv	Δ	Δ	Δ	□	■			□
	Gintuit	Δ	■ ■	■	□	■	■	■	■
	MACI	■	■ ■	■	□	Δ	■	■	■
	Imlygic	□	Δ	■	■	■ ■			■
	Provenge	Δ	■ ■	Δ	Δ	■			□ Δ
	Kymriah	■	■ ■	□	Δ	□	Δ		Δ
	Yescarta	Δ	■	□	■	■			□ Δ
EU	ChondroCelect	□	■	■	□	■	Δ	Δ ■	Δ
	Imlygic	Δ	Δ	Δ	Δ	■		■	□ ■
	MACI	■	■	■	□	Δ		■	■
	Provenge	Δ	■ ■	Δ	■	■	■	■	□ Δ
	Strimvelis	Δ	■ ■	□	■	□		□ Δ	□ Δ
	Spherox	Δ	■	■	□	■	■	■	■
	Holoclar	Δ	■ ■	□	■	Δ	■	□ ■	□ ■
	Zalmoxis	Δ	Δ	■	■	□		□ Δ ■	□ Δ ■
	Glybera	Δ	□	□	■	■	■	■	□ ■
JP	Temcell	□	Δ	□	■	■		Δ	Δ
	Heartsheet	□	□	□	■	■	■	■	■

Italic = expedited/adaptive pathway, JP = Japan.

Study design (pivotal trial): □ = limitations for evaluation clinical data, acceptable, Δ = uncertainty/bias due to design, acceptable, ■ = satisfactory. Clinical benefit: □ = limited indication of efficacy, Δ = possible benefit [in subgroup], ■ = benefit, ■ ■ = substantial benefit. Safety profile: □ = identified risks manageable, clinically acceptable, Δ = relatively well-tolerated, acceptable, ■ = acceptable/balanced safety profile.

Unmet medical needs: □ = not taken into consideration, Δ = acknowledged, decision based on data, ■ = taken into consideration for benefit/risk. Restricted labeling: □ = no, Δ = minor label adjustment, ■ = patient subgroup, ■ ■ = change of indication.

Post-marketing study obligations. Quality: Δ = minor follow up, ■ = post-marketing validation. Efficacy & safety: □ = registry, Δ = observational study, ■ = clinical trial.

Registries facilitate conduct of observational studies, however, designs may not always be suitable to provide confirmatory data. Thus, it is important that designs for post-marketing data collection match with the purpose of those studies.[47] Furthermore, the amount of post-marketing study obligations in the EU shown here and elsewhere[48] impose considerable challenges for patient recruitment and long term follow up, which may lead to delays to complete post-marketing studies. In contrast, post-marketing study obligations focus on long-term management of safety risks instead of post-marketing studies to provide confirmatory data in the US. There appears to be less focus on post-marketing studies in the US in general, as indicated by earlier reports of limited enforcement by US authorities to complete such studies.[49,50] Thus, the trend of a life cycle approach for GCTs is less evident compared to Japan and the EU. Striking a suitable balance between approval and post-marketing study obligations for GCTs could become the largest challenge for regulatory agencies around the world.

Trial design challenges hinder GCT approval,[5] which has also been shown for promising candidates such as CAR-T cells.[51] It is a complex task to incorporate benefits, risks and sources of uncertainties into benefit/risk assessments, which is further complicated when endpoints differ between patient populations or over time, or when data is pooled from various studies.[52] Fields that are moving towards personalized medicine or treatment for specific subpopulations (e.g. oncology), are searching for solutions such as bio-marker driven designs.[53] It is vital that GCT developers invest in their clinical trial methodologies, consider study design challenges during early development stages and possible learn from advances made in other fields.

In conclusion, willingness to accept uncertainty and safety risks for GCT approval is currently evident for all three regulatory authorities. To reduce uncertainties developers and regulators need to find ways early in development to improve study designs,[54] acknowledging the inherit challenges of target populations and GCT characteristics. Furthermore, regulatory experience and future GCT generations are expected to rapidly co-evolve in the coming years. Our results indicate that these advances will mostly take place within adaptive approaches to licensing, under regulatory standards of varying expedited and adaptive pathways.[23] Early access and long-term uncertainties urge authorities to cautiously consider and enforce appropriate post-marketing risk management and collection of confirmatory evidence. Thus, knowledge sharing between agencies and opportunity for parallel scientific advice need to be further strengthened to facilitate clinical development and suitable regulatory standards throughout the GCT life cycle.[13,43]

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Supplementary Material

Table S1: Overview of variables

Category	Variable	Values
Product profile		
Product characteristics	Product type	Gene therapy, cell therapy, combination product
	Product subtype	Dendritic cells, differentiated tissue cells, lymphocytes, MSC, stem cells, *ex-vivo* gene therapy
	Administration route	Local application, systemic application
	Starting material cell-based therapy	Autologous, allogeneic, xenogeneic
	Starting material subtype	Differentiated tissues, blood, tumor tissue, other
	End product	Fresh (2–8°C), fresh (18–24°C), cryopreserved (-196°C), cryopreserved (-80°C)
	Previous approval in other jurisdictions	Yes, No
	Indication	Oncology, cardiovascular disease, congenital/hereditary/neonatal disease, eye disease, immune system disease, musculoskeletal disease, skin and connective tissue disease
Target population	Lack of alternative therapy	Yes (no specific medicinal product treatment available – including standard care), No
	Orphan designation	Yes, No
	Severe disease	Yes (considered serious, life-threatening, or severely debilitating), No (including not mentioned)
Scientific evidence		
Quality	Potency	
	Available	In process, release
	Release testing	Yes, No
	Release testing	
	Sterility	Yes, No
	Purity	Yes, No
	Viability	Yes, No
	Activity	Yes, No
	Shelf-life	Time period

Category	Variable	Values
Preclinical	Preclinical data	
	Toxicity	Yes (studies performed), No
	Efficacy	Yes (studies performed), No
	Dose	Yes (studies performed), No
Clinical development plan	Dose-finding studies	Yes (studies performed), No
	Pivotal trial(s):	
	No. of pivotal trials	No. of pivotal trials
	No. of patients (total)	No. of patients (total, all arms)
	No. of patients (GCT)	No. of patients (treated with GCT)
	RCT design	Yes, No (single arm, observational)
	Phase	Phase II, Phase III
	Blinded	Yes, No
	Comparator	Yes (active comparator, placebo), No (single arm, historical control)
	Primary endpoint(s)	Clinical, surrogate endpoint
	Secondary endpoint(s)	Clinical, surrogate endpoint
	Multicenter	Yes, No
	Multinational	Yes, No
	Clinically relevant primary endpoint	Yes, No
	Clinically relevant secondary endpoint(s)	Yes, No
Clinical outcomes	Significant outcome on primary endpoint	Yes, No (trend, no effect)

Category	Variable	Values
Clinical outcomes	Significant outcome(s) s on secondary endpoint(s)	Yes, No (trend, no effect)
	Safety concerns/ uncertainties	Identified safety concerns, uncertainty due to small sample, uncertainties due to lack of appropriate methodology/technology, unexplored safety concerns, concerns due to study design
	Added clinical benefit	Yes (first available treatment, added clinical benefit over standard treatment), No
Regulatory process		
	Sponsor type (applicant for approval)	Non-profit, SME, large private company
	Country sponsor (applicant for approval)	Country
	External influence on decision-making	Yes (decision-making by regulators influenced by experts or patient representatives), No
	Regulatory approval pathway	Standard pathway for approval, expedited and/or adaptive pathway for approval (defined as all expedited pathways that facilitate regulatory procedures, including US expedited designations such as Breakthrough Therapy Designation, and all adaptive pathways with lower requirements for approval vs. standard approval such as US accelerated approval, EU conditional approval, approval under exceptional circumstances, Japanese Sakigake)
	Time to approval	Days between application and approval
	Special requests	Special requests by developer
Outcome		
	Restricted labeling	Yes (label restricted compared to requested label by sponsor to specific patient groups), No

GCT = gene and cell-based therapy, RCT = randomized clinical trial, SME = small- or medium-sized enterprise, US = United States, EU = European Union.

Table S2: Overview of characteristics of regulatory assessment procedures per jurisdiction (n)

	US (n = 7)	EU (n = 9)	Japan (n = 2)	Total (n = 18)
Product profile				
Product type				
Gene therapy	3	3	0	6
Cell therapy	2	4	2	8
Combination therapies	2	2	0	4
Starting material cell-based therapy				
Autologous	5	6	1	12
Allogeneic	1	1	1	3
Previous approval in other jurisdictions	1	3	1	5
Lack of alternative therapy	1	4	0	5
Orphan designation	3	4	1	8
Severe disease	5	7	2	14
Scientific evidence: quality				
Release-testing				
Potency	7	8	0	15
Sterility	7	7	1	15
Purity	5	7	1	13
Viability	3	7	1	11
Activity	1	5	0	6
Shelf life				
Short	1	2	0	3
Medium	2	4	0	6
Long	4	3	2	9
Scientific evidence: preclinical				
Toxicity studies	3	8	2	13
Efficacy studies	6	8	2	16
Dose studies	1	5	1	7
Scientific evidence: clinical development plan				
Clinical dose-finding studies	1	4	0	5
Pivotal trial design:				
Two pivotal trials	1	1	0	2
RCT/Phase III/comparator design	5	5	0	10

Blinded pivotal trials	2	1	0	3
Total no. of patients in pivotal trial(s)[a]	255	179	16	na
Clinically relevant primary endpoint(s)	7	9	1	17
Clinically relevant secondary endpoint(s)	5	5	1	11
Scientific evidence: clinical outcomes				
Significant outcome primary endpoint	7	7	0	14
Significant outcome secondary endpoint	2	4	0	6
Added clinical benefit	4	4	0	8

US = United States, EU = European Union.

Chapter 3.2:
EU decision-making for marketing authorization of Advanced Therapy Medicinal Products: a case study

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Abstract

A comparative analysis of assessment procedures for authorization of all European Union (EU) applications for Advanced Therapy Medicinal Products (ATMPs) shows that negative opinions were associated with a lack of clinical efficacy and identified severe safety risks. Unmet medical need was often considered in positive opinions and outweighed scientific uncertainties. Numerous quality issues illustrate the difficulties in this domain for ATMP development. Altogether, it suggests that setting appropriate standards for ATMP authorization in Europe, similar to elsewhere, is a learning experience. The experimental characteristics of authorized ATMPs urge regulators, industry and clinical practice to pay accurate attention to post-marketing risk management to limit patient risk. Methodologies for ATMP development and regulatory evaluations need to be continuously evaluated for the field to flourish.

Introduction

Over the past decade there has been increased interest in the development of Advanced Therapy Medicinal Products (ATMPs) towards marketing authorization. In 2009, Regulation EC No.1394/2007 came into force as the first specific regulatory framework for approval of this potentially new class of medicinal products in the European Union (EU).[1,2] By August 2017, the number of ATMP regulatory procedures for marketing authorization was 16, a number that has been coined as relatively low given the recent impressive advances in basic molecular and clinical science in the field of ATMPs.[3–5]

It is well known that ATMP developers face various scientific and technological challenges, from manufacturing and quality issues[6] to preclinical and clinical efficacy and safety issues.[1] Moreover, additional hurdles in the trajectory towards approval are experienced by academic developers, such as a lack of regulatory knowledge, insufficient financial support and clinical trial related problems, such as recruitment.[7] Regulation EC No. 1394/2007 includes high-level requirements for approval, however, as the field is rapidly evolving, standardization of regulatory requirements for approval is difficult and perhaps undesirable. Consequently, during the decision-making process regulators need to deal with novel issues that have not been previously discussed in other regulatory procedures.[8] Considering these developmental and regulatory complexities, scientific uncertainties during benefit/risk assessments are prevalent.

In this study, we provide insight into decision-making for approval of ATMPs in Europe between 1 January 2009 and 1 July 2017 by characterizing regulatory assessment procedures for marketing authorization, and analyzing identified major issues and considerations for benefit/risk outcomes (Table S1).[9–13]

Cohort analysis of assessment procedures

From the 14 ATMPs included in our study, five were standard approvals, three were approved via an expedited pathway (defined as conditional approval or approval under exceptional circumstances for this study), and six were non-approved (Table 1). The product profiles of all assessed ATMPs are shown in Table 2. Characteristics such as ATMP subtype, starting material, administration route and storage conditions were diverse for the different submitted products. Orphan drug designation was assigned to all expedited approved products, whereas only one (out of five) standard

approved product and half (three out of six) of the nonapproved products were designated orphan drugs. For the expedited approved products, no alternative treatment was available, whereas this applied only to one out of five standard approved products and two (out of six) nonapproved products.

All standard approvals were tested according to standards on sterility, purity and viability upon release. However, for the expedited approvals and nonapprovals, these release tests were not always discussed in the European public assessment report (EPAR). Remarkable was the unspecified shelf-life and storage conditions for nonapproved products (four out of six).

The design of pivotal clinical trials was more robust for standard versus expedited approved and nonapproved products. For most (four out of five) of the standard approvals a randomized controlled phase 3 clinical trial was performed. By contrast, this was the case for only two (out of six) non-approved and for none of the expedited approved products. The number of patients recruited was higher for the standard approved products (mean: 244 patients, range: 12-341) compared to nonapproved products (mean: 120 patients, range: 26-241) and expedited approved products (mean: 57 patients, range: 14-106). The defined primary endpoints were considered clinically relevant for all standard approved products, for some expedited approved ATMPs (two out of three) and for half (three out of six) of the nonapproved products.

A significant effect on the primary endpoint was demonstrated for all standard approved products. By contrast, significant effects were not demonstrated in two (out of three) expedited approved products and in five (out of six) nonapproved products. No added clinical benefit was demonstrated for most of the standard approved (four out of five) and for all the nonapproved products. Added clinical benefit was demonstrated for all expedited approved products because to the lack of alternative therapies.

Analysis of major issues

Major issues were evaluated across assessment procedures, regardless of final regulatory opinion (Table 3; for detailed descriptions see Table S2).

For quality, major issues were noted for all products; for example, the vector (expedited approval one out of three, nonapproved: two out of six) and specific release tests (standard approved: one out of five, expedited approved: three out of three, nonapproved: five out of six). Whereas developers

of the approved products were able to resolve the objections before final regulatory decision-making, developers of the nonapproved products were unable to resolve these major issues, which were mostly raised early during the assessment procedure and decided to withdraw their product. Most of the major issues related to preclinical studies were raised for nonapproved products, concerning animal models (one out of six), toxicology (four out of six) and efficacy studies (one out of six). By contrast, no major issues were noted for the approved products, except for one (out of three) expedited approved product, which concerned toxicology and was unresolved upon final decision-making. In addition, major issues indicated for nonapproved products were still unresolved at time of final decision-making.

Table 3: Major issues mentioned in the assessment reports for marketing authorization[a,b]

		Quality	Preclinical	Clinical trial design	Clinical Outcome
Approved (n=8)	Standard (n = 5)	In process control (1)		Endpoint (1)	
		Release specification (1)			
		Specific release test (1)			
	Conditional (n=2)	Specific release test (2)			
	UEC (n=1)	Vector (1)	Toxicology (1)	Endpoint (1)	Efficacy (1)
		Specific release test (1)			Safety (1)
Non-approved (n=6)		Vector (2)	Toxicology (4)	Design (5)	PD (2)
		GMP Facility (3)	Animal model (1)	Endpoint (2)	GCP (3)
		In process control (2)	Efficacy (1)		Efficacy (6)
		GMO test (1)			Safety (5)
		Starting material (1)			
		Specific Release Test (1)			
		Specific release test (4)			

[a] Per category (quality, preclinical, clinical trial design, and clinical outcome) the major issues, including the number of products for which that major objection was raised, are mentioned: Light grey, resolved at time of final decision; middle grey, acceptable at time of final decision; dark grey, unresolved at time of final decision.

[b] Abbreviations: GCP = good clinical practice; GMO = genetically modified organism; PD = pharmacodynamics.

For clinical trial design, most major issues were also raised for nonapproved products. These issues concerned methodological issues or invalid clinical trial design (five out of six) and change of endpoints or uncertain clinical relevance of an endpoint (two out of six). A change of endpoints was also noted as major issue for one standard and one expedited approved product. For the approved products, the major concerns were considered resolved, whereas all major issues around clinical trial design for the nonapproved products were unresolved upon final decision-making.

Major issues related to clinical outcomes were raised for all nonapproved products and for Glybera®, one of the approved products. A lack of favorable clinical outcomes for nonapproved products related to both efficacy (six out of six) and safety (five out of six). Furthermore, good clinical practice (GCP) was an issue in three (out of six) dossiers and pharmacodynamics data were too limited in two (out of six) nonapproved products.

Analysis of benefit/risk assessment

For standard approved ATMPs, benefit/risk balances were mainly based on clinical efficacy results (Table 4). The beneficial efficacy outcomes and favorable safety profile resulted in a positive opinion for MACI®. The beneficial efficacy trend for Chondrocelect® and Imlygic® combined with satisfactory safety profiles resulted in standard approval, despite ample regulatory discussion about the clinical trial design. Significant and clinically relevant efficacy of Provenge® combined with the acknowledged unmet medical need for the target indication (oncology), outweighed the risks and uncertainties related to the safety profile. Compelling efficacy outcomes for Strimvelis®, with the acknowledged unmet medical need outweighed risks and uncertainties surrounding latent severe adverse events[14]. Despite these favorable regulatory opinions, divergent positions were submitted for two approved products (Imlygic®: n=1; Provenge®: n=13).

As a prerequisite for conditional approval pathways, the body of evidence was overall less robust and associated with more uncertainty compared with standard approved ATMPs (Table 4). Uncertainty about significant clinical benefits for Holoclar® was recognized because of the retrospective, non-randomized, uncontrolled observational study design. Yet, this was outweighed by the manageable risks and acknowledged unmet medical need. Unmet medical need outweighed nonconfirmatory clinical benefit and safety because of uncertainty in clinical trial design for Zalmoxis®. A divergent position was undersigned by three members of the Committee for medicinal products for human use (CHMP).

Table 4: Benefit/risk assessment per category[a,b,c]

	Quality	Preclinical	Design	Efficacy	Safety	Unmet Medical Need	Benefit - Risk
Standard approval							
Chondrocelect*	++	+/-	--	+	++		++
Imlygic*			-	+	+		+
MACI*	++		++	++	++		++
Provenge*	--		**+/-**	**++**	**-**	▲	+
Strimvelis*			**+/-**	**++**	**-**	▲	++
Conditional approval							
Holoclar*	-		**+/-**	**+**	**+**	▲	++
Zalmoxis*			**+/-**	**+/-**	**-**	▲	+
Under exceptional circumstances							
Glybera*	--		**+/-**	**+/-**	**+/-**	▲	+
Nonapproval							
Advexin	--	--	--	--	--		--
CLG	--	--		--	--		--
Cerepro	+	+	--	--	--		--
Heparesc			--	--	+/-		-
Hyalograft	--	--	--	+/-	--		--
OraNera	--	--	--	--	--		--

[a] Unsatisfactory, unresolved major objections (--); uncertainty, concerns and risks, trend towards unsatisfactory (-); neutral, mentioned but no clear judgement (+/-); uncertainty, trend towards satisfactory (+); satisfactory (++), not mentioned (empty box), unmet medical need considered in benefit/risk-assessment (▲).

[b] Benefit-Risk: Rejection by most CHMP members, or withdrawal by applicant (--); Rejection by majority CHMP members (-); Authorization by majority CHMP (+); Authorization by most, or consensus CHMP members (++).

[c] Abbreviation: CLG = Contusugene Ladenovec Gendux.

Glybera® was approved under exceptional circumstances (UEC) after a long and extensive assessment procedure, involving many re-evaluations by the Committee of advanced therapies (CAT) and CHMP.[15] Many uncertainties about quality, efficacy and safety led to unfavorable recommendations for approval twice. Before the final re-examination, a lack of robust efficacy outcomes was considered as a major concern. Yet, a post-hoc analysis revealed a beneficial effect with Glybera® for a subgroup of patients (n=5). The unmet medical need for this subgroup was crucial to reach approval UEC, taking the ultra-orphan status into consideration. Consequently, the label was restricted to this patient group. The final CHMP opinion was not supported by 16 members who undersigned a divergent position.

Nonapproval of ATMPs was associated with numerous scientific deficiencies (Table 4). Half of the nonapproved products had an unsatisfactory profile for all scientific evidence elements. For all nonapproved products the clinical trial design was regarded as unsatisfactory, which hindered regulators from evaluating the clinical data. Positive results related to quality and preclinical studies were demonstrated for Cerepro. However, an unsatisfactory clinical trial design and clinical outcomes resulted in nonapproval. For Heparesc, the clinical safety profile was acceptable, but the clinical trial design and clinical efficacy were judged to be unsatisfactory. For Hyalograft only clinical efficacy was acceptable, but other aspects were unsatisfactory. For four (out of six) nonapproved products, unmet medical need was acknowledged, but did not outweigh scientific deficiencies. During the application procedure, five out of six nonapproved products were withdrawn by the company before a final decision was made by the regulators.

Pharmaceutical quality

The numerous scientific issues related to pharmaceutical quality demonstrate that this domain remains problematic in the ATMP field.[6] A main pharmaceutical quality issue in the submitted applications concerned the level of validation of release testing quality control (QC) for different clinical trial stages and for approval. EU GMP requirements appear to be more stringent compared to other jurisdictions (e.g., USA or Japan) and might impose development hurdles. In this context, both the new First-in man clinical trials EU Guideline and the EU GMP guideline for ATMPs give hints towards quality aspects such as potency testing and use of biomarkers, although the proof of that expectation will ‘be in the eating’.[16–18]

Table 1: Products used in the analysis[a]

Product	ATMP subtype	Starting material	Approval type	Date of final outcome
ChondroCelect®	TEP	Autologous	Standard approval	October 2009
Imlygic®	GTMP – *in-vivo*	N/A	Standard approval	October 2015
MACI®	TEP	Autologous	Standard approval	April 2013
Provange®	CTMP	Autologous	Standard approval	June 2013
Strimvelis®	GTMP – *ex-vivo*	Autologous	Standard approval	April 2016
Holoclar®	TEP	Autologous	Conditional approval	December 2014
Zalmoxis®	CTMP	Allogeneic	Conditional approval	June 2016
Glybera®	GTMP – *in-vivo*	N/A	Under exceptional circumstances	October 2012
Advexin	GTMP – *in-vivo*	N/A	Nonapproval (withdrawn)	December 2008
CLG	GTMP – *in-vivo*	N/A	Nonapproval (withdrawn)	June 2009
Cerepro	GTMP – *in-vivo*	N/A	Nonapproval (withdrawn)	April 2007
Heparesc	CTMP	Allogeneic	Nonapproval	October 2015
Hyalograft	TEP	Autologous	Nonapproval (withdrawn)	January 2013
Oranera	TEP	Autologous	Nonapproval (withdrawn)	March 2013

[a] Abbreviations: CLG, Contusugene Ladenovec Gendux; CTMP, cell therapy medicinal product; GTMP, gene therapy medicinal product; TEP, tissue engineering product.

Potency also frequently raised major objections for both approved and nonapproved ATMPs. ATMP developers experience difficulties in proper potency testing, because of the lack of suitable animal models, with little or even no knowledge about the mechanism of action, and therefore also lack validated biomarkers. Developers could prevent failure during late stage development through early investment in potency evaluation.[19] Vector-related problems belong to the fundamental development aspects of such product and should have been resolved before submission for approval. This also accounts for non-defined end product storage conditions and shelf-life, which are all associated with negative opinions for approval.

In contrast to the early days of ATMP regulation, it is now possible to conditionally release a product by using a rapid-release test. Our findings

demonstrate that a lack of a final release test was often resolved by the development of a rapid-release test for approved ATMPs. In this study, we analyzed the quality aspects that were mentioned and thus discussed in the EPARs. although we compare the different approvals, we do not think that the quality requirements depend on the approval pathway. However, the objections that were discussed in the EPARs could have influenced the approval type. Furthermore, incomparability of the commercial product and clinical trial product raised major objections. This should and could be avoided by considering future aspects of development and proper clinical trial design during the early stages of ATMP development[7,20] to prevent withdrawals at Day 120 for those developers that may not have the resources to tackle resolvable major issues.

Clinical development

The observed suboptimal clinical trial designs that create uncertainty around clinical outcomes are in line with earlier reports of development hurdles experienced in the field.[5,21] However, half of currently approved ATMPs target orphan diseases, for which robust clinical trial design is not always possible as a result of small patient populations or a lack of alternative treatment.[5,22,23] Therefore, our observations of suboptimal study designs under expedited approval of ATMPs, such as lower numbers of recruited patients, should be interpreted within the context of orphan drugs. Yet, observations of suboptimal study design, such as nonrandomized trial design without a comparator, are in line with findings for conditionally approved non-orphan drugs in the EU.[13]

Some major concerns related to clinical trial design, such as a change of primary endpoint, were also raised for standard approved ATMPs. Yet, regulators evaluated scientific evidence as sufficient for standard approval. In addition, unmet medical need was acknowledged and taken into account for decision-making. By contrast, a robust clinical trial design and clinical outcomes are mandatory for standard approval of conventional products.[12] This suggests that EU regulators are exploring an appropriate regulatory standard for ATMPs, where conventional products could be used as a useful reference.

Considerations for benefit/risk analysis

Here, orphan designation among the approved ATMPs skewed the level of scientific evidence to a nonconfirmatory nature. There is ample concern that in the field of orphan drugs, but also of targeted oncology products, the

Table 2: Elements with variables scored per marketing approval type[a,b]

Element	Variable	SA (n=5)	CA (n=2)	UEC (n=1)	NA (n=6)
Product profile					
Product Type	GTMP	2	0	1	3
	CTMP	1	1	0	1
	TEP	1	1	0	2
	Combined	1	0	0	0
Starting Material	Autologous	4	1	0	2
	Allogeneic	0	1	0	1
	Not applicable	1	0	1	3
End product	Refrigerated	2	0	0	0
	Room Temperature	2	1	0	0
	Nitrogen-cryopreserved	0	1	0	1
	Other-cryopreserved	1	0	1	1
	Unspecified	0	0	0	4
Previous approved in other jurisdictions	Yes	3	0	0	0
Indication area	Cancer	2	0	0	2
	Congenital, hereditary, neonatal diseases	1	0	1	2
	Eye diseases	0	1	0	1
	Immune system diseases	0	1	0	0
	Musculoskeletal diseases	2	0	0	1
Lack alternative treatment	Yes	1	2	1	2
Orphan drug designation	Yes	1	2	1	3
Scientific evidence					
Quality	Potency assay	5	2	1	6
	Release - sterility	5	1	0	4
	Release - Purity	5	1	0	4
	Release - Viability	5	2	0	2
	Release - activity	3	1	1	3
Preclinical	Toxicity	4	2	1	6
	Efficacy	5	1	1	6
	Dose	3	1	1	6
Pivotal trial Design	RCT	4	0	0	2
	Clinical prim. EP	5	1	0	4
	Clinical Relevance prim. EP	5	2	0	3
	Significant Outcome	5	1	0	1
Clinical Outcome	Significant primary EP	5	1	0	1
	Beneficial Effect	1	2	1	0
Regulatory process					
	Scientific advice	5	2	1	4
	Restricted Labelling	5	1	1	0

[a]Per element, variables are scored for each (non)-approval type of ATMP.
[b] Abbreviations: CA, conditional approved; ATMP, cell therapy medicinal product; EP, endpoint; GTMP, gene therapy medicinal product; NA, non-approved; RCT, randomized controlled trial; SA, standard approved; TEP, tissue engineering product.

nature of evidence becomes less confirmatory with the use of non-randomized data and surrogate endpoints.[24] The relatively high number of orphan designation in the field of ATMPs will impact the regulatory considerations for marketing approval in the future[25]. Unmet medical need has an important role in decision-making for approval of orphan ATMPs, provided that the data should at least show some beneficial trends of efficacy or a favorable safety profile to receive approval. This feature is also seen in the field of regulating orphan drugs.[11] Yet, considerations of unmet medical need did not lead to a higher rate of positive opinions on orphan drug approval compared to treatments without unmet medical need.[12] This apparent dissimilarity between orphan ATMPs and orphan new entities needs to be explored further. Surprisingly, conditional approval and approval UEC for orphan ATMPs are not primarily initiated by the developers, but by the regulators. In line with previous work, these findings suggest that conditional approval is frequently used as a rescue option for approval.[13] For (ultra-)orphan indications, developers should take conditional approval and approval UEC into their strategic considerations for marketing authorization instead of leaving this to the regulators to propose.

Critically, observations of a lack of clinical efficacy for non-approval of ATMPs are in line with argumentation for negative benefit/risk opinions on conventional medicinal products. Earlier research on conventional medicinal products showed that beneficial, clinically relevant efficacy outcomes are determinants for approval.[11] Furthermore, our findings indicate that the process of decision-making leading to nonapproval is similar between ATMPs and conventional medicinal products. Earlier research shows that major issues that were unresolved at time of final decision often led to withdrawal by the applicant.[21] Strikingly, the unresolved major issues of nonapproved ATMPs underline the challenges in development of ATMPs.[6,19,26] Glybera® is the only approved product that appears to be an exception to the rule to be approved despite of its uncertain benefit/risk-profile; it was approved after a long regulatory process with a restricted label and many uncertainties.[27] Currently, the marketing authorization holder decided not to extend the marketing authorization of the product.

Future implications

The current centralized system for ATMPs, including CAT experts and a range of advantages for ATMP developers, creates opportunity to learn and gain experience with these innovative products as well as the underlying science and technology.[28] As the field develops, it is important that regulatory standards (incrementally) coevolve to tailor procedures and decision-making

for these ATMPs. Our observations indicate that EU regulators are inclined to be adaptive[29] and to endorse ATMPs for approval, without compromising necessary evidentiary support for positive benefit/risk opinions. There are also numerous regulatory adaptations that are to be implemented soon (e.g. the new Clinical Trial Regulation) in the EU. These will also affect ATMP development.[30] Others have been recently implemented, such as the new regulatory pathway for priority medicines (PRIME). Many of the investigational medicines that were included in the PRIME scheme are ATMPs.[31] Development efforts are rapidly evolving as well. The ATMPs discussed here reflect a start of a huge clinical development pipeline,[3–5,30] for which applications for approval will be filed in due course. Thus the current analysis reflects decision-making for a small sample of first-generation ATMPs, making it difficult to draw generalizable conclusions for the future. It is possible that some observations are driven by product specificity and/or disease characteristics instead of regulatory approval pathways. Therefore, it is crucial to continue to monitor regulatory outcomes and evaluate the ATMP regulatory framework.

Concluding remarks

EU regulators are making important steps in the field of ATMPs by balancing evidentiary support and medical needs with critical scientific uncertainties that could hamper marketing approval. The development, regulation and clinical use of most ATMPs are still coevolving. In this context, defining appropriate regulatory standards taking into account the complexities inherit to these products is critical. Our observations concur not only with current defined standards for ATMPs, but also with the available space that regulations allow for facilitated pathways. As long as the risks are acceptable, this appears to be the way forward. Yet, because of the novelty and lack of clinical experience in this field, regulators, and those in industry and clinical practice need to pay accurate attention to post-marketing surveillance and risk-minimization measures, in particular for those products with a high degree of scientific uncertainty upon point of approval. For the field to flourish, developers and regulators need to collaborate to continuously monitor and evolve methodologies and regulations for ATMPs.

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Supplementary Material

Table S1: Set of variables per element to characterize assessment procedures

Category	Variable	Scores
Product profile		
	Product type	Gene therapy, cell therapy, tissue engineered product
	Product subtype	Dendritic cells, differentiated tissue cells, lymphocytes, MSC, stem cells, *ex-vivo* gene therapy
	Administration route	Local application, systemical application
	Starting material	Autologous, allogeneic
	Starting material subtype	Differentiated tissues, blood, tumor tissue, other
	End product	Fresh (2-8°C), fresh (18-24°C), cryopreserved nitrogen (-196°C), cryopreserved (-80°C)
	Previous approval in other jurisdictions	Yes, No
	Indication	Oncology, cardiovascular disease, congenital/ hereditary/ neonatal disease, eye disease, immune system disease, musculoskeletal disease, skin and connective tissue disease
Target population	Lack of alternative therapy	Yes (no specific medicinal product treatment available – including standard care), No
	Orphan designation	Yes, No
	Severity of disease	Yes (considered serious, life-threatening, or severely debilitating), No (including not mentioned)
Scientific evidence		
Quality	Potency	
	Available	In process control, release test
	Release testing	Yes, No
	Release test	
	Sterility	Yes, No
	Purity	Yes, No
	Viability	Yes, No
	Activity	Yes, No
	Shelf-life	[Time period]
Preclinical	Preclinical data	
	Toxicity	Yes (studies performed), No
	Efficacy	Yes (studies performed), No
	Dose	Yes (studies performed), No
Clinical development plan	Dose-finding studies	Yes (studies performed), No

	Pivotal trial(s)	
	Number pivotal trials	Number of pivotal trials
	Number patients	Number of patients (total, all arms)
	RCT design	Yes, No (single arm, observational)
	Blinded	Yes, No
	Comparator	Yes (active comparator, placebo), No (single arm, historical control)
	Primary endpoint(s)	Clinical, surrogate endpoint
	Secondary endpoint(s)	Clinical, surrogate endpoint
	Multicenter	Yes, No
	Multinational	Yes, No
	Clinically relevant primary endpoint	Yes, No
	Clinically relevant secondary endpoint(s)	Yes, No
Clinical outcome	Significant outcome on primary endpoint	Yes, No (trend, no effect)
	Significant outcome(s) s on secondary endpoint(s)	Yes, No (trend, no effect)
	Safety concerns/ uncertainties	Identified safety concerns, uncertainty due to small sample, uncertainties due to lack of appropriate Methodology/ technology, unexplored safety concerns, concerns due to study design
	Added clinical benefit	Yes (superiority over alternative treatment, first available treatment), No (superiority not shown or not tested)
Regulatory process		
	Sponsor type	Non-profit, small or medium sized enterprise, large private company
	Country sponsor	[Country]
	External influence on MA advice	Yes (decision-making by regulators influenced by experts or patient representatives), No
	Regulatory approval pathway	Standard approval, expedited approval
	Scientific advice	Yes, No
	Time to decision	Days between application and decision
	Special requests	Special requests by developer
Outcome		
	Restricted labeling	Yes (label restricted by regulator compared to requested label by sponsor to specific patient groups), No

RCT = randomized controlled trial.

Table S2: Major issues per category discussed in the assessment reports

	Category	Topic	Category uncertainties/objections
SA	Quality	IPC	Issues In-process-control and validation
		Release specification	Insufficient release specification
		Specific Release Test	No rapid microbial quality control due short shelf-life
		Specific Release Test	Comparability commercial product and trial product unclear
		Specific Release Test	Unvalidated potency assay
	Design	Endpoint	Change of endpoint, GCP noncompliance
CA	Quality	Specific Release Test	Potency release test insufficient
		Specific Release Test	Purity not demonstrated (non-proliferation of target cell not demonstrated)
		Specific Release Test	No rapid microbial quality control due short shelf-life
UEC	Quality	Vector	Oncogenicity due to structure
		Specific Release Test	Impurity due to residual viral DNA
		Specific Release Test	Lack of replication assay for release
		Specific Release Test	Potency specification unacceptable
	Preclinical	Toxicology	Lack of *in-vivo* testing tumourgenicity / oncogenicity
	Design	Endpoint	Change of endpoint
	Outcome	Efficacy	Lack of robust efficacy outcomes
		Safety	Uncertainty severe adverse event
NA	Quality	Vector	Functionality replicant competent vector unaddressed
		Vector	Assay replication comptent vector dissatisfactory
		Vector	Risk associated with structure of vector
		Specific Release Test	Inconsistency of batches
		Specific Release Test	Multiple unvalidated release testing
		Facility	Lack GMP certification and import license
		Specific Release Test	Inconsistency of batches
		Specific Release Test	Impurity/contamination insufficient controlled
		IPC	Insufficient in-process controls
		GMO Test	Environmental risk analysis lacking
		Starting material	Uncertain impact of reagent
		Specific Release Test	Unvalidated potency assay
		Specific Release Test	Insufficiently specified potency assay
		Facility	Lack of manufacturing site

Preclinical	Toxicology	Limitations of toxicology studies
	Toxicology	Inadequate biodistribution study
	Animal model	Potential dissimilarity animal and human
	Efficacy	Mechanism of action and benefit not established
	Toxicology	Risk of adverse events
Design	Design	Methodological issues and invalid study designs
	Endpoint	Bias due to change of endpoints
	Endpoint	Uncertain clinical relevance
Outcome	Efficacy	No efficacy (benefit)
	Efficacy	Uncertain clinical outcomes
	Pharmacodynamics	Unclear clinical pharmacodynamics
	GCP	GCP noncompliance
	Safety	Insufficient safety reporting
	Safety	Risk of severe adverse events

CA = conditional approval; CLG = contusugene ladenovec gendux; GCP = Good Clinical Practice; GMO = Genetically modified organism; IPC = in-process-control; NA = non-approved; SA = standard approved; UEC = under exceptional circumstances. Light grey = resolved, Middle grey = considered acceptable, although unresolved, Dark grey = unresolved.

CHAPTER 4:
IMPLICATIONS OF REGULATORY CHANGE FOR GENE AND CELL-BASED THERAPY DEVELOPMENT AND THEIR AVAILIBILITY IN CLINICAL PRACTICE

Chapter 4.1:
Publication of clinical trial results in the field of gene and cell-based therapies

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Under consideration for publication

Abstract

Timely publication of clinical trial results is essential to advance gene and cell-based therapy (GCT) development. In a GCT clinical trial cohort (n=105), we investigated publication rates in scientific papers and conference abstracts, used Cox regression to examine associations with the occurrence of trial characteristics, and investigated the type of reported results. Results show a scientific publication rate of 27% and a conference abstract publication rate of 17% (median follow up 1050 days). Academic hospitals published more in scientific papers, whereas private sponsors were more likely to publish in conference abstracts. Technological know-how was underreported compared to clinical outcomes. The rather low publication rates demonstrate a need for enhanced publication to facilitate GCT innovation and future patient access.

Introduction

It is well established that developers of gene and cell-based therapies (GCTs) face numerous scientific, technological, and manufacturing challenges when translating new discoveries from bench to bedside,[1,2] and when scaling up for industrial manufacturing.[3] Scientific uncertainties and technological hurdles[2,4–6] currently complicate standardization of regulatory requirements and guidance for clinical development of GCTs. Timely publication of GCT clinical trial results, through publication of scientific papers or conferences abstracts, can mitigate this problem.[3] Yet, underreporting of trial results caused much debate over the last few years, in particular for privately sponsored drug trials.[7] For emerging fields such as the GCT field, no information is available on the publication of trial results.

Previous work on publication of drug trial results shows that drug trial results are underreported in scientific literature. A meta-analysis reported publication rates ranging between 22-72% of trials, with a weighted pooled rate of approximately 45%.[8] Individual studies reported higher publication rates between 50-70%,[9–11] although these relatively high publication rates appear to be linked to late phase development. Two of these studies include late phase trials,[10,11] while another shows that phase I trials are associated with non-publication.[9] Phase I drug trials typically include healthy subjects to assess pharmacokinetics, which may be less interesting to publish compared to patient data and result in non-publication of first-in-man trials.[9] Furthermore, underreporting of drug trial results is attributed to non-significant or negative clinical outcomes, which creates a publication bias towards positive clinical outcomes.[12–15] Therefore, it is postulated that enhanced publication of drug trial results, including negative clinical outcomes, is vital to prevent duplication of research efforts and biases in medical information that impact clinical practice.[16–18]

The need to improve scientific publication rates and dissemination of trial result via other channels is even more pressing in the GCT field due to scientific and technological uncertainties, and other hurdles that hamper development.[19] Importantly, GCT trials differ from other drug trials, which may lead to different patterns of publication. First, most GCTs in the European Union (EU) are still in early stage development,[20–22] which may limit publication potential similar to limited publication of early stage drug trials.[9] However, similar to the field of oncology,[23] GCTs are likely to be administered directly to patients instead of healthy volunteers in early phase development, with greater potential for publication. Second, the field of GCTs consists of heterogenous technologies that are designed to

target a diverse range of therapeutic areas.[24,25] Designs of GCT technologies are highly specific, with challenges of their own.[4] The state of clinical development may vary between therapeutic areas and technologies due to varying levels of scientific and technological advance, and influence publication. Third, studies consistently show that large proportions of GCT trials are sponsored by academic hospitals and small- and medium-sized enterprises (SMEs), instead of large industry.[20–22] Academic GCT trial sponsors report to aim for generation of knowledge and optimizing experimental technologies,[26] instead of commercialization. Academics have incentives to publish results in scientific papers and to engage in scientific meetings (e.g. conferences, symposia), workshops and consortia.[26,27] Furthermore, academic hospitals are likely to have scientific, technological, and clinical experience under one roof, and have capabilities to generate different types of knowledge[28] such as technological know-how (e.g. manufacturing and quality) and proof of mechanism (biological activity). Therefore, publication rates may be higher for publicly sponsored GCT trials compared to private sponsored GCT trials. However, other studies show that conference attendance and scientific publication by private sponsors are linked to commercial incentives,[29,30] and may drive publication rates up for private sponsors.

Against this background. the study aims to provide insight in publication rates for both scientific papers and conference abstracts, and associations with trial characteristics in a GCT trial cohort. Furthermore, we investigate the type of results reported, distinguishing between technological know-how and clinical outcomes.

Methods

Data collection

Clinical trial cohort

In order to create a cohort of GCT trials, we selected all GCT trials that were authorized in the Netherlands from 2007 until the end of 2017. GCT trial applications are centrally reviewed and authorized by the Dutch central Institutional Review Board (‘Centrale Commissie Mensgebonden Onderzoek’, referred to as IRB from hereon). Data on GCT trials was extracted from the publicly available IRB trial registry (www.toetsingonline.nl) in May 2018. Methods were adapted from previous work.[9,31]

GCT trials were selected from the IRB database by using the European definition of Advanced Therapy Medicinal Products and the Dutch definition of somatic cellular therapy[a]. Search terms for the IRB database included 'somatische celtherapie' [somatic cell therapy], 'xenogene celtherapie onderzoek' [xenogenic cell research], 'gentherapie' [gene therapy], 'genetisch gemodificeerde organismen' [genetically modified organisms], 'weefselmanipulatie' [tissue manipulation], 'tissue manipulation', and 'tissue engineering'. Trial hits were manually selected using the following exclusion criteria: chemical based drugs, non-cellular based biological medicines, surgical procedures, medical devices and vaccines for immunization against infectious disease, as well as non-interventional trials that involved gene or cellular source material such as *in-vitro* studies with human blood samples. In case of secondary trial authorizations (e.g. protocol amendments), the first authorization date was used for analysis.

Search for publications and conference abstracts

For all included GCT trials, we performed a search for publications of trial results in July 2018, allowing for a minimal follow-up of 6 months for each trial. The end of follow-up was defined as 01-07-2018 for trials without outcome, or the date of the first scientific paper for trials with the outcome of scientific publication, and the date of the first conference abstract for trials with the outcome of publication through conference abstracts.

Building on an adapted search algorithm from a previous study[31], we used Google Scholar, PubMed, and EMBASE in a consecutive order to search for scientific papers, and conference abstracts or posters. Search terms for Google Scholar included identifiers of the IRB, EudraCT, and clinicaltrials.gov registries, if available. Search terms for PubMed and EMBASE included a combination of name of GCT product, indication, sponsor name and registry identifier. EMBASE was included in the search algorithm to search for conference abstracts and posters and to supplement findings from Google Scholar and PubMed. EMBASE lists numerous conference abstracts since 2009 (>180.000) and key GCT target journals that publish conference abstract books (Cytotherapy, Molecular Therapy, Journal of Clinical Oncology, Annuals of Oncology, Blood). Registry identifiers were used to match trials and publications. If not available, information on sponsor, study centre, trial name, chronology

a This is a wider definition than the European definition of somatic Cell Therapy Medicinal Product.[32] It is defined as administration of vivid, human autologous or allogeneic cells, or xenogeneic cells that are single cells during isolation, processing, or administration, and are the subject of the research question (non-official translation).

of trial and publication, investigators, indication, name of GCT product, and comparator(s) were used to establish a match. If matching remained inconclusive, the publication was disregarded.

Outcome measures

The main outcome measure of publication was defined as a binary outcome variable of scientific publication. Scientific publication is defined as publishing findings in scientific, peer-reviewed papers after IRB authorization. The second outcome measure was defined as a binary outcome variable of conference abstract publication. Conference abstract publication is defined as publishing findings in conference abstracts or publicly available posters after IRB authorization.

Per publication, the type of reported knowledge was categorized into clinical outcomes, and/or technological know-how (manufacturing and quality). Publication of clinical outcomes was further categorized (not mutually exclusive) into reporting of clinical tolerability/safety (1), proof of interaction and/or affecting target biological systems such as immune system, and/or clinical evidence related to effects on disease biomarkers or surrogate endpoints (2), and clinical evidence related to effects on clinical endpoints/clinical activity (3).

Per scientific paper, it was assessed whether scientific papers reported technological know-how in-detail defined as extensive reporting of manufacturing protocols and quality control methods (1), or not (0). Per conference abstract, it was assessed whether it contained statements on manufacturing steps or quality specifications (1), or not (0). References to previous publications or supplementary material were included for categorization.

GCT trial characteristics

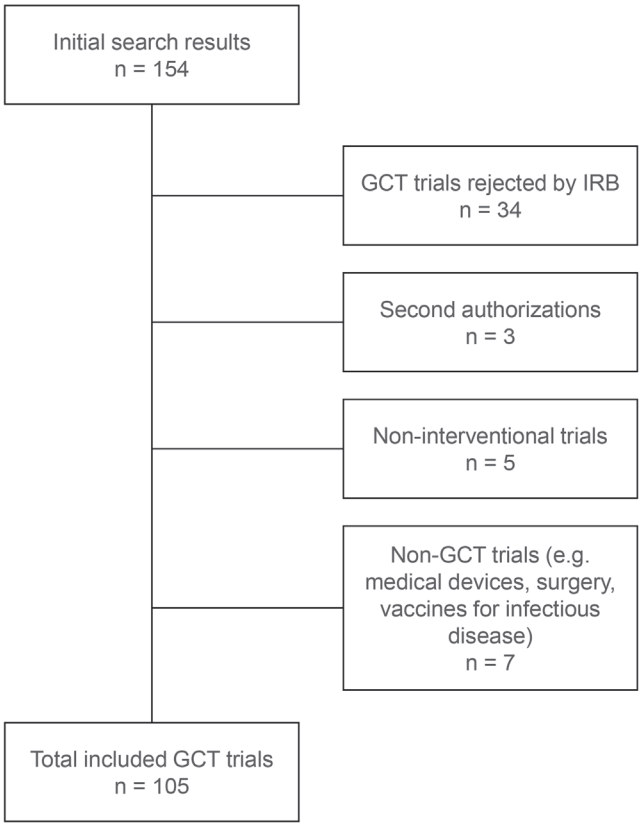
We identified trial characteristic that could be associated with publication. All trials had one sponsor, which were divided into public and private sponsors. Public sponsors are divided into academic hospitals and other public sponsors (e.g. blood or tissue banks). Private sponsors include small private entities (small United States (US) businesses and EU SMEs) and large industry. Other trial characteristics included known determinants for publication of drug trials, such as trial phase,[9] and trial characteristics that are specific to GCTs, such as the active substance. Information on trial characteristics was primarily extracted from the IRB

registry and coded into pre-defined categories (Table 1). We supplemented missing data in the IRB registry with information from EudraCT (www.clinicaltrialsregister.eu).

Data analysis

To illustrate publication proportions over time, trials were stratified and tabulated by year of IRB authorization, and by publication in scientific papers and conferences abstracts. We performed a Pearson correlation test to inspect strong correlations between trial characteristics, using r>0.5 as rule. To illustrate how trial sponsors published different types of knowledge, publications were stratified and tabulated by publication type, and further stratified by sponsor and reported knowledge.

Figure 1: Selection of GCT clinical trial cohort



To account for variation in duration of follow-up, we performed Cox regression analysis to calculate associations between trial characteristics and the outcome measures of time to publication in scientific papers (analysis 1) and conference abstracts (analysis 2). We calculated crude hazard ratios, 95% confidence intervals (CI), and p-values. The significance threshold was set at .05. We did not perform multivariable Cox regression, because of limitations of the data set (small number of events, correlations and multicollinearity between trial characteristics). We used IBM SPSS Statistics version 24 for all data analyses.

Results

Our clinical trial cohort consists of 105 authorized GCT trials in the Netherlands. Between 2007 and the end of 2017, 139 applications for trial authorization were submitted to the IRB. Of these applications, 34 applications (24%) were rejected (Figure 1). The scientific publication rate was 27%, versus a 17% conference abstract publication rate after excluding two events of scientific publication, and nine events of conference abstract publication because they were published before IRB authorization.

Cohort characteristics

Trials

Two third of all trials were sponsored by public sponsors (67%), and one third of all trials were sponsored by private entities (33%). Public sponsors were mainly academic hospitals (n=56 trials, 54% of all sponsors) versus other public sponsors (n=14 trials, 13% of all sponsors) (Table 1). Private sponsors consisted of small companies (n=19 trials, 18% of all sponsors), and large industry (n=16 trials, 15% of all sponsors). Most trials were conducted with cell therapies (76%), compared to gene therapies (24%). The GCT trials included either stem cells or other somatic cells (47%), lymphocytes (19%), dendritic cells (20%), or gene delivery vectors (14%) as the active substance. Trials were equally distributed between oncology and other disease areas, early and late phase development, and randomized and other designs (Table 1). The median follow up duration for the trials (IQR) was 1050 days (426 - 1674 days).

Sponsor, center and geographic location of trials were strongly correlated. Academically sponsored trials are almost exclusively, single-centered, Dutch trials, whereas the majority of privately sponsored trials and trials

sponsored by other public sponsors are multi-centered, multi-national trials. Furthermore, randomized design and study phase, and product type and active substance are strongly correlated. Early phase trials mostly have non-randomized designs, whereas late phase trials mostly have randomized design. Stem cell and dendritic cell-based therapies are exclusively cell therapies, whereas vectors are exclusively gene therapy. Lymphocyte based therapies are both gene and cell therapies (50/50) (not shown). The median follow up duration (IQR) for single-center trials (1428 days (799 – 2057 days)) is approximately twice as high compared to multi-center trials (744 days (113 – 1375 days)).

Figure 2 shows the number of authorized trials per year, stratified by publication outcome. Clinical trial authorizations increased from one trial in 2007 to 20 trials in 2017. Approximately half of all clinical trial authorizations occurred before 2014, and the other half from 2014 onwards. Results were more often scientifically published for trials that were authorized before 2014 (23/30 scientifically published trials), compared to trials authorized since 2014 (7/30 scientifically published trials). In contrast, publication through conference abstracts was comparable for trials authorized before 2014 (12/27 trials published at conferences), versus trials authorized since 2014 (15/27 trials published at conferences). There was little overlap between publication in scientific papers and conferences abstracts. Only for 8% of trials, results were published in conference abstracts first, and subsequently scientifically published (Figure 2).

Figure 2: Year of trial authorization and publication, stratified by publication type (% trials)

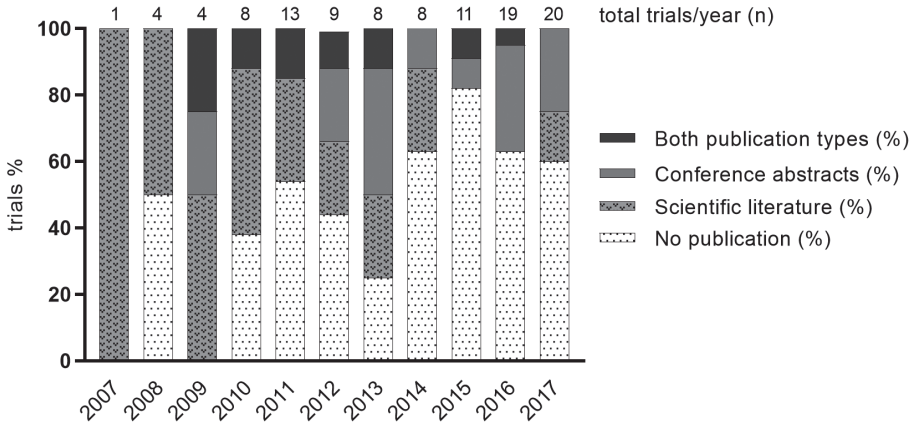
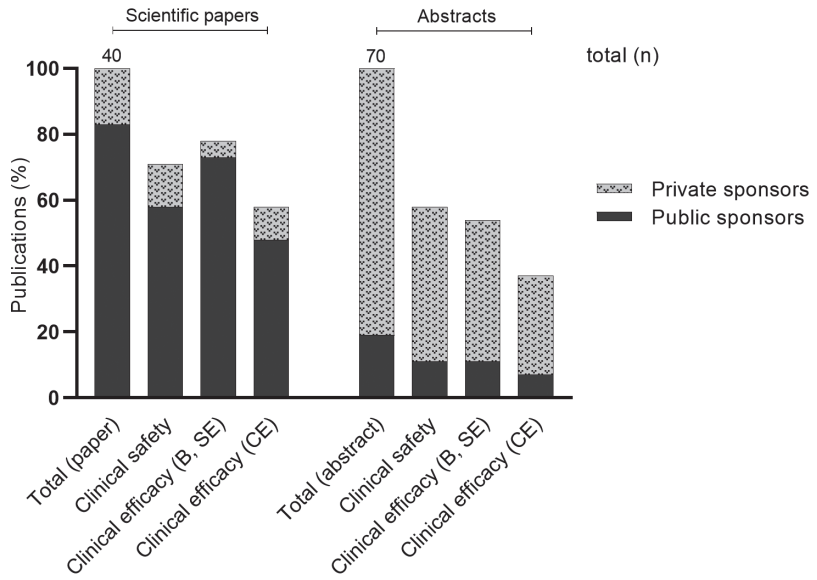


Table 1: Frequencies, publication proportions, and associations of trial characteristics with the outcome of scientific publication, expressed as crude hazard ratios (HR) with 95% confidence intervals (CI), and p-values (n=105)

Trial characteristic	n trials	n published (% published)	n not published (% not published)	crude HR (95% CI)	p-value
All included GCT trials	105	28	77		
Sponsor					
Academic hospital	56	23 (82%)	33 (43%)	2.1 (0.7 – 6.2)	0.17
Other public sponsor	14	1 (4%)	13 (17%)	0.4 (0.04 – 3.2)	0.36
Private sponsor	35	4 (14%)	31 (40%)	ref	
Product type					
Gene therapy	25	4 (14%)	21 (27%)	1.2 (0.4 – 3.4)	0.80
Cell therapy	80	24 (86%)	56 (73%)	ref	
Therapeutic area					
Other disease areas	52	19 (68%)	33 (43%)	2.4 (1.1 – 5.3)	0.03
Oncology	53	9 (32%)	44 (57%)	ref	
Active substance[a]					
Stem and other cells	49	14 (50%)	35 (46%)	ref	
Lymphocytes	21	6 (21%)	15 (20%)	1.3 (0.5 – 3.5)	0.55
Dendritic cells	20	5 (18%)	15 (20%)	0.99 (0.4 – 2.8)	0.99
Gene delivery vectors	15	3 (11%)	12 (16%)	0.97 (0.3 – 3.4)	0.96
Trial phase					
Early phase (phase I, I/II)	48	16 (57%)	32 (42%)	1.6 (0.8 – 3.5)	0.20
Late phase (phase II, II/III, III, IV)	57	12 (43%)	45 (58%)	ref	
Randomized design					
No	57	17 (61%)	40 (52%)	1.6 (0.7 – 3.3)	0.26
Yes	48	11 (39%)	37 (48%)	ref	
Center					
Single-centered	46	20 (71%)	26 (34%)	2.2 (0.98 – 5.1)	0.06
Multi-centered	59	8 (29%)	51 (66%)	ref	
Geographic location					
Netherlands	58	23 (82%)	35 (46%)	1.9 (0.7 – 5.1)	0.19
Multinational	47	5 (18%)	42 (54%)	ref	

a = Active substance refers to the component of a GCT that is hypothesized to enact its mode of action.

Figure 3: Proportions of clinical outcome reporting in publications, stratified by type of publication, and public and private sponsors (n=110)



B = outcomes reported on biomarkers, SE = outcomes reported on surrogate endpoints, CE = outcomes reported on clinical endpoints. NB: Publications frequently reported multiple categories of clinical knowledge. Therefore, the proportions reported under clinical safety, clinical outcomes of biomarkers or surrogate endpoints, and clinical outcome on clinical endpoints do not add up to the total proportion of publications.

Reported knowledge

In total, 110 publications (scientific papers n=40; conference abstracts n=70) were found to match in total 49 out of 105 trials in the cohort. When stratifying publications by sponsor type, results show that most scientific papers were published from publicly sponsored trials (n=33/40), compared to privately sponsored trials (n=7/40). In contrast, relatively few conference abstracts were published from publicly sponsored trials (n=13/70), compared to privately sponsored trials (n=57/70) (Figure 3).

Clinical safety and clinical outcomes on biomarkers or surrogate endpoints was reported in 70% and 78% of scientific papers, respectively. Clinical outcomes on clinical endpoints was reported in 58% of scientific papers. Overall, conference abstracts often reported clinical outcomes (90% - not shown). Clinical safety, clinical outcomes on biomarkers or surrogate endpoints, and clinical outcomes on clinical endpoints were reported in 59%, 54%, and 37% of conference abstracts, respectively (Figure 3).

Table 2: Frequencies, publication proportions, and associations of trial characteristics with the outcome of presenting results at conferences, expressed as crude hazard ratios (HR), with 95% confidence intervals (CI) (n=105)

Trial characteristic	n trials	n presented (% presented)	n not presented (% not presented)	crude HR (95% CI)	p-values
All included GCT trials	105	18	87		
Sponsor					
Academic hospital	56	7 (39%)	49 (56%)	0.3 (0.1 – 0.7)	0.01
Other public sponsor	14	1 (6%)	13 (15%)	0.2 (0.02 – 1.2)	0.08
Private sponsor	35	10 (55%)	25 (29%)	ref	
Product type					
Gene therapy	25	5 (28%)	20 (23%)	1.9 (0.7 – 5.5)	0.23
Cell therapy	80	13 (72%)	67 (77%)	ref	
Therapeutic area					
Other disease areas	52	8 (44%)	44 (51%)	0.7 (0.3 –1.8)	0.50
Oncology	53	10 (56%)	43 (49%)	ref	
Active substance[a]					
Stem and other cells	49	6 (33%)	43 (49%)	ref	
Lymphocytes	21	5 (28%)	16 (18%)	2.6 (0.8 – 8.6)	0.11
Dendritic cells	20	4 (22%)	16 (18%)	1.8 (0.5 – 6.5)	0.35
Gene delivery vectors	15	3 (17%)	12 (14%)	2.2 (0.5 – 8.7)	0.28
Trial phase					
Early phase (phase I, I/II)	48	7 (39%)	41 (47%)	0.7 (0.3 – 1.9)	0.51
Late phase (phase II, II/III, III, IV)	57	11 (61%)	46 (53%)	ref	
Randomized design					
No	57	11 (61%)	46 (53%)	1.4 (0.5 – 3.6)	0.50
Yes	48	7 (39%)	41 (47%)	ref	
Center					
Single-centered	46	4 (22%)	42 (48%)	0.2 (0.1 – 0.8)	0.01
Multi-centered	59	14 (78%)	45 (52%)	ref	
Geographic location					
Netherlands	58	7 (39%)	51 (59%)	0.3 (0.1 – 0.8)	0.02
Multinational	47	11 (61%)	36 (41%)	ref	

a = Active substance refers to the component of a GCT that is hypothesized to enact its mode of action.

In total, three scientific papers reported detailed manufacturing protocols and quality control methods. A small proportion of conference abstracts reported technological know-how (9/70) (not shown).

Scientific publication

The overall scientific publication rate is 27% of GCT trials (n=28/105). The publication rate would be slightly higher without exclusion of trials for analysis (29%; n=30/105). The scientific publication rate for all GCT trials sponsored by academic hospitals is highest (41%, n=23/56 trials) (Table 1).

The univariate Cox regression analysis shows that trial results are significantly more likely to be published for trials that were conducted in other disease areas than oncology, compared to oncology (crude HR 2.4; 95% CI 1.1 – 5.3, p=0.03). Furthermore, it is likely that results of single-center trials are scientifically published more compared to multi-center trials (crude HR 2.2; 95% CI 0.98 – 5.1, p=0.06), although this association approaches significance. In addition, associations between sponsor, trial phase, randomized design, and geographic location and the outcome of scientific publication are uncertain (p=0.1-0.2), as well as the size of their potential association. Univariate analysis indicates no association between product type and active substance and the outcome of scientific publication (Table 1).

Conference abstract publication

The overall conference abstract publication is 17% of GCT trials (n=18/105). This rate would be higher without exclusion of trials for analysis (26%, n=27/105). Most of the excluded trials for analysis (n=8/9) were multi-center, multinational trials, authorized in 2016-2017 (n=7/9), and sponsored by private entities (n=7/9). All deleted trials were in the field of oncology.

The univariate Cox regression analysis shows that trial results are significantly less likely to be published in conference abstracts if trials were sponsored by academic hospitals, compared to privately sponsored trials (crude HR 0.3; 95% CI 0.1 – 0.7, p=0.01), if trials were single-center trials, compared to multi-center trials (crude HR 0.2; 95% CI 0.1 – 0.8, p=0.01), and if trials were Dutch trials compared to multi-national trials (crude HR 0.3; 95% CI 0.1 – 0.8, p=0.02). Furthermore, results suggest that GCT trials with lymphocytes as the active substance, compared to stem

cells, are published more in conference abstracts (crude HR 2.6; 95% CI 0.8-8.6, p=0.11), although the effect size is uncertain and the association is non-significant. Univariate analysis indicates no association between product type, therapeutic area, trial phase, randomized design and the outcome of publication through conference abstracts (Table 2).

Discussion

The aim of this study was to provide insight into GCT publication rates, associations between publication and trial characteristics, and which type of results are reported. Our cohort mainly consisted of academically sponsored, single-centered, national (i.e. Dutch) trials, and privately sponsored, multi-center, multi-national trials. These characteristics are similar to the characteristics of GCT trials conducted throughout the whole EU.[20] Results were either published in scientific papers (27% scientific publication rate), or conference abstracts (17% conference abstract publication rate). Results are indicative of more scientific publication by academic hospitals compared to private sponsors, whereas academic hospitals are less likely to publish results in conference abstracts compared to private sponsors. Detailed knowledge on technological know-how was underreported compared to clinical outcomes in scientific literature.

Our observations underline the important role of single-centred academic trials[28] to build up the GCT knowledge base. This is consistent with the important role of public sponsors in drug discovery in general, particularly in novel fields.[33] The scientific publication rate of 41% by academic hospitals is within range of earlier shown publication rates for clinical drug trials that were sponsored academic hospitals in the US.[34] In contrast, scientific publication by private sponsors is limited. A large proportion of private sponsors consist of small companies in our cohort, who struggle to comply with regulatory requirements and to complete development trajectories for marketing authorization.[19] Resources and priorities for scientific publication are probably limited within those firms. In addition, private sponsors may not publish because of intellectual property rights and other commercial considerations, similar to observations in the field of biotechnology.[35] For example, private sponsors face technological competition when bringing new products to the market that are based on the same collective knowledge base.[29] Therefore, it is important that small companies become more attentive to scientific publications considering their substantial role in the GCT field.[19]

Part of the low scientific publication rate of 27% after a median follow-up period of 5.5 years found here is likely to originate from the rather short follow up period for multi-center trials that were authorized in more recent years of the cohort. Previous work shows a higher likelihood of scientific publication for multi-centre trials that were all followed up for a period of 8-9 years.[9] We observed a substantially shorter median follow up period for multi-centre trials compared to single-centre trials. Considering the lengthy process of conducting large multi-centre trials over the course of a few years, and time needed for publication, it is very likely that for these trials publication of results is not yet possible. Despite these methodological limitations, our explorative Cox analysis contradicts previously reported associations between scientific publication and multi-centred, late phase, oncology drug trials.[9,36] The GCT field is relatively new, which is supported by the relatively high proportion of single-centred and early phase trials in our cohort. Results show a higher likelihood of scientific publication for other disease areas than oncology, which can be explained by substantial early GCT development for severe indications across therapeutic areas. Early phase GCT trials are typically directly conducted in patients, which is postulated to account for higher likelihoods of scientific publication.[9] This provides an explanation why we did not find previously reported associations between scientific publication and late phase trials in the field of oncology.[9,36]

The publication rate of conference abstracts was found to be rather low (17%), and can partly be explained by the low publication rate of conference abstracts by academically sponsored trials. This is surprising, and needs to be investigated further. Our results indicate publication through conference abstracts by private sponsors, which is encouraging. In addition, many recent events of conference publication had to be excluded from analysis for multi-centered, multinational trials, because knowledge of other sites had been shared before trial authorization in the Netherlands. These trials are illustrative of successful commercial developments in the GCT oncology field, most evidently with T cell therapies to target malignancies.[37–39] Without excluding these trials, the publication rate of conference abstracts would have been higher but still suboptimal (26%). Therefore, to fully understand publication rates of multi-centered trials, larger cross-country cohort studies are needed in order capture initial trial authorization. Furthermore, full peer-reviewed reporting can only be achieved through scientific publication.[40] Previous work shows that 20-33% of published conference abstracts are thereafter published in scientific papers.[40–42] Publication of trial results through conference abstracts may be part of strategies to maximize commercial value of available scientific

data, with potential knowledge biases.[43] Therefore, it is important that private sponsors continue to share their GCT trial results after publishing conference abstracts.

The novelty of the GCT field and the limited knowledge base may in itself account for the rather limited publication rates. The high rejection rate of GCT trial applications shown here underlines translation difficulties from pre-clinical to clinical testing.[44] Challenges to translate *in-vivo* results from animal studies to humans can result in clinical trial failure, which may explain the high rate of non-publication here due to publication biases.[12–15] Limited biological understanding of GCT interactions in humans is illustrated by the high reporting of findings based on biomarkers or surrogate endpoints. Other previously reported factors for non-publication include having other priorities and rejection by journals.[9,45,46] Journals may be more inclined to accept results of late phase trials conducted with pharmaceuticals, forcing sponsors of early phase trials that study niche GCT technologies to compete for limited publication space in specialized journals. However, clinical trials registers provide another destination for publication of trial results, including those for early terminated or failed trials. Before data collection, we defined publication of trial results in EudraCT as an outcome measure. However, results were reported in EudraCT for only two trials in the cohort, and was excluded from methodology due to this limited count of events. This is rather surprising as publication of trial results in registries is required within 12 months after trial completion.[47] It clearly underlines earlier reports that result reporting in clinical registries is not standard practice and needs to be improved.[34,48]

Currently, quality and trial design standardization remains complicated due to relatively limited clinical experience and heterogeneity of different GCT technologies. Publication is one of several strategies to enhance learning among academia and to facilitate collaboration with industry. Collaboration can be achieved through development in public-private partnerships, engagement in license agreements, or spinning off small companies that are later acquired by large industry.[49–51] The proportions of technological-know how reporting shown here probably do not suffice to increase the knowledge base on manufacturing and quality, and to work towards standardized manufacturing protocols. Therefore, there is a need for increased sharing of knowledge on key quality attributes among researchers, either through publication or collaboration. This includes large-scale initiatives for pooling of knowledge on technological know-how to facilitate standardization of manufacturing protocols which was recently

done for mesenchymal stromal cells.[52] Furthermore, it is paramount that GCT developers carefully develop in-process and release specifications to prevent objections by regulators in later development stages,[53] or failures to transfer technology to industry.[54] Innovative medicines that reach marketing authorization are traditionally transferred to industry after successful early clinical development,[51,55] of which transfer or partnering with large industry is most successful.[56] If public GCT trial sponsors prefer to commercialize their products, it is crucial to establish target product profiles and joint services to streamline collection of patient material, manufacturing and distribution efforts.[28]

A strong collective knowledge base is critical to ensure technical and clinical information synthesis in new fields.[35] Due to the large proportion of local clinical activities, this is particularly relevant for the GCT field.[20,28] The rather low publication rates shown here underline a need for enhanced publication of GCT trial results, which facilitates mutual learning in the field and is instrumental in making GCT development more open and collaborative.[57,58]

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Chapter 4.2:
ATMP manufacturing under the Hospital Exemption and other exemption pathways in seven EU countries

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Abstract

As part of the Advanced Therapy Medicinal Products (ATMP) Regulation, the Hospital Exemption (HE) was enacted to accommodate manufacturing of custom-made ATMPs for treatment purposes in the EU. However, how the HE pathway has been used in practice is largely unknown. Using a survey and interviews, we provide insights into the product characteristics, scale, and motivation for ATMP manufacturing under the HE and other, non-ATMP specific, exemption pathways in seven European countries. Results show that ATMPs were manufactured under the HE by public facilities located in Finland, Germany, Italy, and the Netherlands, which enabled availability of a modest number of ATMPs (n=12) between 2009-2017. These ATMPs showed to have close proximity to clinical practice; manufacturing was primarily motivated by clinical needs and clinical experience (gained historically in clinical practice, and/or in early clinical trials). Furthermore, public facilities used the HE when patients could not obtain treatment in ongoing or future trials. Regulatory aspects motivated (Finland, Italy, Netherlands), or limited (Belgium, Germany) HE utilization, whereas financial resources generally limited HE manufacturing by public facilities. Public facilities manufactured other ATMPs (n=11) under Named Patient Use (NPU) between 2015-2017, and used NPU in a similar fashion as the HE. For public facilities, the scale of manufacturing under the HE over nine years was shown to be rather limited, in comparison to manufacturing under NPU over three years. In Germany, ATMPs were mainly manufactured by facilities of private companies under the HE. In conclusion, the HE supported availability of ATMPs with close proximity to clinical practice for patients in need. However, in some countries HE provisions limit utilization, whereas commercial developments could be undermined by private HE licenses in Germany. Transparency through a public EU-wide registry, guidance to distinguish between ATMPs that are, or are not, commercially viable, as well as public-private engagements, are needed to optimize the use of the HE pathway and regulatory pathways for commercial development in a complementary fashion.

Introduction

Gene and cell-based therapies (GCTs) are a heterogenous group of medicinal products that hold great potential to improve health care. They offer new modalities for treatment compared to pharmaceuticals (i.e. small molecules and biologics), in particular for therapeutic areas in which current treatment is lacking or has unsatisfactory clinical outcomes.[1] For instance, GCTs have the potential to regenerate damaged or lost tissue, and provide new treatment modalities for autoimmune diseases, cancers, and monogenetic disorders.[2,3] GCTs, defined as Advanced Therapy Medicinal Products (ATMPs) in the European Union (EU), are regulated as medicinal products and marketed through the central authorization procedure in the EU. Yet, reports of hurdles to reach patients through commercial development are numerous.[1,4–10] This is partly due to their complex product characteristics and scientific uncertainties which challenge commercial development and regulatory pathways.[11] Moreover, many ATMPs are rooted in clinical practice,[12] and early clinical developments are largely undertaken by academic hospitals.[13] Yet, it is reported that academic hospitals and other public institutes struggle to complete developments all the way to the market, through the centralized authorization procedure.[9,14,15]

There are three EU regulatory pathways that exempt ATMPs from the centralized authorization pathway (i.e. exemption pathways): the Hospital Exemption (HE), Named Patient Use (NPU), and Compassionate Use. The HE exempts ATMPs from clinical trial regulations and the centralized pathway for authorization of the ATMP Regulation (1394/2007). It accommodates manufacturing of 'custom-made' ATMPs on a 'non-routine' basis for treatment purposes in hospital settings (ATMP Regulation, Article 28).[16,17] NPU and Compassionate Use are historically used for manufacturing of medicinal products outside of clinical trials. NPU exempts medicinal products (not limited to ATMPs) from the regulations of Directive 2001/83/EC, and enables manufacturing of medicinal products without centralized authorization for individual patient treatment (Directive 2001/83/EC, Article 5). In addition, medicinal products (not limited to ATMPs) that are in the process of centralized authorization can also be manufactured under Compassionate Use until central authorization is granted (Regulation 726/2004, Article 83). The HE, NPU and Compassionate Use are all authorized on a national level by the competent authorities of EU countries, and national regulatory provisions vary.[18,19] How these pathways are used to manufacture ATMPs without central authorization, outside of clinical trials, is largely unknown.

Previous work published in 2012 showed that in numerous EU countries the HE had not been used for ATMP manufacturing yet, except for Germany and the Netherlands.[20] More recent studies indicate that HE utilization has increased over time, and expanded to a few other countries including Finland and France, among others.[19,21] Different types of ATMPs are manufactured under the HE, including lymphocytes, chondrocytes, dendritic cells, and stem cells.[21] Public stakeholders stated that the HE is particularly suited to manufacture ATMPs with historic experience in clinical practice, and ATMPs that target ultra-rare diseases.[9,19,22,23] However, the scale of manufacturing, the characteristics of the targeted patient populations (e.g. indication), and motivation of facilities to manufacture under the HE pathway, are largely unknown. Regulators recently reported that public ATMP manufacturing facilities experience difficulties to comply with national provisions for the HE,[19] which could impede ATMP manufacturing and treatment within clinical practice.[9,15,24] Furthermore, companies can apply for HE licenses in numerous EU countries.[19] In addition, there are indications that alternative exemption pathways are preferred over to the HE pathway in some countries, such as the Specials scheme (i.e. NPU pathway) in the United Kingdom (UK).[19,22]

In this study, we investigate ATMP manufacturing under the HE in practice. We provide first insights into product characteristics and scale of ATMP manufacturing and treatment under the HE and other exemption pathways. Furthermore, we provide insights into the motivation to manufacture ATMPs under the HE and other exemption pathways. The comparative analysis includes manufacturing activities of public and private ATMP facilities that are located in seven EU countries (Belgium, Finland, France, Germany, Italy, Netherlands, UK). Provided insights may substantiate debates on the impact of the HE on ATMP availability in clinical practice, and on commercial ATMP development.

Methods

Selection of ATMP manufacturers

We selected ATMP manufacturers in European countries that 1) were a Member State of the EU, 2) implemented regulatory provisions for the HE by June 2018, and 3) showed indications of ATMP clinical activity, either evident through the conduct of clinical trials[25] and/or ATMP manufacturing under the HE.[20] Based on these criteria, we initially selected nine countries (Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Spain, UK) for the purpose of this study.

In the selected countries, we attempted to identify all public ATMP manufacturing facilities (i.e. hospitals, blood and tissue banks; from here-on referred to as public facilities) regardless of regulatory pathways, and all private HE license holders (i.e. commercial entities, from here-on referred to as private facilities). The ATMP working group of the Netherlands and Flemish academic medical centers, and ATMP experts from the other selected countries, were consulted to identify public facilities in their respective country. Based on a snowball approach, we identified public facilities in seven countries (Belgium, Finland, France, Germany, Italy, Netherlands, UK). We were not able to obtain contact information for hospitals in France, and public facilities in Austria and Spain. However, previous work showed that no HE licenses were granted in the latter two countries up to June 2018.[19] Therefore, manufacturing in Austria and Spain is not further described. In addition, we identified all private facilities in the nine selected countries building on previous engagement with competent authorities and public regulatory information.[19]

Data sources

We used a mixed-methods approach to collect data on ATMP manufacturing under exemption pathways. First, we used public sources to identify public and private HE license holders, which were found for France[26] and Germany[27] only. Second, we collected data from public facilities through a survey, which was depending on the availability of survey respondents followed up with interviews. We collected data from private facilities through interviews only.

Data collection

Survey

We collected data from the identified public facilities with a survey that was developed in the LimeSurvey platform belonging to the Utrecht Pharmacy Practice Network for Education and Research (UPPER).[28] The work was conducted in compliance with the requirements of the UPPER institutional review board of the Department of Pharmacoepidemiology and Clinical Pharmacology. We attributed entry codes for each facility, which allowed anonymization of individual respondents, while the facility and country could be identified. The survey was sent out per country in a staggered manner, between November 2018 – March 2019.

The survey consisted of two parts in order to distinguish between ATMP manufacturing under the HE versus other exemption pathways (i.e. Named Patient Use, Compassionate Use). The period of analysis for manufacturing under the HE ranged from 1 January 2009 until 31 December 2017. The period of analysis for ATMP manufacturing under other exemption pathways was restricted to 1 January 2015 until 31 December 2017, because documentation for NPU manufacturing activities before 2015 was foreseen to be potentially less accessible to facilities and lead to non-responses.

Survey outcomes

The survey consisted of questions and pre-filled checkboxes per product (Table S1), for ATMPs that had been manufactured under exemption pathways. HE licenses that were not used for manufacturing were not included. The entries directly related to product characteristics, scale, and motivation to manufacture under exemptions. Product characteristics entailed the product type (i.e. ATMP classification), origin of cellular starting material, the proposed active substance, and the targeted therapeutic area of the manufactured ATMP. Scale entailed the scale of manufacturing, scale of patient treatment, and period of manufacturing. Lastly, respondents could select one main reason to motivate their choice to manufacture the ATMP under the used exemption pathway. For possible entries per variable, see Table S1.

Interviews

All survey respondents were invited to participate in a short follow up interview by telephone. A semi-structured questionnaire was used to discuss 1) survey entries for the ATMPs that were manufactured under exemption pathways (if applicable), and 2) their motivation to manufacture under the HE, other exemption pathways, and/or clinical trials (whichever applicable to the facility). Interviews were conducted between February – March 2019. All interviewees were employees of their public facility.

Chief executives or executives of regulatory or manufacturing departments of private facilities were also invited for interviews by telephone. A semi-structured questionnaire was used to discuss 1) the product characteristics and scale of ATMP manufacture under the HE (similar to the survey), and 2) their motivation to manufacture under the HE. Interviews were conducted between February – March 2019. Oral consent for recording was sought before all interviews with public and private facilities started. Recordings were used to minute interviews.

Data analysis

Product characteristics and scale of ATMP manufacturing under exemption pathways

First, responses from the public facilities were tabulated to capture the survey response rate and number of ATMPs manufactured under exemption pathways per country. Second, data per ATMP manufactured under exemptions pathways by public facilities was categorized according to the set of predefined variables and values to determine product characteristics, the scale of manufacturing and treatment, and the main reason to manufacture under an exemption pathway (Table S1). We subsequently conducted a descriptive sample analysis based on the assigned values by tabulating and stratifying data by regulatory pathway and country, using IBM SPSS Statistics 24. Product characteristics and scale of ATMP manufacturing under the HE by private facilities was extracted from the interview minutes and tabulated. Due to small numbers statistical analysis was not performed.

To estimate the total patient exposure to exemption ATMPs, we calculated the sum of the minimum and maximum number of patients per range (Table S1), for all manufactured ATMPs per exemption pathway, stratified by public and private facilities. We assumed a range of 200 patients to a maximum of 500 patients for the range of more than 200 patients, and one patient to a maximum of 500 patients when the scale of treatment was unknown. We did not correct for the response rate (public facilities), or the total number of HE license holders (private facilities), because presented data for the HE for public facilities approaches a complete data set in the selected countries, and it is unclear whether all private facilities used their HE license for manufacturing.

Motivation to manufacture under exemption pathways

Interview minutes were used to capture a more nuanced perspective on how facilities are motivated to manufacture under exemption pathways. Building on previous work on institutional readiness to adopt ATMPs in clinical practice,[29,30] we developed a preliminary coding tree to capture the motivation for manufacturing under exemption pathways by coding reasons within the following categories: clinical needs, clinical skill base and expertise (e.g. historic experience in clinical practice, previous clinical trial conduct), regulation, financial resources, logistical and manufacturing capacities, and professional/institutional interests.[29,30] After an initial round of open coding, a second round of axial coding was performed to group open codes into common, coded reasons (Table S2-4).

For facilities that manufactured ATMPs under exemption pathways, we coded 1) reasons to manufacture under exemption pathways, per manufactured product (i.e. product specific reasons), and 2) product transcending reasons (i.e. nonproduct specific) to manufacture under exemption pathways. For facilities that did not manufacture ATMPs under exemption pathways, we coded reasons (i.e. nonproduct specific reasons) to not to manufacture under exemption pathways. Coded product specific reasons were extracted and stratified by regulatory pathway, tabulated and pooled for comparative analysis (Table S2). Coded nonproduct specific reasons were extracted, tabulated and pooled for comparative analysis (Table S3-4). To indicate differences in national provisions among the selected countries, we indicated in which countries reasons to manufacture, or not manufacture, in relation to regulation were described. For other reason categories, the number of observations allowed to report on aggregate level only.

Subsequently, the motivation of private facilities to manufacture under the HE was coded using the same approach as for public facilities, and captured separately from the motivation of public facilities. Results were extracted, tabulated and pooled for comparative analysis. All qualitative analyses were performed in NVivo Pro v11.

Results

Public ATMP manufacturing under exemption pathways

We identified 67 public ATMP manufacturing facilities in seven countries (Belgium, Finland, France, Germany, Italy, Netherlands, UK). Of these 67 public facilities, 27 public facilities provided input to our survey (40% overall response rate). Overall, the respondent public facilities manufactured 12 ATMPs under the Hospital Exemption (HE) between 2009-2017, and 11 ATMPs under Named Patient Use (NPU) between 2015-2017 (Table 1). The survey respondents did not manufacture ATMPs under Compassionate Use pathways.

Product characteristics and scale of manufacturing under the Hospital Exemption

Overall, seven public facilities manufactured 12 ATMPs (Finland n=1/12, Germany n=3/12, Italy n=2/12, Netherlands n=6/12) under the HE during 2009-2017 (Table 1). The other 20 respondent public facilities did not manufacture ATMPs under a HE license.

Table 1: Survey response rate and number of ATMPs manufactured under exemption pathways by public facilities, per country

	Public facilities		ATMPs (public)	
	Recipients (n)	Respondents (n)/ Response rate (%)	HE (n) 2009-2017	NPU (n) 2015-2017
Belgium	7	3 (43%)	0	0
Finland	2	1 (50%)	1	0
France	1	1 (100%)	0	0
Germany	22	3 (14%)	3	0
Italy	5	3 (60%)	2	5
Netherlands	9	8 (89%)	6	2
United Kingdom	21	8 (38%)	0	4
Total	67	27 (40%)	12	11

HE = Hospital Exemption, NPU = Named Patient Use.

Manufactured ATMPs under the HE were mainly somatic Cell Therapy Medicinal Products (n=11/12), plus one Combination ATMP (n=1/12). The origin of cellular starting material was mostly allogeneic (n=8/12). Out of all possible proposed actives substances (Table S1), ATMPs consisted of mesenchymal stromal cells (MSCs) (n=8/12), hematopoietic stem cells (n=2/12) and lymphocytes (excluding CAR-T lymphocytes) (n=2/12). These ATMPs mainly targeted diseases or conditions in the therapeutic areas of immunological diseases (n=4/12) and hematologic oncology (n=3/12). Other therapeutic areas included cardiovascular (n=2/12), infectious (n=1/12), and musculoskeletal diseases/conditions (n=1/12), or was unknown (n=1/12) (Table 2). The MSCs mainly targeted immunological diseases (n=4) and hematologic oncology (n=2), the hematopoietic stem cells targeted cardiovascular (n=2), and the lymphocytes targeted infectious disease (n=1) and hematologic oncology (n=1).

For most ATMPs that were manufactured under the HE, the scale of manufacturing did not exceed 10 batches (n=6/12), or 50 batches (n=3/12) during 2009-2017. Yet, for some, the scale of manufacturing was relatively large. For one ATMP in the Netherlands (n=1/12), the scale of manufacturing ranged between 50 to 200 batches. In Germany, more than 200 batches were manufactured for two ATMPs (n=2/12) (Table 2). The range of manufacturing largely overlapped with the range of patient treatment. Yet, for one MSC product, a maximum of ten batches was manufactured for treatment of over 200 patients (not shown), while for another MSC product more batches were manufactured (more than 200), compared to patient treatment (between 50-200). The manufactured batches were used to treat up to 10 patients (n=5/12), up to 50 patients (n=3/12), 50-200 patients (n=1/12), more than 200 patients (n=1/12), or the scale of treatment was unknown (n=1/12). The

Table 2: Scope and scale of manufactured ATMPs under exemption pathways by public facilities, per country

Regulatory pathway	Hospital Exemption					Named Patient Use			
Country	**FI (n=1)**	**DE (n=3)**	**IT (n=2)**	**NL (n=6)**	**Total HE (n=12)**	**IT (n=5)**	**NL (n=2)**	**UK (n=4)**	**Total NPU (n=11)**
ATMP subtype									
Somatic Cell Therapy Medicinal Product	0	3	2	6	11	5	2	4	11
Combination ATMP	1	0	0	0	1	0	0	0	0
Origin of cellular material									
Autologous	1	1	0	2	4	2	0	0	2
Allogeneic	0	2	2	4	8	3	2	4	9
[Proposed] Active substance									
Lymphocytes	0	1	0	1	2	3	1	2	6
Hematopoietic stem cells	0	1	0	1	2	0	0	0	0
Mesenchymal stromal cells	1	1	2	4	8	2	1	2	5
Target disease/condition									
Immunology	0	1	0	3	4	1	0	1	2
Infection	0	0	0	1	1	2	1	1	4
Cardiovascular	0	1	0	1	2	0	0	0	0
Hematological oncology	0	1	1	1	3	2	1	1	4
Musculoskeletal	1	0	0	0	1	0	0	1	1
Unknown	0	0	1	0	1	0	0	0	0
Scale of manufacturing									
0 – 10 batches	1	0	2	3	6	2	2	1	5
10 – 50 batches	0	1	0	2	3	3	0	0	3
50 – 200 batches	0	0	0	1	1	0	0	1	1
More than 200 batches	0	2	0	0	2	0	0	0	0
Unknown	0	0	0	0	0	0	0	2	2
Scale of patient treatment									
0 – 10 patients	1	0	1	3	5	4	1	0	5
10 – 50 patients	0	1	0	2	3	1	1	1	3
50 – 200 patients	0	1	0	1	2	0	0	1	1
More than 200 patients	0	1	0	0	1	0	0	0	0
Unknown	0	0	1	0	1	0	0	2	2
Period of manufacturing									
2009 – 2015	0	0	1	1	2	NA	NA	NA	NA
2015 – 2017	0	0	0	3	3	5	2	4	11
Both periods	1	3	1	2	7	NA	NA	NA	NA
Main motivation for regulatory pathway									
Few patients to be treated	1	0	0	0	1	0	0	0	0
Clinical urgency to treat	0	2	1	1	4	4	1	0	5
Lack of alternative treatment	0	0	1	5	6	0	1	3	4
Continue availability	0	1	0	0	1	0	0	0	0
Data collection for clinical trials	0	0	0	0	0	1	0	0	1
Unknown	0	0	0	0	0	0	0	1	1

FI = Finland, DE = Germany, IT = Italy, NL = Netherlands, UK = United Kingdom. NA = not applicable, as the period of analysis for other exemption pathways was restricted to 2015-2017.

patient exposure ranged from a minimum of 336 to a maximum of 1600 patients under the HE. Most ATMPs were manufactured and used for treatment during 2009-2017 (n=7/12). Two ATMPs were manufactured before 2015 (manufactured only between 2009-2015), whereas three others were manufactured after 2015 (manufactured only between 2015-2017) (Table 2).

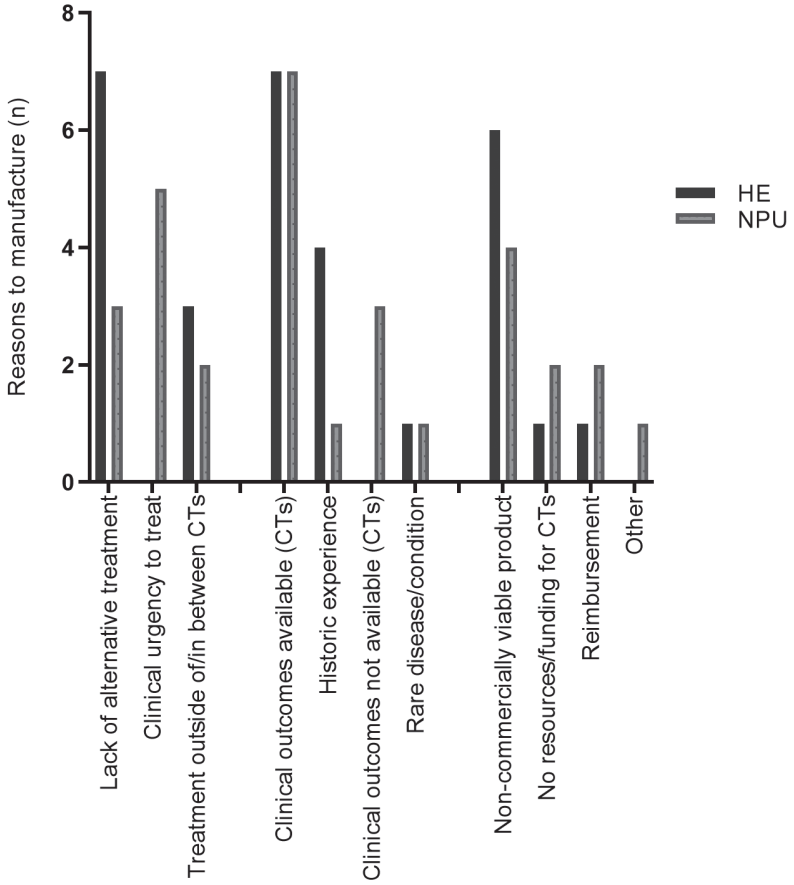
The respondent German public facilities are part of the German blood bank, which is HE licensed.[27] In France, there are five public facilities (hospitals) that together have seven HE licenses to manufacture a particular class of ATMP for national use (somatic Cell Therapy Medicinal Products, Tissue Engineering Products, Combination ATMPs). Furthermore, hospitals are licensed to manufacture HE products under the clinical trial framework.[26] If and to which extent these HE licenses where used for manufacturing in France is unknown and not described further.

Product characteristics and scale of manufacturing under Named Patient Use

Overall, five public facilities manufactured 11 ATMPs (Italy n=5/11, Netherlands n=2/11, and the UK n=4/11) under NPU pathways during 2015-2017. These are different products than the ATMPs that were manufactured under the HE. Manufactured ATMPs were all somatic Cell Therapy Medicinal Products (NPU n=11/11), mostly based on allogeneic starting material (n=9/11). The ATMPs consisted of lymphocytes (excluding CAR-T lymphocytes) (n=6/11), or MSCs (n=5/11). These ATMPs targeted mainly infectious diseases (n=4/11) and hematologic oncology (n=4/11). Other therapeutic areas included immunological diseases (n=2/11) and musculoskeletal disorders (n=1/11) (Table 2). The lymphocytes targeted infectious diseases (n=4) and hematologic oncology (n=2), and the MSCs mainly targeted immunological diseases (n=2) and hematologic oncology (n=2).

The scale of manufacturing under NPU did not exceed 10 batches (n=5/11), or 50 batches (n=3/11) for most ATMPs, during 2015-2017. The scale for one ATMP manufactured in the UK ranged between 50-200 batches (n=1/11). For two other ATMPs manufactured under NPU in the UK the scale was unknown (n=2/11). The scale of patient treatment showed identical ranges as for scale of manufacturing. The patient exposure ranged from a minimum of 87 to a maximum of 1400 patients under NPU (Table 2).

Figure 1: Motivation of public facilities to manufacture ATMPs under exemption pathways (product specific), stratified by reasons and exemption pathway



Multiple reasons per ATMP were described to motivate manufacturing under HE or NPU, including reasons within the clinical, skill base, and financial categories. Only product reasons that were mentioned for more than one product were depicted. See Table S2 for full description of reason subcategories and categories. HE = Hospital Exemption, NPU = Named Patient Use, CT = clinical trial.

Motivation to manufacture under exemption pathways

The survey allowed to select one, main reason to motivate to manufacture ATMPs under an exemption pathway. Results show that manufacturing under the HE was primarily motivated by clinical needs. For most ATMPs, it was indicated that no alternative treatment was available at all, or that all other treatment options had been exhausted (i.e. lack of alternative treatment) (n=6/12), and/or that there was an urgent, time limited need for

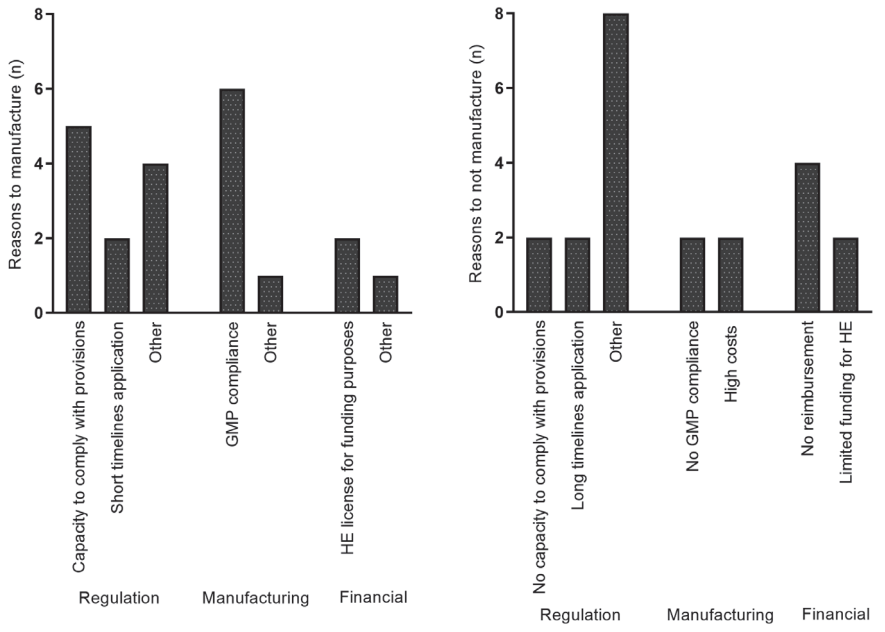
ATMP treatment (i.e. clinical urgency to treat) (n=4/12). Other reasons included ensuring continued availability after the implementation of the ATMP Regulation (n=1/12), or enabling treatment for a low number patients (n=1/12). Similar to the HE, manufacturing under NPU was mainly motivated by clinical needs, most evidently due to a clinical urgency to treat (Table 2).

From the survey respondents, we interviewed ten public facilities that were located in Belgium, Finland, Germany, Italy, Netherlands, and the UK. Public facilities that participated in interviews had manufactured 17 ATMPs under exemption pathways (HE n=7, NPU n=10). For each manufactured ATMP, a combination of reasons were described to motivate manufacturing under exemption pathways. First, the clinical needs (lack of alternative treatment, clinical urgency to treat, for definitions see Table S2) were consistently described as the main reason to motivate manufacturing under both the HE and NPU pathway (as indicated in the survey). Respondents emphasized that the ATMPs were used as a last resort treatment. For instance, patients that suffered from Graft versus Host Disease, but did not respond to steroid treatment, were treated with MSCs that were manufactured under the HE. Patients that suffered from an acute, life-threatening infection, such as the Epstein Barr Virus or Cytomegalovirus, and did not respond to antiviral treatment, were treated with virus targeting lymphocytes manufactured under NPU. Furthermore, these clinical needs were described to occur in situations in which treatment in a clinical trial was not possible, because patients did not adhere to the inclusion criteria of ongoing trials, or that trials were not ongoing when treatment was needed (Figure 1, Table S2).

In combination with clinical needs, facilities described reasons that motivated manufacturing under the HE that related to clinical skill base and expertise on a product; for all ATMPs that were manufactured under the HE, early clinical trials had been conducted, or historic experience in clinical practice had been gained when the ATMP was available as human cells or tissue in the past. For one ATMP, the targeted rare disease or condition and the small patient population motivated to use the HE for manufacturing. With respect to financial aspects, it was indicated that most ATMPs were not considered commercially viable (e.g. due to a lack of interest by industry to pick up late clinical development), and therefore, manufactured under the HE. For one ATMP, it was indicated that resources for continued in-house commercial development were lacking. In contrast, manufacturing of one ATMP under the HE was financed through reimbursement. Similar reasons were described to motivate manufacturing under NPU (Figure 1). Other reasons are included in Table S2.

From the ten interviewed facilities, three facilities manufactured ATMPs under the HE, and three facilities manufactured ATMPs under NPU. Four facilities did not manufacture ATMPs under exemption pathways (only for clinical trials). These facilities described nonproduct specific reasons to motivate manufacturing, or no manufacturing, under exemption pathways. Facilities located in Finland, Italy, Netherlands, and UK reported reasons to motivate manufacturing under exemption pathways. They reported to comply with HE or NPU regulatory provisions, and to comply with GMP. Short timelines for HE application procedures in Italy and the Netherlands facilitated manufacturing under the HE. Few financial aspects, which were not directly described in relation to a product, were described to motivate manufacturing under exemption pathways. Two facilities indicated that they applied for a HE license to support funding opportunities to conduct clinical trials through grants, instead of ATMP manufacturing under the HE (Figure 2A). Details and other nonproduct specific reasons for manufacturing under exemption pathways are provided in Table S3.

Figure 2: Motivation of public facilities to manufacture (A), or to not manufacture (B), ATMPs under exemption pathways (nonproduct specific), stratified by reasons[a]



[a] Only nonproduct reasons that were mentioned by more than one facility were depicted. See Table S3-4 for full description of reason subcategories and categories.

In contrast, facilities located in Belgium indicated that stringent provisions (mainly for clinical data), long timelines for HE applications, and non-compliance with full GMP (e.g. QP release) were reasons not to manufacture under the HE. Other frequently mentioned reasons to not manufacture under exemption pathways included high costs for manufacturing and payment from hospital budgets. Facilities indicated that possibilities for reimbursement, and other funding options for HE manufacturing in case of no reimbursement, are limited (Figure 2B). Details and other nonproduct specific reasons to not manufacture under exemption pathways are provided in Table S4.

Private ATMP manufacturing under the HE

We identified nine private facilities that are HE license holders in two selected countries; six in Germany[27] and three in the Netherlands. We interviewed two private facilities in Germany, which manufactured three ATMPs under the HE during 2009-2017. One private facility in the Netherlands indicated that their HE license was inherited from an acquired facility, and was not used for manufacturing.

Results from interviews show that three ATMPs were manufactured by two private German facilities. These three ATMPs were autologous chondrocyte products for musculoskeletal disorders. For one ATMP, the scale of manufacturing and patient treatment was over 200 batches and patients, respectively, during 2009-2017, and for the other two ATMPs the scale was unknown (not shown). The patient exposure ranged from a minimum of 202 to a maximum of 1500 patients under the HE. Information in the public domain showed that four other private facilities in Germany are licensed to manufacture ATMPs under the HE that consist of chondrocytes, MSCs, skin cells, and hematopoietic stem cells. However, no other information is provided, including the targeted indication.[27] Details on the ATMP manufacturing activities of two other HE licensed private facilities in the Netherlands are not available in the public domain.

The motivation to manufacture under the HE by German private facilities included reasons related to historic product availability on the market and changing regulations. When the ATMP Regulation was issued, pre-existing German tissue product manufacturing licenses were transferred to HE licenses over time. Under German law, tissues are regulated as medicinal products and manufacturing needs to be GMP compliant.[19] Private facilities had capacity to comply with provisions for clinical data, and HE licenses were issued to continue their operations after the implementation of the

ATMP Regulation. Financial reasons that motivated to manufacture under the HE included reimbursement and to generate revenue from HE product sales to conduct large clinical trials. Institutional interests included interest in commercial development and centralized authorization in the EU.

Discussion

We aimed to substantiate debates on the Hospital Exemption (HE) by investigating product characteristics, scale, and motivation of ATMP manufacturing under exemption pathways by public and private facilities. Results show that a modest number of ATMPs (n=12) were manufactured under the HE by public facilities. Most ATMPs consisted of mesenchymal stromal cells, and targeted diseases or conditions within immunological diseases and hematologic oncology. The scale of manufacturing and patient treatment generally did not exceed 50 batches or treated patients per ATMP during 2009-2017. However, three ATMPs were manufactured and used for patient treatment on a relatively large scale by public facilities in Germany and the Netherlands. The total patient exposure to the ATMPs captured in the survey (40% response rate) ranges between 336-1600 patients under the HE. ATMPs manufacturing under the HE was primarily motivated by clinical needs and clinical experience, when treatment within clinical trials is not possible (either ongoing or future trials). Regulatory aspects were described to motivate (Finland, Italy, Netherlands), or limit (Belgium, Germany) manufacturing under the HE by public facilities, depending on national procedures and in-house capacities. Financial resources often limited manufacturing under the HE by public facilities. In most selected countries, ATMPs manufacturing under Named Patient Use (NPU) was comparable to manufacturing under the HE by public facilities. The scale of manufacturing and patient treatment was generally modest (up to 50 batches or treated patients) during 2015-2017. In the UK, NPU manufacturing (i.e. Specials scheme) occurred on a relatively large scale compared to other countries. The total patient exposure to the ATMPs captured in the survey (40% response rate) ranges between 87-1400 patients under NPU. Similar to the HE, ATMP manufacturing under NPU was primarily motivated by clinical needs. Overall, public facilities used the HE in a compassionate use manner[18] (excluding Germany) to provide treatment for patients with clinical needs, and/or as a tool to mitigate commercial development challenges. In Germany, ATMPs were manufactured for the national market under the HE by several private facilities. The total patient exposure to the ATMPs that were manufactured by private facilities, captured in interviews ranges between 202-1500 patients under the HE (2009-2017).

With the enactment of the ATMP Regulation, definitions of what would be considered an ATMP and therefore medicinal product, now included numerous human cell and tissue therapies that were historically used in hospital settings outside of medicinal product legislation (i.e. transition ATMPs).[15] Most manufactured ATMPs under the HE were MSC products, and the reasons and situations in which public facilities used the HE are indicative of a close proximity of the manufactured ATMPs to clinical practice. Manufacturing was primarily motivated by clinical needs and used as a last resort treatment option, and product experience that was gained historically in clinical practice, or in clinical trials. Furthermore, they were manufactured for patients that cannot be treated in ongoing clinical trials (due to non-adherence to inclusion criteria), and/or the ATMP was not considered suited for commercial development, due to financial limitations to conduct late phase clinical trials or a lack of interest of commercial parties to continue development. Thus, our results demonstrate that the HE has been used to support availability of ATMPs with close proximity to clinical practice, and played a critical role to enable treatment for patients with clinical needs.[9,22,23]

The HE resembles NPU pathways because both enable manufacturing to treat individual patients, under the responsibility of health care professionals. The differences are that 1) the HE is a specific pathway for ATMPs only, while NPU is a pathway for all medicinal products, 2) the HE provisions entail more requirements in comparison to NPU, particularly in countries that mandate clinical data for the HE,[19] 3) HE licenses require more prospective planning through more elaborate application procedures compared to NPU, but 4) one HE license can be used for multiple patients, whereas applications for NPU typically are per patient.[18,19] The latter insinuates that NPU manufacturing is used on a more ad-hoc basis compared to the HE, but both are used to treat few patients with custom made ATMPs in selected countries. Yet, under the Specials scheme in the UK, manufacturing facilities obtain a license to manufacture a particular class of ATMPs, such as somatic Cell Therapy Medicinal Products. Thus, Specials licenses enable to manufacture ATMPs in similar situations as the HE in other countries (except Germany).[19] However, regulatory provisions for a Specials license and NPU in general are focused on manufacturing and quality,[18,31] which indicates less centralized oversight on clinical safety and benefits under NPU in comparison to the HE.

Public stakeholders feared that the implementation of the ATMP Regulation could impair availability of ATMPs in clinical practice.[9,24] The environment of public facilities is centered around treatment and innovation in clinical

practice, and is different from pharmaceutical commercialization.[32] A previous study showed indications of limited institutional readiness[33,34] of hospitals and other public institutes to switch from point-of-care settings, or human cells and tissue regulations, to HE provisions.[19] Judged on previous reported numbers of HE license holders,[19] limited capacity to comply is more prominent in countries with most stringent quality and clinical data requirements for HE manufacturing, such as Belgium, and Spain.[19] Furthermore, the regulatory reasons to not use the HE for ATMP manufacturing shown here indicate that hospitals may struggle with GMP compliance, which requires substantial financial and human capital.[15] Yet, reported hurdles for HE manufacturing extend well beyond regulatory and manufacturing challenges. Financial resources to manufacture ATMPs under the HE proved to be limited, similar to marketed ATMPs.[21,33,35,36] Without feasible regulatory provisions and sufficient financial resources, the use of the HE to manufacture ATMPs with close proximity to clinical practice could be limited or is even impaired in some countries. Central coordinating bodies for public facilities can strengthen collective technological know-how and reduce manufacturing and logistical costs,[14] which in turn may improve opportunities for financial support. However, reimbursement is unlikely for products manufactured under the HE with an uncertain benefit/risk balance. Stakeholders are exploring financing models for hospital products, such as conditional financing.[37]

One of the main arguments against the HE is that it could undermine commercial ATMP development by central EU authorization.[10,38–41] Our results indicate that the tension between manufacturing under the HE by public facilities and commercial development is currently rather limited and that the pathways are rather complementary than overlapping. Many ATMPs were manufactured under the HE on a similar scale as early clinical trials, and the number of ATMPs manufactured under the HE is modest compared to the vast number of clinical trials that are sponsored by academic centers in the EU.[13] Furthermore, the scale of HE versus NPU manufacturing was similar for most ATMPs (max. 50 batches). Thus, considering the larger period of analysis for HE (9 years) vs. NPU (3 years) manufacturing, the scale of manufacturing under the HE is rather limited. In addition, many marketed ATMPs are gene or cellular based products with different active substances compared to HE ATMPs. There is overlap between some publicly manufactured ATMPs under the HE and marketed ATMPs for the therapeutic areas immunological diseases and hematologic oncology, although the exact indications are different.[42] UK authorities have legislative power against potential competition of the Specials scheme with marketed medicinal

products (including pharmaceuticals and ATMPs),[31] and some but not all competent authorities of selected countries restrict HE manufacturing when alternative marketed medicinal products are available. A lack of legislative power against potential competition could create tension between manufacturing under the HE by public facilities and commercial development (e.g. Germany, Spain).[19] As scientific and technological advance progresses, and more public facilities are able to adopt ATMPs in clinical practice, this tension could increase over time.

In contrast, the HE creates a competitive advantage for German companies in comparison to other companies, which are located in other EU countries and bound to different HE provisions and utilization.[19] HE licenses discussed here were critical to continue operations after the ATMP Regulation was implemented for transition tissue engineering products (TEPs),[43] and the HE licenses were regarded as temporary until central authorization is reached. However, not all German HE licenses were granted for transition TEPs, some concern relatively new ATMPs.[27] Furthermore, the HE represents a national authorization for use and provides access to the German market, and can be used as a stepping stone towards central EU authorization.[19] It represents a unique situation in comparison to the other selected countries where more restrictive provisions limit manufacturing under the HE to last resort treatments and/or to public facilities, which reduce incentives for manufacturing under the HE relative to commercial ATMP development.[19] Manufacturing of chondrocytes under the HE in Germany contributed to withdrawal of a marketed ATMP in the past. While patients may benefit from more available ATMPs under the HE in Germany, patient access in other countries could be impaired due to EU market failure.[44]

Competent authorities currently assess whether the scale of manufacturing is small and suited for a HE license, amongst other provisions.[19] However, whether the ATMP is not commercially viable is not assessed. Some ATMPs are unsuited for commercial development in the EU,[23] for instance ATMPs that target multiple rare indications and other ATMPs with low commercial value and a high risk profile for commercial development.[14,23] As a result, ATMPs with positive clinical outcomes are at risk of getting stuck in early clinical development,[14] or disappear without manufacturing under the HE. Therefore, it is paramount to go beyond criteria of scale for the HE, and to assess whether ATMPs are not commercially viable. For instance, when opportunities for intellectual property protection and reimbursement are limited.[45] Other ATMPs with high commercial value and acceptable risk profiles are better suited to be transferred to industry or developed in public-private partnerships.[14,46] This would facilitate to use the HE pathway

to meet clinical needs when the market fails, whereas commercially viable ATMPs are developed further for centralized marketing authorization. Yet, criteria to determine whether ATMPs are not commercially viable are likely to be a moving target as a result of scientific and technological advance and changing commercial opportunities, and require a continuous, open dialogue between the European Commission, competent authorities and public and private stakeholders in the field.

Our results are a first step towards insight into product characteristics, scale, and motivation for ATMP manufacturing under the HE in selected EU countries. Data on the HE in selected countries is nearly complete except for France and Germany, judged on earlier reported numbers of HE license holders.[19] The response rate to the survey (40%) mainly leads to missing NPU data, and to missing HE data of potentially one or two public facilities in Finland, Italy, and UK. Yet, we did not reach public HE license holders in France and private HE license holders in Germany out of initially nine selected EU countries.[19] Public sources are available for these HE licenses in France and Germany, however, they do not provide detailed information on product characteristics.[27,47] These limitations underline the lack of transparency on ATMP manufacturing activities under exemptions throughout the EU. A multi-stakeholder mandate for an EU-wide public registry is encouraged to enhance transparency on HE manufacturing.[41] More transparency on available treatments and clinical outcomes facilitates coordination between public facilities, whereas more transparency on product characteristics informs business opportunities and market access planning for industry.[44]

In conclusion, manufacturing under the HE by public facilities supported availability of ATMPs with close proximity to clinical practice for patients in need. However, in some countries HE provisions limit utilization of the pathway, whereas elsewhere private HE licenses undermine commercial developments that go through the centralized procedure. Guidance to distinguish between ATMPs that are, or are not, commercially viable, transparency through a public EU-wide registry on HE manufacturing, as well as collaboration between public facilities and commercial developers, are needed to optimize the use of both the HE and regulatory pathways for commercial development.

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Supplementary Material

Table S1: Variables to measure scope and scale of public ATMP manufacture under exemption pathways

	Variables	Values
Manufacturer	Country	Belgium, Finland, France, Germany, Italy, Netherlands, United Kingdom
Scope	ATMP subtype	Gene Therapy Medicinal Product, somatic Cell Therapy Medicinal Product, Tissue Engineering Product, Combined ATMP
	Origin of cellular starting material	Autologous, allogeneic, xenogeneic
	[Proposed] Active substance	CAR- T cells, Lymphocytes (B, T, NK cells), Dendritic cells, Hematopoietic stem cells, Mesenchymal stem/stromal cells, Other stem cells, Chondrocytes, Other differentiated somatic cells, Vector with genetic material, Combination of different types of cells, other
	Target disease (therapeutic area)	Immunology (immunodeficiency, transplantation, Crohn's disease, GvHD), Rheumatology (ulcerative colitis, vasculitis, sclerosis, rheumatoid arthritis, osteoarthritis, cartilage defects), (rare) Genetic disorders (monogenetic disorders, congenital disease, mitochondrial mutations), Infection, Cardiovascular, Hematological oncology, Other oncology, Musculoskeletal (bone fracture, cartilage defects), Other
Scale	Scale of manufacturing (overall period of analysis)	Range of produced batches [Ranges 0 – 10 batches, 10 – 50 batches, 50 – 200 batches, > 200 batches, unknown]
	Scale of patient treatment (overall period of analysis)	Range of number of patient treatments [Ranges 0 – 10 patients, 10 – 50 patients, 50 – 200 patients, > 200 patients, unknown]
	Period of manufacturing	2009 – 2015, 2015 – 2017, Both periods
Regulatory pathway	Regulatory pathway	Hospital Exemption, Named Patient Use, Compassionate Use
	Main reason for regulatory pathway	Data collection for future clinical trial conduct, Data collection for marketing authorization, Clinical urgency to treat, Lack of alternative treatment, Few patients to be treated, Barriers to conduct clinical trials, Continue availability after implementation of ATMP Regulation, Regulatory recommendation/ requirement, Ease of procedure, Fast patient access, Policy of manufacturing facility or hospital, Other, Unknown

Table S2: Overview of reasons that motivated to manufacture under exemption pathways, per product (n=17) that were discussed with public facilities in interviews

Reason category	Reasons	HE (n=7)	NPU (n=10)	Total (n=17)
Clinical needs	Lack of alternative treatment[a]	7	3	10
	Clinical urgency to treat[b]	0	5	5
	Treatment outside of/in between clinical trials	3	2	5
Clinical skill base and expertise	Clinical outcomes available from clinical trials	7	7	14
	Product with historic clinical experience[c]	4	1	5
	Clinical outcomes not available from clinical trials	0	3	3
	Product for rare disease/ condition	1	1	2
Financial resources	Product not considered commercially viable[d]	6	4	10
	No resources/funding for commercial development	1	2	3
	Reimbursement	1	2	3
	Privately funded	0	1	1
Regulation	Product not suited for ODD	1	0	1
	Application for clinical trials rejected	1	0	1
	Post-treatment authorization	0	1	1
	Start manufacturing and treatment (vs. start clinical trial)	0	1	1
	Collect clinical data	0	1	1
Professional interests	No interest in commercial development	1	0	1
	Advocacy for treatment	1	0	1
	Manufacturing for external party	0	1	1
	Interest in commercial development	0	1	1

[a] No alternative treatment = no alternative treatment is available at all, or all other treatment options had been exhausted for the patients to be treated, [b] Clinical urgency to treat = an urgent (i.e. time limited) need for ATMP treatment, [c] Gained clinical experience with ATMP over extended periods of time, in clinical practice outside of clinical trials, [d] Not considered commercially viable by public facility, due to no interest of industry, or very rare targeted disease/condition. ODD = orphan drug designation in the EU.

Table S3: Overview of nonproduct specific reasons that motivated public facilities (n=10) to manufacture under exemption pathways

Reason category	Reasons	Total facilities (n=10)	HE facility (n=3)	NPU facility (n=3)	No exemption facility (n=4)
Regulation	Capacity to comply with provisions (FI, IT, NL, UK)	5	3	1	1
	Short timelines application (IT, NL)	2	2	0	0
	Regulatory clarity (IT)	1	1	0	0
	HE only national exemption pathway (FI)	1	1	0	0
	Regulatory mandate for HE over NPU (regulatory authority NL)	1	1	0	0
	Regulatory mandate for trials and NPU over HE (IT)	1	0	1	0
Manufacturing and logistical capacities	GMP compliance	6	2	3	1
	In-house storage	1	1	0	0
Financial resources	HE license for funding purposes	2	0	0	2
	Limited funding for clinical trials	1	0	1	0
Institutional interests	Collaboration with other centers	3	1	1	1
	No interest to collaborate with industry	1	0	0	1

FI = Finland, IT = Italy, NL = Netherlands, UK = United Kingdom.

Table S4: Overview of nonproduct specific reasons that motivated public facilities (n=10) to not manufacture under exemption pathways

Reason category	Reasons	Total facilities (n=10)	HE facility (n=3)	NPU facility (n=3)	No exemption facility (n=4)
Regulation	No capacity to comply with HE provisions (BE)	2	0	NA	2
	Long timelines application (BE)	2	0	0	2
	Delayed HE implementation (BE)	1	0	NA	1
	Clinical trial regulations more flexible than HE provisions (BE)	1	0	NA	1
	All patients adhere to inclusion criteria clinical trials (NL)	1	0	0	1
	HE not used for compassionate use situations (DE)	1	0	NA	1
	Not eligible HE license holder (e.g. blood bank) (UK)	1	0	1	0
	Restrictions when alternative licensed treatment is available (UK)	1	0	1	0
	Reduced transparency – no advertising (UK)	1	NA	1	0
	No other exemption pathways than HE (BE)	1	0	0	1
Manufacturing and logistical capacities	No GMP compliance	2	0	0	2
	High manufacturing costs	2	0	1	1
Financial resources	Limited funding for HE	2	0	NA	2
	No reimbursement	4	1	1	2
Institutional interests	Limited collaboration with other centers	2	0	0	2
	Perform outsourced manufacturing under CT licenses (CT license is choice client)	1	0	0	1

BE = Belgium, GE = Germany, UK = United Kingdom.

CHAPTER 5:
GENERAL DISCUSSION

This thesis aimed to investigate regulatory change to accommodate gene and cell-based therapies (GCTs) for human administration as medicinal products, regulatory decision-making under the current frameworks, and the implications of regulatory change for GCT development and their availability in clinical practice. The general discussion describes the general findings and the implications of the findings for GCT development and their availability in clinical practice, perspectives on the way forward and recommendations for future regulatory and innovation studies, and provides a general conclusion.

General findings

In chapter **2.1** we showed that policy makers used two main strategies for regulatory change to accommodate gene and cell-based therapies for human administration as medicinal products: 1) to stretch the boundaries of existing regulations for marketing authorization of medicinal products by implementing specific regulations for GCT marketing authorization, and 2) to implement new regulations that exempt GCTs from clinical development and marketing authorization regulations (i.e. regulatory exemption pathways).[1] These two strategies for regulatory change to accommodate GCTs aim to protect public health, but they have different intended purposes. Regulatory changes for GCT marketing authorization are aimed at commercial development and market entry of new GCTs as medicinal products (by both public and private developers), while exemption pathways are aimed to facilitate activities in clinical practice. Below, we first describe findings for regulatory change for GCT marketing authorization, and exemption pathways including regulatory decision-making under these frameworks. We subsequently point towards general trends that emerged from the thesis and discuss the implications of regulatory change and trends on GCT product development and availability in clinical practice.

Regulatory change for gene and cell-based therapies

Regulatory change for GCT marketing authorization

In chapter **2.1**, we showed that regulatory requirements for standard GCT marketing authorization overlap with regulatory requirement for authorization of pharmaceuticals to a large extent in the multiple jurisdictions (Canada, EU, Korea, US). Confirmatory quality, safety, and efficacy outcomes are required in the selected jurisdictions, as well as compliance with good practice standards for medicinal products, including but not limited to, Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). However, results also indicated regulatory flexibility through legal changes in order to deviate from the standard requirements for marketing authorization. New

legislation for GCTs was implemented in the European Union (EU) in 2007,[2] in Japan in 2014,[3–5] and more recently in the United States (US) in 2016.[6]

Legal changes (i.e. legislation or regulation) for GCT marketing authorization were found in EU, Japanese, and US legislation. EU legislation showed to entail specific quality, safety and efficacy requirements for Advanced Therapy Medicinal Product (ATMP) authorization, and a risk-based approach to determine to which extent quality, safety and efficacy data is necessary for a positive confirmatory benefit/risk profile.[7] Japanese legislation entails numerous regulations for regenerative medicine that are different from regulations for pharmaceuticals, including GCT specific manufacturing practices.[18] Furthermore, we found two GCT specific regulatory pathways for marketing authorization; the Japanese conditional authorization pathway for GCTs[18] and the US Regenerative Medicine Advanced Therapy (RMAT) Designation.[6] The Japanese conditional authorization pathway enables authorization based on non-confirmatory evidence of a positive benefit/risk balance,[3,4,8] which shifts the point of authorization to earlier phases of development in comparison to traditional binary decision-making for approval.[8] To compensate for non-confirmatory evidence, developers are subject to mandatory post-marketing data collection on clinical outcomes after conditional, time-limited authorization.[5] The RMAT Designation lowers eligibility criteria for GCTs only to enter other US facilitated regulatory pathways for marketing authorization. Instead of clinical indications of added clinical benefits that are required for Breakthrough Therapy Designation (BTD) and Accelerated Approval, RMAT Designation requires clinical indications to address unmet medical needs. Yet, GCTs with RMAT Designation have all the benefits of BTD Designation, and are eligible for Accelerated Approval. The latter provides flexibility from standard marketing authorization requirements, including the use of surrogate endpoints.[9]

The described legal changes for GCTs entail high-level changes and requirements for marketing authorization. In the EU, Japan and the US, legal changes are further substantiated in various scientific guidelines (Chapter **2.1**). Despite the implementation of high-level legal requirements and the provision of scientific guidelines for GCT marketing authorization, standardization of regulatory requirements on product or technology level remains difficult because of the novelty and heterogeneity of GCT technologies, and their 'precision medicines' approach for patient subgroups or even individual patients.[10] Consequently, regulatory authorities likely face novel scientific issues in assessment procedures for which there is no previous experience. Consequently, decision-making for GCT marketing authorization largely takes place on a case-by-case basis.[11]

In Chapter **3.1** and **3.2**, we showed that many scientific uncertainties and safety risks were evident in the studied assessment procedures of marketed GCTs. These issues underline the well-established developmental and regulatory challenges in the GCT field.[12–19] For the authorized GCTs in Chapter **3.1**, a substantial number of uncertainties resulted from a suboptimal clinical study design of the pivotal trial(s). For instance, single arm design, uncertain relevance of endpoints, retrospective data collection, and a lack of biomarkers, lead to limitations to interpret the clinical outcomes by the regulatory authorities. Yet, Chapter **3.1** illustrated that regulatory authorities were willing to authorize GCTs based on less comprehensive clinical data, including unresolved scientific uncertainties and safety risks. In contrast, the results of Chapter **3.2** showed a substantial difference between authorized and non-authorized GCTs in the EU. Negative opinions for authorization were issued for GCTs with severe safety risks, and without proof of clinical benefits. This observation shows that EU decision-making between GCT authorization and non-authorization is based on the same principles as decision-making for authorization of pharmaceuticals:[20] a positive benefit/risk balance needs to be established, with or without uncertainties that are deemed acceptable for marketing authorization. Furthermore, the numerous illustrated scientific issues in relation to pharmaceutical quality underline the challenges for GCT manufacturing and quality control.[13] Most prominently, Chapter **3.2** showed that the level of validation of release testing, potency assays, and in-process control and incomparability between clinical trial and commercial products, raised most major objections for quality control. Whether applicants were able to resolve major pharmaceutical quality objections determined the outcome to large extent; only those GCTs were authorized for which the major pharmaceutical quality objections could be resolved. Other applicants of non-authorized GCTs typically withdrew their application during the assessment procedure.

When comparing jurisdictions, Chapter **3.1** showed that the willingness to accept scientific uncertainties and safety risks in decision-making for marketing authorization was most prominent in Japan, followed by the EU and US. The Japanese authorities granted early access to GCTs, and mandated further data collection after authorization under new GCT legislation.[4] This approach for GCTs is considerable more flexible in comparison with stringent Japanese regulations for pharmaceuticals.[21] Many authorized GCTs in the EU are niche products, and were designated as orphan drugs. EU regulators were shown to have an adaptive approach to licensing in their decision-making for GCT authorization. Uncertainties and non-confirmatory evidence were mostly evident for orphan drugs, which were authorized under the EU

conditional marketing authorization pathway. Earlier observations support that small patient populations and a lack of alternative treatment may explain an increased willingness of EU regulators to accept uncertainties and non-confirmatory evidence for CGT authorization.[22,23] In contrast, US regulators had a more traditional approach to GCT licensing before 2016, which is in line with an earlier report of stringent assessments by US regulators.[24] Yet, in the more recent assessments a more permissive approach was demonstrated, which was facilitated by recent reforms (Breakthrough Therapy Designation).[25]

Considerations of the target population and unmet medical needs were most evident in Japanese and European assessment procedures. These non-evidentiary factors were part of decision-making and considered together with uncertainties and safety risks, and resulted in positive benefit/risk opinions. In other words, in the EU and Japan the marketing authorization of GCTs is highly centered around granting early access for patients that suffer from severe diseases or conditions, for who other treatment options have been exhausted, and have a very poor prognosis without further treatment. Within this context of unmet medical need, EU and Japanese marketing authorizations were granted based on non-confirmatory evidentiary support, and authorities imposed substantial obligations to continue data collection in the post-marketing phase. In contrast, earlier GCT authorizations in the US demonstrated a more traditional, binary approach to licensing. Yet, more recent authorizations in the US indicated a shift towards a more permissive approach to licensing due to considerations of added clinical benefit and unmet medical need.

Regulatory change through exemption pathways

In Chapter **2.1** we showed that regulatory authorities in the EU and Japan implemented GCT regulatory exemption pathways. The Act on the Safety of Regenerative Medicine was enacted in Japan for the purpose of clinical research, in contrast to clinical trials for commercial authorization purposes.[3,5,26] Policy makers in the EU considered to exempt local manufacturing activities in hospitals from medicinal product regulations during the drafting of the ATMP Regulation. This resulted in an exemption pathway in EU legislation, which is known as the Hospital Exemption (HE).[27]

The Japanese Act on the Safety of Regenerative Medicine and European HE entail subpar requirements in comparison with marketing authorization requirements,[4,19] which facilitate GCT treatment in clinical practice and possibilities to enhance clinical experience with tailored made, in-house hospital innovations.[28,29] In Chapter **2.2** we investigated regulatory change

under the HE further. Criteria for the HE were laid down in Article 28 of the ATMP Regulation, and needed to be translated into national law of countries that are Member States of the EU through a political process that is called transposition.[30] Transposition resulted in national regulatory provisions for the HE, which entail legal changes in national law, regulations, and guidance through regulatory documentation.

In Chapter **2.2**, we showed that as a result of national transposition processes, national regulatory provisions for the HE varied among nine EU countries. Different bodies of the competent authorities were responsible for the drafting of HE provisions. Based on their discretionary interpretation of the ambiguous terminology of Article 28, competent authorities considered three regulatory principles in various ways that determined national purposes for the HE; clinical principles, evidentiary principles of evidence-based medicine (EBM), and innovation principles. The clinical principles reflect a purpose to manufacture ATMPs to address unmet medical needs. Clinical principles and the criteria in Article 28 resulted in national provisions for the HE that are focused on manufacturing and quality. On top of these basic provisions, some authorities chose to mandate clinical data in order to perform preliminary benefit/risk assessments. This indicated that principles of the EBM paradigm were considered, which lead to HE pathways that are more aligned with centralized marketing authorization procedures. Furthermore, authorities had two contradicting approaches towards the role of the HE as an innovation pathway in relation to regulatory pathways for centralized marketing authorization. Some authorities implemented restrictions to prevent competition with marketed medicinal products, including pharmaceuticals and ATMPs. In other countries, the HE can be used as a stepping stone for the centralized marketing authorization procedure.

Chapter **4.2** showed that ATMP manufacturing under the HE by public facilities (i.e. academic hospitals and blood banks) enabled availability of 12 ATMPs between 2009-2017. Most ATMPs consisted of mesenchymal stromal cells, and targeted diseases or conditions within immunological diseases and hematologic oncology (e.g. Graft versus Host Disease, Crohn’s disease). Critically, these ATMPs showed to have close proximity to clinical practice. ATMPs manufacturing under the HE was primarily motivated by clinical needs and clinical experience that was gained historically in clinical practice or in early clinical trials. Furthermore, public facilities indicated that they manufactured under the HE when patients could not be treated within clinical trials (either ongoing or future trials). The ATMPs manufactured under the HE were used as a last resort to treat patients that had no further treatment options, either because alternative treatment was not

available at all, or other treatment options had been exhausted. Public facilities generally did not considered these ATMPs as commercially viable, and therefore, they were not developed further in-house, or transferred to industry. Furthermore, 11 ATMPs were manufactured under Named Patient Use (NPU) pathways between 2015-2017. The scale of HE manufacturing over nine years showed to be modest, in comparison to manufacturing under NPU over three years. Overall, public facilities used the HE in a compassionate use manner[31] (excluding Germany) to provide treatment for patients with clinical needs, and/or as a tool to mitigate commercial development challenges.

Chapter **2.2** showed that in most selected countries, competent authorities did not restrict eligible license holders for the HE to hospitals and other public facilities (Belgium, Finland, France, Germany, Netherlands, United Kingdom (UK)). Yet, we found companies that are HE license holders (i.e. private facilities) in Germany and the Netherlands only. Chapter **4.2** showed that private facilities in Germany had used their HE licenses to manufacture chondrocyte products for musculoskeletal defects. These ATMPs were available on the German market as tissue products, previous to the ATMP Regulation end the implementation of the HE. The HE licenses were used to continue manufacturing operations after the implementation of the ATMP Regulation, and to manufacture for the national market.

We showed that competent authorities attributed no or limited utilization in some countries (Austria, Belgium, Spain, UK) to limited capacity to comply with national provisions, mainly those for manufacturing, quality, and clinical trial requirements), implementation delays, or alternative regulatory pathways to manufacture ATMPs (Chapter **2.2**). These findings were substantiated with observations from Chapter **4.2**. Public facilities in Belgium reported to struggle with stringent national provisions for the HE, whereas UK facilities indicated to manufacture under an alternative exemption pathway (Specials scheme).[32] In addition, facilities indicated that financial resources for high cost ATMP manufacturing are generally limited.

General regulatory trends

The cumulative findings of chapters **2.1**, **3.1**, and **3.2** are illustrative of a convergence across regions towards regulatory flexibility for GCT marketing authorization, which is facilitated by legislative changes that enable to deviate from standard requirements for pharmaceuticals. Due to unmet medical needs and added clinical benefits, but also limited experience with new GCT technologies, and their unknown long-term effects, authorities

appear to move towards a regulatory approach for marketing authorization that is based on less comprehensive data and to resolve knowledge gaps on risks and uncertainties during the post-marketing phase. The substantial use of facilitated regulatory pathways and GCT authorization based on non-confirmatory evidence, within the context of unmet medical needs and/or added clinical benefit, which is combined with a relatively large emphasis on post-marketing monitoring and collection of confirmatory evidence, is in strong synergy with the regulatory model of an adaptive approach to licensing or a life cycle approach.[25,33] An adaptive approach to licensing entails early access while quality, efficacy and safety uncertainties may be unresolved at authorization, which are mitigated with post-marketing data collection and risk management.[25,34] In Japan, GCT regulations even represent a legislative model of an adaptive approach to licensing. The conditional authorization is time-limited, and the collection of confirmatory evidentiary support for a positive benefit/safety balance after authorization is mandatory in order to perform secondary regulatory assessments.[3,4,8,26]

In new fields for medical innovation, regulatory authorities are caught between hopes and uncertainties for new medical breakthrough that could revolutionize patient care.[35] They are constantly faced with the dilemma how to reconcile the need for potentially life-saving medicinal products while ensuring patient safety, under conditions of uncertainty, when they decide for medicinal product authorization.[36] On one hand, regulators may decide to grant early approval with uncertainty to products with promising clinical outcomes to ensure that patients can benefit, in particular for those that suffer from severe of life-threatening diseases. On the other hand, decisions that are based on less than comprehensive data may lead to patient exposure to harmful effects, and result in product withdrawals, restrictions, or warnings. Yet, when regulatory authorities are overly stringent, innovation and public health could be impaired.[36] Our findings indicate that regulatory authorities are searching for justified flexibility from institutionalized, stringent requirements for medicinal product authorization, and are attempting to find the delicate balance between the protection of public health, and the facilitation of GCT development.

With respect to the HE, the tension between the need for potentially life-saving treatment and the need for benefit/risk data is even greater in comparison to regulations for GCT marketing authorization. Lenient national provisions could put patients at risk,[37] and quality controlled manufacturing could be at stake due to the production of a few batches only.[18] Chapter **2.2** showed that national provisions safeguard GMP manufacturing. Yet, there is variation in the evidentiary support for benefits and risks that

is required to obtain a HE license among EU countries. Some authorities choose to implement additional provisions in order to perform preliminary benefit/risk assessments based on the available clinical data, whereas other authorities regulate based on the basic provisions of Article 28. ATMP manufacturing under the HE typically occurred for patients without further treatment options and poor prognosis (Chapter **4.2**). Consequently, decision-making on whether risks and uncertainties of a treatment are acceptable in this context are based on the clinical expertise, and responsibility, of health care professionals. However, regulatory authorities have a gatekeeping role to protect patients and society from unacceptable risks.[19,37] Furthermore, treatment may not always have benefits for patients, who need to be protected from malicious practices.[38] In comparison to the centralized authorization procedure, more comprehensive or confirmatory evidence of a benefit/risk balance is not required under the HE in all selected countries. Therefore, it seems justified to demand some level of evidentiary support for benefits and risks in order to protect public health and guarantee patient safety, in particular when the HE is used to manufacture ATMPs that were available in point-of-care settings or regulated as human cells and tissue before the ATMP Regulation was implemented.

With regard to pharmaceutical quality, there appears to be a trend towards process control, instead of product control, to deal with the peculiarities of GCT characteristics. Chapter **3.2** underlined that pharmaceutical quality is problematic for GCT development in the EU. Major objections during regulatory assessment related to pharmaceutical quality were noted in all EU assessment procedures, including authorized and non-authorized GCTs. However, how regulatory authorities enable flexibility for GCT manufacturing and quality differs among regions. In Chapter **2.1** we showed that Japanese legislation includes good manufacturing standards that are specific for GCTs (Good, gene, Cellular and Tissue-based product manufacturing – GCTP).[5] This legislative change is unique in comparison to other jurisdictions. An important distinction between GMP and GCTP is a shift towards process control, instead of product control through release specifications.[11] Chapter **3.1** underlined quality flexibility for authorization in Japan. For instance, authorization was granted while in-process specifications remained to be verified on cumulative data, enabled by the new Japanese GCT legislation.[4,5] Furthermore, quality requirements incrementally increase during clinical development in Japan and the US, whereas EU developers need to be GMP compliant from early clinical trials onwards.[11] Thus, EU GMP requirements appear more stringent in comparison with other regions. Yet, there are indications of flexibility with respect to pharmaceutical

quality in the EU as well. For instance, quality issues were acceptable for the authorization of Glybera (Table 1), which was authorized after a long and extensive assessment procedure.[39] It is expected that the revised GMP guideline for ATMPs[40] that came into force in 2018 in the EU will enable some regulatory flexibility for pharmaceutical quality, which could mitigate major pharmaceutical quality objections as shown in Chapter **3.2** for future assessments. The new EU guideline for early ATMP clinical trial development[41] could provide some quality flexibilities in earlier phases of clinical development. Moving towards process control suits fields that are heterogenous and in which outputs are difficult to establish and monitor,[42] yet, within the context of the GCT field it urges for continuous monitoring of pharmaceutical quality.

A shift towards early access and an adaptive approach for licensing, and process control for pharmaceutical quality, calls for enhanced post-marketing data collection and risk management. Japanese authorities implemented enhanced post-marketing risk management as part of their GCT conditional approval pathway,[5,26] which includes mandatory collection of confirmatory clinical data[11] and legislative power to revoke conditional authorizations in case the collected clinical data is unsatisfactory.[4] The findings of Chapter **3.1** show that decision-making for authorization is embedded within these legislative measures in Japan. In Japan, and also in the EU, a substantial amount of post-marketing study obligations were part of regulatory risk management strategies, in particular in combination with facilitated regulatory pathways. Yet, substantially less obligations for post-marketing data collection were imposed in the US compared to the EU and Japan, including GCTs for which scientific uncertainties were unresolved at the point of marketing authorization. Thus, there is less focus on a life cycle approach in the US, which undermines to learn from post-marketing clinical experience with GCTs and to develop knowledge on long-term benefits. Thus, using an adaptive regulatory approach for systems therapeutics such as GCTs fits well with scientific uncertainties and unknown long-term effects, but urges for continuous regulatory monitoring and evaluation of clinical outcomes.[10]

Chapter **2.1** showed that regulatory authorities around the world chose to regulate a wide variety of different GCT subtypes as medicinal products, including therapies with historical use in clinical practice.[43] Regulators hereby reduce risks for patients and restrict experimenting to regulated environments, but may limit availability and affordability of GCTs in clinical practice as a result of stringent medicinal product regulation.[18,44] As a solution, regulatory authorities implemented regulatory pathways that

exempt GCTs from the authorization process altogether. Chapter **4.2** showed that the HE has been used to manufacture ATMPs with close proximity to clinical practice by public facilities. However, the HE has also been used as a national authorization for ATMP manufacturing by companies. These findings raise questions to which extent the HE and the centralized procedure for marketing authorization overlap, or whether they are complementary. Moreover, it is important to consider what their respective roles should be to stimulate GCT development and availability in the future, assuming that the GCT field will mature over time.

Implications of regulatory change for GCT development and availability

Regulatory change for GCT marketing authorization

The regulatory changes for GCT marketing authorization in the EU, Japan, and US indicate a political mandate to mitigate well-established development challenges.[2,6,7,9,10,35] Like in other fields of medical innovation, authorities are under pressure to find an appropriate balance between the need for rapid access and need to ensure comprehensive data on benefits and risks when deciding on GCT marketing authorization.[36] The illustrated shift towards justified flexibility for GCT marketing authorization, using an adaptive or life-cycle approach for licensing under facilitative regulatory pathways, facilitated early GCT market entry globally. At time of writing (September 2019), most marketing authorizations were granted in the EU (14), followed by nine authorizations in the US,[b] and seven in Japan since the first authorizations in 2009 (Table 1). Although it is challenging to directly link legislative changes to more successful GCT marketing authorization, the number of authorizations in the EU, Japan, and US increased substantially over the last few years. In total, 22 out of 30 authorizations in the EU, Japan, and US were granted since 2015 (Table 1). Future generations of GCTs are likely to be regulated and marketed with an adaptive approach to licensing, using facilitated regulatory pathways, which is driven by unmet medical need, indications of added clinical benefits, and scientific uncertainties.

The overall trend of convergence towards justified flexibility for GCT marketing authorization compared to pharmaceuticals, coincides with a trend of regulatory diversification when looking closer to the specific

b There are more cell therapies in the US that were authorized as a biologic medicine (due to a wider definition of GCTs that require authorization compared to other regions). These are minimally manipulated cord blood products for allogeneic stem cell therapy purposes (Chapter **2.1**).

Table 1: Overview of authorized GCTs in the European Union, Japan, and United States

Juris-diction	Product	Year of approval	Approval pathway	Product description	Indication[a]	Orphan drug
EU	Chondro-Celect	2009	Standard	Autologous cartilage cells	Cartilage defects of the knee	N
	Glybera	2012	Approval under exceptional circumstances	Adeno-associated viral vector for gene delivery	Familial lipoprotein lipase deficiency	Y
	MACI	2013	Standard	Matrix applied characterized autologous cultured chondrocytes	Cartilage defects of the knee	N
	Provenge	2013	Standard	Autologous peripheral blood mononuclear cells	Prostate cancer	N
	Imlygic	2015	Standard	Genetically modified oncolytic viral therapy	Melanoma	N
	Holoclar	2015	Conditional	Autologous human corneal epithelial cells containing stem cells	Corneal lesions	Y
	Strimvelis	2016	Standard	Autologous CD34+ transduced cells with retroviral vector	Adenosine deaminase deficiency (ADA-SCID)	Y
	Zalmoxis	2016	Conditional	Allogeneic T cells genetically modified with retroviral vector	Adjunctive treatment in haploidentical hematopoietic stem cell transplantation of adult patients with high-risk hematological malignancies	Y
	Spherox	2017	Standard	Spheroids of human autologous matrix-associated chondrocytes	Cartilage defects of the knee	N
	Alofisel	2018	Standard	Allogeneic mesenchymal stem cells	Complex perianal fistula(s) in adult patients with Crohn’s disease	Y
	Kymriah	2018	PRIME	Genetically modified autologous T cell immunotherapy	Pediatric B cell acute lymphoblastic leukemia (ALL); Relapsed or refractory diffuse large B cell lymphoma	Y
	Yescarta	2018	PRIME	Genetically modified autologous T cell immunotherapy	Relapsed or refractory large B cell lymphoma	Y
	Luxturna	2018	PRIME	Adeno-associated viral vector for gene delivery	Biallelic RPE65 mutation-associated retinal dystrophy	Y
	Zynteglo	2019	PRIME	Autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene	Patients with transfusion dependent TDT without β0 /β0 genotype, in need of HSC transplantation	Y

JP	JACC	2012	Medical device[b]	Autologous cultured chondrocytes and collagen gel	Cartilage defects or osteochondritis dissecans of the knee	N
	Temcell	2015	Standard	Allogeneic bone marrow-derived mesenchymal stem cells	Graft versus Host Disease	Y
	Heartsheet	2015	Conditional	Autologous skeletal myoblast-derived cell sheet	Severe heart failure (ischemic heart disease)	N
	JACE	2016	Standard[c]	Autologous human epidermal cell sheet	Severe burns; Giant congenital melanocytic nevi	Y
	Stemirac	2019	Conditional	Autologous bone marrow-derived mesenchymal stem cells	Spinal cord injury and ASIA impairment	N
	Kymriah	2019	Standard	Genetically modified autologous T cell immunotherapy	B cell acute lymphoblastic leukemia (ALL); Relapsed or refractory diffuse large B cell lymphoma	Y
	Collategene	2019	Standard	Plasmid vector encoding human hepatocyte growth factor	Ulcers in patients with chronic arterial occlusion (arteriosclerosis obliterans and Burger's disease)	N
US	Provenge	2010	Fast track	Autologous peripheral blood mononuclear cells	Prostate cancer	N
	Laviv	2011	Standard	Autologous cultured fibroblasts	Moderate to severe nasolabial fold wrinkles	N
	Gintuit	2012	Standard	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen	Mucogingival conditions	N
	Imlygic	2015	Fast track	Genetically modified oncolytic viral therapy	Lesions in patients with melanoma	Y
	MACI	2016	Standard	Autologous cultured chondrocytes on a porcine collagen membrane	Cartilage defects of the knee	N
	Kymriah	2017	BTD	Genetically modified autologous T cell immunotherapy	Pediatric B cell precursor acute lymphoblastic leukemia (ALL)	Y
	Yescarta	2017	BTD	Genetically modified autologous T cell immunotherapy	Relapsed or refractory large B cell lymphoma	Y
	Luxturna	2017	BTD	Adeno-associated viral vector for gene delivery	Biallelic RPE65 mutation-associated retinal dystrophy	Y
	Zolgensma	2019	Fast track & BTD	Adeno-associated viral vector for gene delivery	Pediatric spinal muscular aptrophy	Y

EU=European Union, JP=Japan, US=United States, BTD = Breakthrough Therapy Designation, Y = yes, N = no, a = abbreviated according to authorized label, b = authorized under medical device regulations, c = initially authorized as medical device, authorized under GCT legislation in 2016. NB: Table lists marketing authorizations in September 2019.

requirements and processes among jurisdictions.[45] The legislative level of stringency versus flexibility for marketing authorization, as well as the interpretation of clinical evidentiary support in benefit/risk assessments, differs between jurisdictions. The required level of evidentiary support is largely dependent on the criteria to enter facilitated regulatory pathways, and the requirements for marketing authorization under these pathways.[46,47]

The emergence of jurisdiction specific regulatory strategies for GCT marketing authorization complicates the global regulatory landscape. This is not surprising as most GCT clinical trials are still undertaken locally by academic hospitals and small and medium-sized enterprises,[48,49] which likely have regional regulatory and marketing strategies. This is supported by the fact that most authorized GCTs are exclusively marketed in one jurisdiction (Table 1). As a result, regulatory experience and capabilities are shaped by geographically fragmented scientific and technological expertise and knowledge of developers.[48] Region specific requirements that are laid down in guidance documents, as well as decisions that are made in scientific advice meetings, could become increasingly diverse between jurisdictions. Synergy between activities and regulations typically benefits local opportunities for development,[50] which is supported with observations of large early stage clinical pipelines and promising clinical trial results.[49,51] This approach currently suits the GCT field because of the novelty of the field, as it allows for experiential learning. However, an increasingly global diverse regulatory landscape, in particular for manufacturing and quality requirements, may impose serious hurdles for the field to mature to more late stage developments in the future, global development programs, and widespread availability in multiple jurisdictions.

The jurisdiction specific regulatory strategies for GCT marketing authorization may skew development efforts and subsequent availability of marketed GCTs to particular regions. For instance, the relatively low requirements for conditional GCT approval in Japan may facilitate regional product development and attract foreign developers more compared to other regions.[47] Furthermore, the illustrated diverse regulatory requirements and considerations for marketing authorization, ranging from manufacturing standards to clinical outcomes, complicate the conduct of multinational clinical trials and global marketing strategies.[50] However, some GCTs are not suited for global marketing strategy, which urges for alternative solutions to ensure more widespread availability to potentially life-saving treatments.

GCTs are regulated on a case-by-case basis despite diverse high-level regulatory changes for marketing authorization. The illustrated scientific uncertainties that were discussed in regulatory assessment procedures for marketing authorization underline an overall challenge for regulatory standardization on technology and product level, as a result of the relatively limited clinical experience and heterogeneity of different GCT technologies. Authorities mitigate regulatory unclarities to some extent by providing regulatory guidance documents. Early interaction between developers and regulatory authorities is another way of mitigating regulatory hurdles in later stages of development, or even the risk of non-authorization.[52] Many facilitated regulatory pathways for marketing authorization include enhanced regulatory support.[46,53,54] More regulatory support through interactions likely puts pressure on regulatory authorities and scientific advice services. However, regulating GCTs in practice through guidance documents and interactions conduces flexibility and trial-and-error learning most, which suits novel fields and technologies. It is vital to maintain a flexible approach to facilitate development opportunities for novel GCT technologies. However, for those GCT technologies for which technological know-how in relation to manufacturing and quality has been gained and clinical outcomes appear promising, more regulatory clarity could catalyse development efforts and lead to more mature stages of product development.

Diverse manufacturing and quality requirements and the trend towards process control instead of product control by various regulatory authorities, undermines to scale up local manufacturing to manufacturing that spreads across several jurisdictions and continents. Small changes of the conditions of the manufacturing process and quality control, which may be a result of jurisdiction specific regulations for manufacturing and quality (e.g. regulations for starting material, excipients, product characterization, batch release control), may alter key product characteristics that relate to the mode of action. Yet, product comparability among sites is stringently regulated. For example, product comparability issues between the US and EU manufacturing site for Provenge (Table 1) were evident when the license holder filed for marketing authorization in the EU (Chapter **3.2**). Furthermore, limited product characterization and control may also undermine the value of a GCT as a commercial medicinal product, because of uncertain clinical outcomes and intellectual property (IP) protection.[55]

As regulatory standardization of detailed requirements for manufacturing, clinical development and marketing authorization is currently complicated, we argued that a strong collective knowledge base and information synthesis

is needed for GCT technological advance,[56] in particular because of the large proportion of local clinical activities.[48,49] Consistent with EU wide trial characteristics, our cohort of GCT clinical trials contained a large proportion of academically sponsored, single-centered national trials. Indications of more scientific publication by public sponsors compared to private sponsors underlined their important role in the field, and their role to build up the collective GCT knowledge base.[48] However, publication rates in scientific literature (27%) and conference abstracts (17%) were suboptimal (median follow up 1050 days), and technological know-how was underreported in scientific literature compared to clinical outcomes (Chapter **4.1**). These findings indicate that is a pressing need to improve publication rates and dissemination of trial result via other channels to stimulate knowledge transfer and learning for GCT development.[17]

Regulatory change through exemption pathways

Not all GCTs that are administered to humans may be intended for commercial development. The original intent of the European Commission (EC) to include an exemption structure in the draft proposal of the ATMP Regulation was to accommodate those ATMPs that are not industrially prepared and not intended for the market, and to avoid unnecessary regulatory burden for certain hospital activities, such as research and production of tailored made, in-house treatment. For ATMPs prepared “in full and used in a hospital, in accordance with a medical prescription for an individual patient”, the ATMP Regulation with its regulations for commercial medicinal product development would not be applicable.[57] Critically, it reveals that the HE was intended to facilitate local availability of ATMPs in clinical practice, instead of EU wide availability of commercially developed and authorized ATMPs.

Judged on the number of HE license holders (Chapter **2.2**) and ATMP manufacturing under the HE in clinical practice (Chapter **4.2**), we showed that the HE licenses were granted to in-house ATMP manufacturing activities in hospitals in France, Italy, and the Netherlands, and to some extent in Finland and the United Kingdom (UK). In these countries, ATMP manufacturing under the HE by public facilities enabled availability of ATMPs with close proximity to clinical practice. No HE licenses had been granted in Austria, Belgium, and Spain since 2009 until the time of investigation (June-October 2018). We also found that private ATMP manufacturing facilities hold HE licenses in Germany and the Netherlands (Chapter **2.2**, **4.2**).

The national provisions in Chapter **2.2** illustrate a diversification of national provisions for the HE within the EU, which has been a point of critique.[19] Harmonization of national provisions for the HE could provide more regulatory clarity and reduce variety as to how it is used among countries in the EU.[58,59] However, harmonization across several regions is naturally less aligned with local activities and opportunities.[50] The variety of national provisions of the HE and utilization in clinical practice underline differences in political choices and differences between ATMP developers (ratio public/private, and product expertise) among countries in the EU. This underlines a need for national approaches for the HE, which need to be aligned with national health care systems to enable HE utilization and ATMP availability in clinical practice. The observation that the HE was used to manufacture ATMPs with close proximity to clinical practice is in line with the original purpose for the HE of the EC. However, the regulatory diversification for the HE, as a result of the ambiguous terminology of Article 28, also limited utilization and availability in some countries, or utilization of the HE pathway for commercial purposes.

In Chapter **2.2**, we showed that in some selected EU countries the HE was not used due to limited capacities to comply with national provisions. Some public facilities reported to struggle in countries with more stringent provisions, which indicates a limited institutional readiness to switch from point-of-care settings, or from national human cells and tissue regulations, to principles of medicinal product regulation and EBM.[60–62] Furthermore, Chapter **4.2** showed indications of limited financial resources to manufacture under the HE, which often needed to be financed from hospital budgets. Similar to marketed ATMPs,[55,60,63,64] financial resources are an additional hurdle for availability in clinical practice for ATMPs manufactured under the HE. Without feasible national provisions and financial support, availability of ATMPs with close proximity to clinical practice may be impaired,[18,44] or disappear in the future.

It has been argued extensively that the HE could provide a competitive advantage and undermine commercial ATMP development as medicinal products, if used inappropriately.[19,37,58,65,66] Yet, the cumulative findings of Chapters **2.2** and **4.2** indicated that the tension between manufacturing under the HE by public facilities and commercial ATMP development and other marketed pharmaceuticals is currently rather limited. The pathways are rather complementary than overlapping. Manufacturing under the HE by public facilities facilitated availability to ATMPs with close proximity to clinical practice. Furthermore, competent authorities prohibit to use

the HE when alternative marketed medicinal products (including ATMPs) are available for treatment, or restrict eligible HE license holders to public facilities. Furthermore, Chapter **4.2** showed that 12 ATMPs were manufactured under the HE, and many were manufactured on a similar scale as early clinical trials. Thus, the scale of ATMP manufacturing under the HE by public facilities was modest in comparison with the vast number of clinical trials that are conducted by EU academic centers.[49] In addition, there is overlap between some publicly manufactured ATMPs under the HE and marketed ATMPs for the therapeutic areas immunological diseases and hematologic oncology, but the exact indications differ.[67] However, without restrictive provisions the tension between HE manufacturing by public facilities and commercial development may change over time as scientific and technological advance progresses, and more public facilities are able to adopt ATMPs in clinical practice.

In contrast, the combination of national provisions and ATMP developer landscape in Germany represent a unique situation. The HE can be used as a stepping stone towards centralized authorization in Germany, and HE manufacturing is not restricted when alternative marketed medicinal products are available. This facilitates national market entry of ATMPs under the HE 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 in Germany provide a competitive advantage to developers located in Germany, compared to developers in other EU countries. ATMP market withdrawals have occurred in the past, and are illustrative of pricing and reimbursement issues in the EU.[55,60] 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 Germany short-term, it is undesirable to manufacture ATMPs for the national German market under the HE. Furthermore, it conflicts with the intended purpose of the EC to regulate ATMP manufacturing within clinical practice that is not intended for the market.

The way forward

Throughout this thesis we demonstrated substantial regulatory efforts to accommodate GCT as medicinal products. We showed that regulatory authorities are searching for the delicate balance between the need for rapid access and need to ensure comprehensive data on benefits and risks, in order to stimulate public health and innovation, while ensuring patient safety. Currently, the first wave of GCT marketing authorizations (Table

1) and large clinical pipelines and promising clinical outcomes[49,51] raise expectations of improved health care. However, to truly impact health care the GCT field needs to mature. Clinical developments efforts need to be optimized to facilitate marketing authorizations in the future, and more downstream issues need to be tackled to enable more widespread availability of breakthrough therapies. Below we describe perspectives on the way forward, together with suggestions for future studies within regulatory sciences to improve scientific and technological information synthesis and to continuously monitor regulatory impact on public health and patient safety, and within innovation sciences to evaluate the role and impact of regulatory and non-regulatory aspects on GCT innovation.

For a large part, GCT clinical development efforts are currently geographically fragmented, and even confined to individual academic hospitals.[49] It is reported that GCTs often get stuck in early clinical development, and are not developed further through late clinical development. Regardless of the clinical outcomes, there appears to be a gap between early and late clinical phases that is creating a valley of death for GCT clinical development.[55] Public developers, mainly academic centers, are one of the main drivers of GCT innovation. Academic centers have strengths for early clinical development, such as expertise pathophysiological and clinical knowledge and access to human derived materials.[48] However, they often do not have the capacities and resources to complete marketing trajectories, and often rely on industry to complete late clinical development and gain market entry.[48,55] This depends on public-private engagements, and can be achieved through transfer to industry, public-private partnerships, or spin-outs that are later acquired for example.[68–71] For instance, the development of Strimvelis serves as an example of a successful partnership with industry that resulted in marketing authorization of a GCT that originated from an academic center.[72] However, failures to transfer or engage with industry are attributed to a poor understanding of modes of action and poorly defined product characteristics.[55] For example, the latter implies that early clinical trials would need to be conducted again with optimized products. If pubic developers prefer to continue late development in-house, they need to attract financial capital to conduct late stage clinical development within a competitive R&D environment.[69] The designing of products for marketing authorization goals, including target product profiles, regulatory experience, and financial resources need to improve to transfer ATMPs successfully from a pre-competitive environment to a competitive environment.[48]

An optimized pre-competitive R&D environment would increase efficiency of clinical development efforts. Therefore, the field would benefit from a strong collective knowledge base of ongoing, rapidly evolving scientific and technological advances and methods for clinical development, manufacturing processes, and quality control, similar to previous experiences in biotechnology.[56] The scientific issues that were raised during assessments procedures for marketing authorization in the EU are demonstrative of the scientific challenges that developers face, in particular for pharmaceutical quality and clinical trial design.[13] Yet, some of these scientific issues could have been prevented. Therefore, it is vital that developers who wish to obtain marketing authorization interact with regulatory authorities in scientific meetings in early development stages to determine satisfactory manufacturing processes, quality control, and clinical trial design.[52] Careful development of in-process and release specifications, from early clinical phases onwards, prevents incomparability between clinical trial and commercial product specifications and other quality issues. Considerations early on for later phases of development, in relation to both quality and clinical trial design, mitigate the risk of market rejection or withdrawal. However, as scientific advice services may become increasingly overburdened, other means of knowledge development, knowledge dissemination, and information synthesis are critical to stimulate development considering the geographical fragmentation of GCT early developments.[49,73]

Regulatory authorities can contribute to a strong collective knowledge base. For instance, discussed issues and decisions that are made in scientific advice meetings could serve as guidance for future developments, or feed into a research agenda to investigate how particular scientific issues could be resolved.[55] For instance, previous experience with trial design, clinical or surrogate endpoints, and quality control assays could serve as an example for other developers, because many GCTs are entering new areas for which validated methods are lacking. Furthermore, platforms for knowledge dissemination and learning among academia, developers and regulators can optimize scientific progress with regulatory requirements.[74] One example of such a platform is the framework of collaboration between the European Medicines Agency and academia. In order to facilitate global developments, platforms for knowledge sharing and collaboration among regulatory authorities is needed to find consensus for GCT standards and requirements, in particular for manufacturing and quality standards.[55]

It was described earlier that global regulatory diversification can impose hurdles for the GCT field to mature, because they might hinder widespread availability. More downstream hurdles for widespread availability of GCTs

relate to distribution along the supply chain, scaling up of manufacturing, and reimbursement.[55] Many GCTs are very susceptible to damage during distribution, in particular for fresh cellular products with very limited shelf lives, such as Holoclar (Table 1). Centers of excellence are one way of solving manufacturing and distribution issues, and seem a suitable solution for GCTs that are manufactured on a relatively small scale, including GCTs that target rare diseases or conditions such as Strimvelis.[72] However, for other cellular products that would require a larger scale of manufacturing due to a larger patient population such as Kymriah (Table 1),[75] de-centralized manufacturing at multiple sites seems the only way how distribution between sites and scaling up issues can be mitigated. Yet, manufacturing needs to adhere to diverse manufacturing standards among regions, while product comparability among sites is stringently regulated. Therefore, it is important to promote standardized manufacturing processes and quality control methods for GCT technologies that reached more advanced levels of development.

More guidance and regulatory clarity would optimize and align methods for clinical development, and facilitate more widespread availability of breakthrough therapies that reached more mature phases of development, such as chimeric antigen receptor T cell therapies.[76] Other GCTs, most prominently *in-vivo*, vector based, gene therapies, are better suited for global distribution because these can be cryopreserved. GCTs that are suited for global distribution would benefit from regulatory standardization on a global level, for instance for potency assays for transgene activity and methods to test risks of replication-competent vectors.[12] However, globally diverse regulations for genetically modified organisms currently lead to clinical development delays of *in-vivo* gene therapies and genetically modified cell therapies.[77] Procedures to streamline dossier submission and parallel scientific advice meetings, in which developers can interact with multiple regulatory authorities simultaneously to determine regulatory criteria for global registration strategies, need to be further strengthened.[78] However, whether global development combined with parallel scientific advice is indeed the way forward needs to be evaluated over time. GCT regulations and regulatory decision-making among jurisdictions needs to be continuously monitored, and impact assessments of parallel scientific advices are needed to determine the effects on the course of innovation within the GCT field.

GCT technologies demand increased attention to continued monitoring throughout their life cycle to safeguard public health. The demonstrated trend towards early access and accepting uncertainties and safety risks for

GCT marketing authorization puts pressure on the traditional gatekeeper role of regulatory authorities to protect public health, which warrants attention to long-term post-marketing surveillance and enforcement measures. Furthermore, long-term safety and efficacy is highly uncertain.[79–81] The success of the Japanese GCT legislation, and other regulatory changes for GCTs, may even depend on how post-marketing surveillance and enforcement measures are implemented in practice. A substantial part of data collection is shifted to the post-marketing phase, yet, previous work indicates that post-marketing study obligations may not always be completed or delayed, which hinder proper re-assessments.[82] To which extent marketing authorizations are revoked based on post-marketing experience, in particular when preliminary efficacy outcomes are not confirmed, is unclear for GCTs. Public registries could facilitate a continuous monitoring, or to re-evaluate, benefit/risk balances. Stakeholder are exploring whether existing registries such as the European Society for Blood and Marrow Transplantation registry are fit for several purposes, including to evaluate clinical outcomes.[83] However, it needs to be explored whether new registries are needed that are tailored to the specifics of subfields or regions. Continuous monitoring of uncertainties and safety risks, and whether they are resolved or that new concerns arise over time, could also be evaluated using risk management plans in the EU for instance.[84] In addition, for GCTs that are manufactured under exemption pathways there are no regulations for long-term surveillance and data collection, except pharmacovigilance procedures. Continuous long-term surveillance and data collection is needed to evaluate the impact on public health by conducting observational studies, for both marketed and exemption GCTs. Lastly, we focused on regulatory change for GCTs that are centrally governed as medicinal products. GCT human administration that occurs in a point-of-care setting represents a knowledge gap with respect to GCT clinical activities, parallel to exemption and clinical trial pathways. Research is needed to investigate the extent of GCT administration in point-of-care settings, and the implications for public health and patient safety, which would require to collect data from medical centers, similar to the methods used in Chapter **4.2**.

Furthermore, other processes than regulatory change and guidance influence the course of GCT innovation, such as knowledge development and dissemination by developers, market formation, and financial and human capital.[85] In Chapter **4.1**, we showed that knowledge dissemination through scientific publication and presentations at conferences by developers is suboptimal in the GCT field. Future research is needed to evaluate whether publication rates remain suboptimal over extended periods of time, by conducting large

clinical trial cohort studies with long follow up periods. However, there are other means for knowledge dissemination by developers, including platforms to pool clinical data, clinical trial registries, and central coordinating bodies that facilitate a collective knowledge base. Publication of trial results in registries was found for only two included trials in Chapter **4.1**, and information on trial progression was often lacking. This indicates that trial progress and result reporting is not standard practice, and urges for enforcement measures to improve transparency on GCT trial conduct. Furthermore, there are central coordinating bodies that provide support to developers to tackle challenges ranging from manufacturing to assessments of commercial value, such as the UK Cell Therapy Catapult and the Canadian Centre for Commercialization of Regenerative Medicine.[86] These central coordinating bodies can strengthen collective technological know-how for instance, and facilitate pre-competitive collaboration.[87] In addition, public developers may have technology transfer offices that can mediate transfers or partnerships, but to knowledge, platforms to facilitate interaction between public and private developers do not exist. In Korea, grants for GCT development mandate public-private collaboration, which is judged on the number of marketing authorizations quite successful.[11] How knowledge dissemination and collaborative efforts can be optimized requires studies that transcend regulatory change for GCTs, and evaluate the entire GCT innovation system.[85]

The heterogeneity of the GCTs 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.[10] Orphan drug designation (ODD) is a regulatory tool to stimulate market formation for medicinal products that target very small patient populations. However, not all GCTs that target rare diseases are suited for ODD,[88] or they have low commercial value due to limited IP options for example, and have a high risk profile for development.[48,88] Thus, some may be better regulated within clinical practice settings under exemption structures, such as the Hospital Exemption. Other GCTs with commercial value are better suited to be transferred to competitive environments in order to facilitate market entry.[48,74] 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.[86] More consideration of commercial aspects in early development could facilitate an optimized use of exemption pathways versus pathways for commercial development in a complementary fashion, and inform business opportunities and facilitate market access planning.[89] However, criteria to determine

commercial values are likely to be a moving target because of scientific and technological advance, and require a continuous, open, multi-stakeholder dialogue.

The implementation of the ATMP Regulation in the EU had regulatory consequences for therapies with close proximity to clinical practice. Chapters **2.2** and **4.2** showed that the HE can be a useful regulatory tool to facilitate ATMP availability in clinical practice under controlled circumstances. However, the feasibility to comply with stringent provisions is limited in some countries, whereas in other countries more flexible provisions enable manufacturing for the national market under the HE. For future HE transpositions and implementations, it is recommended that competent authorities carefully consider and provide clarity for which kind of activities the HE should be used, and which provisions facilitate appropriate use in clinical practice without putting public health and commercial GCT development at risk. Furthermore, a EU-wide public registry for HE manufacturing is recommended to facilitate knowledge dissemination and collaboration among manufacturing facilities, to monitor clinical outcomes, and to facilitate future regulatory impact assessments of the HE.

General conclusion

Numerous regulatory changes for GCTs have been implemented globally in order to stimulate public health and innovation, while ensuring patient safety. For marketing authorization, regulatory change entails a shift to early market access and enhanced post-marketing surveillance and data collection. For clinical practice, regulatory change entails the implementation of exemption pathways such as the Hospital Exemption. To move forward, the GCT field is in dire need of more centralized knowledge dissemination, information synthesis and collaborative efforts. More transparency on clinical trials and activities in clinical practice, and on clinical outcomes, would facilitate coordination and collaboration in pre-competitive environments, public-private engagements, inform business opportunities, and facilitate market access planning. This would not only benefit the fate of individual GCTs, but also stimulate an optimized use of commercial development pathways and exemption pathways in a complementary fashion, which ultimately benefits patients on a regional and global level.

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CHAPTER 6:
SUMMARIES

Chapter 6.1: Summary

Gene and cell-based therapies (GCTs) have the potential to revolutionize health care. In comparison to pharmaceuticals (i.e. small molecules and biological medicinal products) they have different modes of action and could provide treatment for therapeutic areas in which current treatment is lacking, or is unsatisfactory. For instance, genetically modified T cell products recently reached the market, which were shown to have remarkable clinical benefits for patients with relapsed or refractory B cell malignancies. However, there are also concerns about the implementation of GCTs into regulatory systems for medicinal products. The characteristics of GCTs do not fit well with regulations for pharmaceuticals because they are based on different starting material (i.e. cellular source material or vectors for gene delivery), they interact with the human body through highly complex modes of action, and function by targeting molecular defects that underlie disease that can be specific for subgroups or even individual patients. Furthermore, the innovation context of GCTs is different from pharmaceutical development. Early GCT developments largely take place in academic hospitals; many GCTs have been historically used in clinical practice as human cells and tissue, and learning in clinical practice plays a relatively large role compared to pharmaceutical development. These differences impose a wide array of questions as to how to implement regulatory change for GCTs, in such a way that it promotes public health, facilitates innovation, and ensures patient safety.

This thesis aims to investigate regulatory change to accommodate GCTs for human administration as medicinal products, regulatory decision-making under the current frameworks, and the implications of regulatory change for GCT development and their availability in clinical practice.

We investigated regulatory change, specifically implemented for GCTs, in Chapter **2**. We showed that policy makers used two strategies to change regulations for GCTs; to stretch the boundaries of existing regulations for medicinal products, or designing and implementing new GCT regulations that are separate from existing systems (i.e. exemption pathways). In Chapter **2.1**, we provide a comparative analysis of regulatory requirements for GCT marketing authorization in Canada, European Union (EU), Japan, Korea and United States (US). Results indicated that jurisdictions differ in 1) GCT subtypes that require authorization including the possibilities to use GCTs in clinical practice under exemption pathways, 2) whether authorization is regulated under GCT specific legal provisions (EU, Japan) or legislation for biologics (Canada, US, Korea), and 3) the degree of flexibility in interpreting safety, efficacy and quality requirements and good practice standards. In conclusion, authorities are searching for

regulatory flexibility from standard requirements to facilitate early access and to stimulate innovation in the GCT field, while safeguarding patient safety. The observed regulatory variability appears to be a natural outcome of GCTs' emergence within local clinical governance systems, yet they are illustrative of a global diversification of GCT regulations.

In Chapter **2.2**, we investigated regulatory change for GCTs through the implementation of an exemption pathway in the EU, which is known as the Hospital Exemption (HE). The HE is stipulated in Article 28 of the Advanced Therapy Medicinal Product (ATMP) Regulation, and is aimed to accommodate manufacturing of custom-made ATMPs for treatment purposes on a non-routine basis. We documented the implementation process in multiple EU countries (Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Spain, and United Kingdom (UK)), and associated differences in this process with two outcomes; national regulatory provisions, and the amount of HE license holders. National provisions vary substantially due to discretionary interpretation of Article 28 by the competent authorities. In some countries, additional provisions such as clinical data requirements or restrictions on the use of the HE were implemented. Judged by the amount of HE license holders, manufacturing of ATMPs in clinical practice is facilitated by the HE in four countries. 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. In contrast, ATMP manufacturing by companies is facilitated by the HE in two countries. These results are illustrative of a regulatory diversification for the HE throughout the EU.

In Chapter **3,** we investigated decision-making for marketing authorization of GCTs**.** In Chapter **3.1**, we examined differences in decision-making for GCT authorization among the US, EU, and Japan. A cohort of 18 assessment procedures for authorized GCTs shows that product characteristics of authorized GCTs were very heterogeneous, only three products were marketed in multiple jurisdictions, and almost half of all authorized GCTs were designated as an orphan drug. Confirmatory evidence or indications of clinical benefit were evident in US and EU applications, whereas in Japan authorization was solely granted based on non-confirmatory evidence. Due to scientific uncertainties and safety risks, substantial post-marketing study obligations were requested in the EU and Japan. EU and Japanese authorities often took unmet medical needs into consideration in decision-making for authorization. In the US, two more recent assessments of CAR-T cell products were suggestive of a trend towards a more permissive approach

for GCT authorization, in contrast to a more binary decision-making approach for previous authorizations. All three regulatory agencies were willing to take risk by authorizing GCTs with scientific uncertainties and safety risks. This observation urges them to pay accurate attention to post-marketing risk management.

In Chapter **3.2**, we compare positive and negative opinions for ATMPs in the EU. A cohort of 14 assessment procedures shows that negative opinions were associated with a lack of clinical efficacy and identified severe safety risks. Many authorized ATMPs in the EU were niche products, and designated as orphan drugs. Uncertainties and non-confirmatory evidence were mostly evident for orphan drugs, which were authorized under the EU conditional marketing authorization pathway. Furthermore, numerous major issues in relation to pharmaceutical quality were demonstrated, which were mostly related to the level of validation of release testing, potency assays, and in-process control and incomparability between clinical trial and commercial products. Whether applicants were able to resolve major pharmaceutical quality objections determined the outcome of authorization to large extent, which underlines the importance and challenges for ATMP manufacturing and quality control. Altogether, results suggest that setting appropriate standards for ATMP authorization in Europe, similar to elsewhere, is a learning experience.

In Chapter **4.1**, we investigated publication of GCT clinical trial results. Standardization of regulatory requirements and guidance for clinical development is currently complicated due to numerous scientific, technological, and manufacturing challenges.. Timely publication of GCT clinical trial results can mitigate this problem. A cohort of GCT clinical trials (n=105) that were authorized in the Netherlands between 2007 until the end of 2017 mainly consisted of academically sponsored, single-centered, national (i.e. Dutch) trials, and privately sponsored, multi-center, multi-national trials. The scientific publication rate is 27% and the conference abstract publication rate is 17% (median follow up 1050 days). Results are indicative of more scientific publication by academic hospitals compared to private sponsors, whereas academic hospitals are less likely to publish results in conference abstracts compared to private sponsors. Detailed knowledge on technological know-how was underreported compared to clinical outcomes in scientific literature. These observations underline the important role of single-centred academic trials to build up the GCT knowledge base, and show that private sponsors need to become more attentive to scientific publication. However, the rather low scientific publication rate partially originates from shorter follow up periods

for multi-centre trials. In conclusion, publication rates in scientific literature and conference abstracts are currently suboptimal in the GCT field, yet these may improve over time.

In Chapter **4.2**, we investigated ATMP manufacturing under the HE in practice. We compare manufacturing activities of public and private ATMP facilities that are located in seven EU countries (Belgium, Finland, France, Germany, Italy, Netherlands, UK). Results show that 12 ATMPs were manufactured under the HE by public facilities located in Finland, Germany, Italy, and the Netherlands between 2009-2017. Manufacturing was primarily motivated by clinical needs and clinical experience that was gained historically in clinical practice, and/or in early clinical trials. Furthermore, public facilities used the HE when patients could not obtain treatment in ongoing or future trials. Regulatory aspects motivated (Finland, Italy, Netherlands), or limited (Belgium, Germany) HE utilization, whereas financial resources generally limited HE manufacturing by public facilities. In Germany, mostly private facilities manufactured ATMPs under the HE for the national market. Thus, the HE facilitates availability of ATMPs with close proximity to clinical practice, whereas commercial developments could be undermined by private HE licenses. These results indicate that the use of the HE pathway and regulatory pathways for commercial development need to be optimized in a complementary fashion.

The general discussion describes regulatory trends that were evident from the findings, and the implications on GCT development and their availability in clinical practice. Regulatory authorities are searching for justified flexibility for GCT authorization in comparison to existing regulations for pharmaceuticals, in an attempt to balance the protection of public health, and the facilitation of GCT development. Due to unmet medical needs and added clinical benefits, but also limited experience with new GCT technologies, and their unknown long-term effects, authorities are moving towards a regulatory approach for marketing authorization that is based on less comprehensive data and to resolve knowledge gaps on risks and uncertainties during the post-marketing phase. With respect to exemption pathways, the trade-off between the need for potentially life-saving treatment and the need for benefit/risk data is particularly pressing for the HE in comparison to other regulatory pathways. While comprehensive or confirmatory evidence of a benefit/risk balance is not required under the HE, there is variation in the required evidentiary support for benefits and risks to obtain a HE license among EU countries. These findings indicate that the traditional role of regulators as a gatekeeper is under pressure. Enhanced post-marketing data collection and risk management are needed

to support continuous regulatory monitoring and evaluation of quality optimization and clinical outcomes.

The overall trend of convergence towards regulatory flexibility coincides with a trend of regulatory diversification when looking closer at specific requirements and processes among jurisdictions. A globally diverse regulatory landscape, in particular for manufacturing and quality requirements, may impose serious hurdles for the field to mature into more late stage developments in the future and to widespread GCT availability in multiple jurisdictions. Furthermore, not all GCTs that are administered to humans may be intended for commercial development. Exemption pathways such as the HE can serve as a regulatory tool to facilitate ATMP availability in clinical practice under controlled circumstances. However, the feasibility to comply with stringent provisions is limited in some countries, whereas in other countries more flexible provisions enable manufacturing for the national market under the HE. To move forward, the GCT field is in need of more centralized knowledge dissemination, information synthesis and collaborative efforts. More transparency on clinical trials and activities in clinical practice, and on clinical outcomes, would facilitate coordination and collaboration in pre-competitive environments, public-private engagements, inform business opportunities, and facilitate market access planning. This would not only benefit the development of individual GCTs, but also stimulate an optimized use of commercial development pathways and exemption pathways in a complementary fashion, which ultimately benefits patients on a regional and global level.

Chapter 6.2:
Samenvatting

Gen- en celtherapieën (GCT) hebben de potentie om de gezondheidszorg te verbeteren. Ze hebben andere werkingsmechanismes dan bestaande geneesmiddelen (farmaceutica en biologische geneesmiddelen), waardoor ze mogelijkheden voor behandeling bieden in therapeutische gebieden waar geen geneesmiddelen beschikbaar zijn, of niet voldoende toereikend zijn. Recentelijk zijn genetische gemodificeerde T cel producten toegelaten op de markt. Deze T cel producten hebben opmerkelijke klinische effecten voor de behandeling van patiënten met recidiverende of refractaire B cel maligniteiten. Er zijn echter ook zorgen over de implementatie van GCTs in de huidige geneesmiddelenregulering. De product karakteristieken van GCTs sluiten niet goed aan bij geneesmiddelenregulering aangezien ze gebaseerd zijn op ander startmateriaal (i.e. celmateriaal of vectoren voor gen afgifte), ze interacteren met het menselijk lichaam via andere, complexe werkingsmechanismen en functies zijn gericht op onderliggende moleculaire defecten die ziekte veroorzaken in subgroepen van patiënten of bij individuele patiënten. De context waarin innovatie plaatsvindt is ook anders dan voor geneesmiddelen. Exploratief klinisch onderzoek vindt voornamelijk plaats in academische ziekenhuizen, veel GCTs zijn in het verleden gebruikt in de klinische praktijk als humane cellen of weefsel en kennisontwikkeling in de klinische praktijk speelt een relatief grote rol. Deze verschillen tussen GCTs en andere geneesmiddelen roepen veel vragen op over hoe bestaande geneesmiddelenregulering aangepast en geïmplementeerd kan worden voor GCTs, opdat de volksgezondheid en innovatie worden gestimuleerd en de patiënt veiligheid wordt gegarandeerd.

In dit proefschrift bestuderen we hoe geneesmiddelenregulering is aangepast en geïmplementeerd voor GCTs die gereguleerd worden als geneesmiddelen en bestemd zijn voor humane toediening, de besluitvorming onder deze regulering en de implicaties van aangepaste regulering voor GCT ontwikkeling en de beschikbaarheid van GCTs in de klinische praktijk.

In Hoofdstuk **2** bestuderen we de aanpassingen in regulering die specifiek voor GCTs geïmplementeerd zijn. Beleidsmakers hebben twee strategieën gebruikt om de regelgeving voor GCTs aan te passen; door de grenzen van de bestaande geneesmiddelenregulering op te rekken om GCTs te accommoderen, of door het opstellen en implementeren van nieuwe regelgeving voor GCTs die los staat van bestaande regulering (i.e. regulatoire vrijstellingen). In Hoofdstuk **2.1** hebben we de vereisten voor toelating van GCTs tot de markt vergeleken tussen Canada, de Europese Unie (EU), Japan, Zuid-Korea en de Verenigde Staten (VS). Jurisdicties verschillen op de volgende punten: 1) GCT subtypes die als geneesmiddelen worden gereguleerd, inclusief de mogelijkheid om GCTs in de klinische praktijk te gebruiken

via regulatoire vrijstellingen, 2) of toelating tot de markt is gereguleerd onder GCT specifieke wettelijke provisies (EU, Japan), dan wel wetgeving voor biologische geneesmiddelen (Canada, US, Korea) en 3) de mate van flexibiliteit voor het interpreteren van de veiligheid, effectiviteit en kwaliteitvereisten en processtandaarden. Autoriteiten zijn op zoek naar regulatoire flexibiliteit ten opzichte van standaardvereisten, om zodoende toegang tot de markt te bespoedigen, innovatie te stimuleren en de patiëntveiligheid te garanderen. De geobserveerde regulatoire variatie lijkt een natuurlijke consequentie van de lokale opkomst van GCTs. De variatie laat echter zien dat er op wereldwijd niveau sprake is van een diversificatie van GCT regelgeving.

In Hoofdstuk **2.2** bestuderen we regulatoire aanpassingen in de vorm van een regulatoire vrijstelling voor Advanced Therapy Medicinal Products (ATMPs) in de EU, de zogeheten Hospital Exemption (HE). De HE is uitgezet in Artikel 28 van de ATMP verordening en reguleert productie van 'custom-made' ATMPs voor behandelingsdoeleinden op een non-routine basis. We hebben het implementatie proces van de verordening in meerdere landen gedocumenteerd (België, Duitsland, Finland, Frankrijk, Italië, Nederland, Spanje en het Verenigd Koninkrijk (VK)) en het verloop van dit proces geassocieerd met twee uitkomstmaten; nationale regulatoire provisies en het aantal HE licentiehouders. Nationale provisies verschillen substantieel van elkaar ten gevolge van discretionaire interpretatie van Artikel 28 door de nationale autoriteiten. In sommige landen zijn additionele provisies geïmplementeerd, zoals klinische data vereisten of restricties op het gebruik van de HE. Het aantal HE licentiehouders laat zien dat ATMP productie in de klinische praktijk wordt gefaciliteerd door de HE in vier landen. Gelimiteerd gebruik van de HE werd vaak beschreven in relatie tot een beperkte capaciteit om aan de provisies te voldoen (voornamelijk productie, kwaliteit en klinische data vereisten), implementatie vertragingen, of andere regulatoire routes die de voorkeur hebben ten opzichte van de HE. ATMP productie door bedrijven wordt gefaciliteerd door de HE in twee landen. Deze verschillen laten zien dat er sprake is van een diversificatie van HE regelgeving binnen de EU.

In Hoofdstuk **3** bestuderen we besluitvorming voor toelating van GCTs tot de markt. In Hoofdstuk **3.1** laten we verschillen zien in besluitvorming tussen de Verenigde Staten (VS), de EU en Japan. Uit 18 beoordelingsprocedures van geregistreerde GCTs blijkt dat productkarakteristieken heterogeen zijn, dat maar drie GCTs in meerdere jurisdicties zijn geregistreerd en dat bijna de helft van de GCTs weesgeneesmiddelen zijn. Robuust bewijs, of indicaties van, klinische effectiviteit werden teruggevonden in Amerikaanse en Europese beoordelingen, terwijl in Japan de klinische effectiviteit veelal

niet onomstotelijk bewezen waren. Toelating tot de markt in de EU en Japan ging gepaard met overwegingen van onbeantwoorde medische nood, maar ook met aanzienlijke verplichtingen tot post-autorisatie studies als gevolg van wetenschappelijke onzekerheden en veiligheidsrisico's. Autoriteiten in de VS waren flexibeler in de beoordeling van twee CAR-T cel producten, in tegenstelling tot meer conservatieve beoordelingen voor eerdere producten. Hieruit blijkt dat alle drie de autoriteiten bereid zijn om risico te nemen door GCTs toe te laten op de markt, op basis van bewijsvoering met onzekerheden en potentiele veiligheidsrisico's. Dit wijst op de belangrijke rol voor risicomanagement van GCTs gedurende de post-autorisatie fase.

In Hoofdstuk **3.2** vergelijken we positieve en negatieve beoordelingen voor ATMP toelating op de Europese markt. Uit 14 beoordelingsprocedures blijkt dat negatieve opinies geassocieerd zijn met een gebrek aan bewijs omtrent klinische effectiviteit en geïdentificeerde veiligheidsrisico's. Veel geregistreerde ATMPs zijn weesgeneesmiddelen die voorwaardelijk zijn toegelaten. Onzekerheden en minder robuuste bewijsvoering waren het meest evident voor deze weesgeneesmiddelen. We laten ook zien dat beoordelaars vaak grote bezwaren hadden op de productkwaliteit, met name op het valideren van testen voor batchvrijgave, testen voor potentie, controles tijdens productie en verschillen tussen studieproduct en product voor toelating. Of aanvragers de regulatoire bezwaren konden oplossen had grote invloed op de besluitvorming, wat wijst op bekende problemen voor productkwaliteit in het ATMP veld. Het vinden van geschikte vereisten voor toelating van ATMPs in Europa is zoals in andere jurisdicties, een leerervaring.

In Hoofstuk **4.1** bestuderen we publicatie van resultaten van klinische studies met GCTs. Door de vele wetenschappelijke, technische en productie uitdagingen is regulatoire standaardisatie en begeleiding voor klinische ontwikkeling momenteel gecompliceerd. Tijdige publicatie van klinische resultaten van GCT studies zou dit probleem mogelijk kunnen verminderen. Een cohort van klinische studies met GCTs die geautoriseerd zijn in Nederland tussen 2007 en 2017 (n=105) laat zien dat de meeste klinische studies gesponsord en geïnitieerd werden door academische ziekenhuizen in Nederland en monocentrisch waren opgezet, of gesponsord werden door industrie en multicentrisch en internationaal waren opgezet. Na een mediane follow-up van 1050 dagen was het percentage studies dat gepubliceerd was in de wetenschappelijke literatuur 27% en voor 17% van de studies waren resultaten gepubliceerd in conferentie abstracts. Het is meer waarschijnlijk dat academische ziekenhuizen publiceren in wetenschappelijke literatuur, terwijl het meer waarschijnlijk is dat industrie resultaten publiceert in conferentie abstracts. Technische know-how was onder gerapporteerd in

vergelijking met klinische uitkomsten in wetenschappelijke literatuur. Dit wijst op de belangrijke rol van monocentrische, academische studies voor kennisopbouw en dat industrie meer aandacht kan besteden aan wetenschappelijk publiceren. Het is echter mogelijk dat vanwege de relatief korte follow-up tijd voor multicentrische studies het gevonden wetenschappelijke publicatiepercentage relatief laag is. Momenteel is publicatie van GCT klinische studies suboptimaal, maar dat zou mogelijk kunnen verbeteren in de komende jaren.

In Hoofdstuk **4.2** bestuderen we ATMP productie in de praktijk. We brengen de productieactiviteiten van publieke en private ATMP productie faciliteiten in zeven EU landen in kaart (België, Duitsland, Finland, Frankrijk, Italië, Nederland, VK). Er zijn 12 ATMPs geproduceerd onder de HE door publieke faciliteiten uit Duitsland, Finland, Italië en Nederland tussen 2009-2017. Productie was primair gemotiveerd door klinische behoeftes en klinische ervaring uit het verleden, dan wel uit experimentele klinische studies. De HE werd ook vaak gebruikt wanneer patiënten niet in een lopende of toekomstige klinische studie behandeld kunnen worden. Regulatoire aspecten motiveren (Finland, Italië, Nederland), of hinderen (België, Duitsland) gebruik van de HE, terwijl financiële middelen over het algemeen gebruik van de HE door publieke faciliteiten hinderen. In Duitsland zijn voornamelijk ATMPs geproduceerd onder de HE door private faciliteiten voor de nationale markt. Dit laat zien dat de HE zowel beschikbaarheid van ATMPs in de klinische praktijk faciliteert, maar ook commerciële ontwikkelingen kan belemmeren door private HE licenties. Het gebruik van de HE en trajecten voor commerciële ontwikkelingen zouden beter op elkaar afgestemd en complementair kunnen worden.

De algemene discussie beschrijft de regulatoire trends die volgen uit de bevindingen en de implicaties voor GCT ontwikkeling en de beschikbaarheid in de klinische praktijk. Autoriteiten zijn op zoek naar gerechtvaardigde flexibiliteit voor GCT goedkeuring in vergelijking met andere geneesmiddelen, zodat de volksgezondheid wordt gewaarborgd en GCT ontwikkeling wordt gefaciliteerd. Vanwege de onbeantwoorde medische nood en therapeutische meerwaarde, maar ook de beperkte ervaring met nieuwe GCT technologieën en de onbekende lange-termijn effecten, hebben autoriteiten een benadering die gebaseerd is op vroege toelating gecombineerd met meer data verzameling gedurende de post-autorisatie fase om onzekerheden en risico’s verder te onderzoeken. Voor regulatoire vrijstellingen zoals de HE is de spanning nog groter tussen mogelijk levensreddende behandeling en robuuste uitkomsten voor effectiviteit en veiligheid. Terwijl robuuste klinische uitkomsten niet vereist zijn onder de HE, is er variatie tussen

EU landen in de mate van bewijsvoering voor effectiviteit en veiligheid om een HE licentie te bemachtigen. Dit laat zien dat de traditionele rol van autoriteiten als poortwachter onder druk staat. Meer nadruk op dataverzameling en risicomanagement gedurende de post-autorisatie fase is nodig voor constante regulatoire toezichthouding en evaluatie van zowel productkwaliteit als klinische uitkomsten.

De convergentie naar regulatoire flexibiliteit hangt samen met een trend van regulatoire diversificatie van specifieke regulering voor GCTs tussen jurisdicties. Een globaal divers regulatoir landschap, in het bijzonder voor productie- en kwaliteitseisen, kan substantiële barrières vormen voor het volgroeien van het veld in meer late fase ontwikkelingen en beschikbaarheid in verschillende jurisdicties. Echter, niet alle GCTs voor humane toediening zijn bedoeld voor commerciële ontwikkeling. Vrijstellingen zoals de HE kunnen als een regulatoir instrument fungeren om ATMP beschikbaarheid in de klinische praktijk te faciliteren onder gecontroleerde omstandigheden. Desalniettemin beperken nationale provisies het gebruik van de HE in sommige landen, terwijl de HE in andere landen voor commerciële doeleinden wordt gebruikt. Om vooruitgang te bereiken zijn centrale kennisdeling, informatiesynthese en samenwerkingsverbanden essentieel. Meer transparantie over zowel klinische studies en activiteiten in de klinische praktijk als klinische uitkomsten, zou coördinatie en samenwerking in pre-competitieve omgevingen en publiek-private samenwerkingsverbanden faciliteren, ontwikkelingskansen voor bedrijven informeren en het managen van marktoegang faciliteren. Geoptimaliseerd en complementair gebruik van commerciële ontwikkelingstrajecten en vrijstellingen zou niet alleen ontwikkelingstrajecten van individuele GCTs ten goede komen, maar ook gezondheidsbaten voor patiënten op regionaal en globaal niveau opleveren.

CHAPTER 7:

APPENDICES

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Chapter 7.4:
About the author

Delphi Coppens was born in Nijmegen, the Netherlands, on 28 April 1983. After completing highschool in Silvolde in 2001, she went abroad for a year to participate in a cultural exchange program in Panama. After returning to the Netherlands she moved to Amsterdam for her university studies.

She first obtained a Bachelor degree in Biomedical Sciences, and subsequently completed an interdisciplinary research Master in Cognitive Science at the University of Amsterdam in 2007. As part of the curriculum, Delphi conducted both *in-vitro* and *in-vivo* animal studies in the field of neuroscience, which were part of research internships at the Swammerdam Institute for Life Sciences in cooperation with the Netherlands Institute for Neuroscience, and at the Free University Medical Centre.

After graduation from university, Delphi worked for pharmaceutical and biotechnology companies. She gained experience with setting up and conducting global clinical trials for rare genetic diseases at Genzyme Europe. She was involved in the preparation and maintenance of essential study documents that were needed for trial authorization and conduct in several European countries. At Merck Sharp & Dohme she provided medical information to health care professionals and patients.

Due to her interest in pharmaceuticals in relation with wider societal topics, Delphi completed a Master in Medical Anthropology and Sociology at the University of Amsterdam in 2011. She conducted fieldwork at a rehabilitation clinic in South Africa for her master thesis. After returning to Amsterdam, she worked as a researcher at the Access to Medicine Foundation. Her research was focused on R&D activities of large industry to meet the needs of patients in developing countries.

In 2015, Delphi started working at the Utrecht/WHO Collaborating Center for Pharmaceutical Policy and Regulation of the Utrecht Institute for Pharmaceutical Sciences on a project on global regulations for gene and cell-based therapies. This project sparked a PhD track, which gave Delphi the opportunity to engage with various regulatory authorities and health care professionals, to collaborate with the Leiden University Medical Center, to attend expert meetings, and to present her studies at several conferences. She is currently looking forward to future endeavors.