Chapter 19

Regulatory Developments for Nonhematopoietic Stem Cell Therapeutics: Perspectives From the EU, the USA, Japan, China, India, Argentina, and Brazil

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1. INTRODUCTION:[1]

The development of therapies with nonhematopoietic stem cells has received widespread attention in recent years. The prospect of creating new treatments for previously incurable medical conditions has given rise to new hopes among patients and steep economic and healthcare expectations. A key problem of this emerging research field has been, however, that existing regulatory frameworks for the clinical testing and market approval of pharmaceutical drugs do not neatly map onto stem cell treatments. The biological characteristics of stem cells and specific risks for patients require novel and tailormade

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regulatory approaches. As a result, the regulatory landscape for clinical research with nonhematopoietic stem cells is an unfinished project. Regulatory arrangements, as we will show in this article, are in many societies still evolving and a high level of regulatory variation has emerged between countries. This rapidly changing and internationally diverse situation has posed challenges to researchers and to the governance and conductance of cross-country clinical trials and market approval procedures. It has also caused controversies about the ethical limits, risks, clinical methods, and scientific standards under which stem cells should be applied in human bodies and societies. Disagreements have arisen in particular regarding the acceptability of experimental stem cell interventions without clinical trials, which has evolved into a common practice in many countries, often on a for-profit basis. McMahon has in this respect spoken of the emergence of a "global industry" of unproven stem cell interventions [1]. She has estimated that in the last 15 years several hundred thousands of patients have received experimental stem cell treatments. These interventions have been offered for prices between 5000 and 30,000 US dollars, sometimes more. The estimated revenue for these unproven applications lies between 3 and 7.5 billion US dollars.[2]

As we will show in this chapter, regulatory authorities have reacted to this development in many varied ways. What can be observed at a global level is a conflict that unfolds between two dynamics: the striving for international harmonization on the one hand, and an increasing process of regulatory diversification on the other hand. Attempts of regulatory harmonization are exemplified, for instance, by the 2016 Guidelines for Stem Cell Research and Clinical Translation by the International Society for Stem Cell Research [2], the Advanced Therapy and Medicinal Products (ATMP), Regulation of the European Medicines Agency (EMA), or by the ATMP Cluster of the US Food and Drug Administration (FDA), EMA, and Health Canada [3]. These processes of harmonization have evolved from a pharmaceutical model of drug development and the ideal of evidence-based medicine (EBM), with the multiphase randomized controlled trial (RCT) system as methodological gold standard. In parallel to these developments, however, discontent with the use of the multiphase trial system for the clinical validation of nonhematopoietic stem cell–based medicinal approaches and products has grown. A politics of opposition has emerged that has called for the use of alternative methods and forms of evidence, to reduce the costs of clinical testing and to increase access to non-systematically proven innovative interventions at an earlier stage. Calls for international harmonization in the stem cell field have been undermined too, by practical challenges to standardize clinical and cell processing procedures in large-scale, multicountry trials, which require a complex logistical

2. This number is based on the assessment that in the last 15 years between 200,000 and 500,000 patients have received these treatments at an average cost of 15,000 US dollars. This is a total estimated revenue of 3–7.5 billion US dollars.

infrastructure and significant financial resources. For academic researchers and small to midsize biotech companies these resources are often not available [4]. Since industry involvement in stem cell medicine has remained at a low level, the mobilization of resources to take investigational stem cell products or therapies through rigorous multiphase trials remains typically a challenge. This politics of alter-standardization has taken an increasingly global form. Many impulses for regulatory change and a shift away from multiphase trials for stem cell–based treatments have come from Asia; for instance, from Japan, India, China, and also South Korea [5]. But opposition to EBM and the multiphase trial system, and calls for the emerging of new models and methodologies of clinical innovation in the stem cell field, has also increasingly evolved in the European Union and the USA. These clashes have resulted in three central dynamics of regulatory diversification. These developments challenge the use of multiphase trial methodology as the central methodological instrument for therapy development in the stem cell field in many respects. Section I of this chapter will explore regulatory developments for nonhematopoietic stem cell therapies in Japan, China, India, Argentina, Brazil, the USA, and the EU. We will illustrate that the research methods, ethical standards, and approval procedures for the market use of nonhematopoietic stem cell interventions have become increasingly diverse and are characterized by important differences from pharmaceutical drugs research. Section II discusses these findings and discerns three central dynamics of regulatory diversification among the countries we have studied. Section III considers the advantages and disadvantages of different regulatory approaches across countries from the perspective of regulatory agencies, patients, as well as research and small to midsize biotech corporations. Section IV examines some of the roadblocks that prevent the successful clinical translation of nonhematopoietic stem cell–based therapies.

2. THE REGULATORY COMPARISON

2.1 United States of America

The USA was the first country to have issued a formal regulation for clinical use and market approval of stem cell interventions. FDA rules went into effect with the interim rule, Human Cells, Tissues, and Cellular and Tissue-Based Products: Donor Screening and Testing, and Related Labeling, which was issued on May 25, 2005 [6]. On June 19, 2007 this interim rule was adopted as a final rule, without change, and released as the US FDA's Regulation for Human, Cellular and Tissue Products (HCT/Ps) [7]. This regulatory framework introduced a risk-based, tiered approach that regulates stem cells as biological products within two categories: "351 products" and "361 products" [7]. (Please see Table 19.1) The "351" category refers to cells that are more than minimally manipulated and to cells that are used in a nonhomologous manner. The term "minimal manipulation" means "that the processing of the

TABLE 19.1 HCT/Ps Regulation in the USA: 351 Versus 361 Human Cell and Tissue Products

351 HCT/P Products	HCT/P 361 Products
HCT/Ps that are more than minimally manipulated	HCT/Ps that are minimally manipulated
Intended for nonhomologous use	Intended for homologous use only
Can involve the combination of cells with another medicinal products or articles	Are not allowed to be combined with other medicinal products or articles
Are subject to US FDA premarket approval	Premarket review by FDA not required
Market approval involves multiphase clinical trial processes that are assessed and authorized by the FDA	No premarketing trials required, but applications must comply with the US Human Tissue Regulation

HCT/P does not alter the relevant biological characteristics of cells or tissues." [7a]. Homologous use refers to "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with cells or stem cells that perform the same basic function or functions in the recipient as in the donor (21 CFR 1271.3(c)), including when such cells or tissues are for autologous use." [7b]. These cells are classified as a biological drug product and they are subject to US Food and Drug Administration (FDA) premarket approval. Three hundred and fifty-one biological products must "by law […] go through the multiphase drug pipeline approval process starting after preclinical studies with an Investigational New Drug (IND) application and proceeding to Phase 1 trials" and then to phase 2 and 3 trials [8].

On the other hand, the "361" category regulates the use of minimally manipulated stem cells that are applied for homologous use. These cells are not subject to premarket approval by the FDA, and they can be used in patients under compliance with the US human tissue regulation [15]. A large direct-to-consumer market with "361" stem cell products has emerged in the USA in recent years [8]. While many of these clinics purport to offer self-classified "361" products, there have been reports that several of these interventions were actually unproven "351" products which were offered to patients illegally [8].

In a recent effort to create more flexible procedures to grant market approval of new drugs and biological products that address unmet health needs, including stem cell products in the "351" category, the FDA introduced special pathways that diverge from the traditional review scheme and which can also be applied to human cell and tissue products [8]. (Please see Table 19.2 below.)

TABLE 19.2 Nonstandard Pathways for the Market Approval of Medicine Products

		US	EU
Modification in the standard of scientific evidence?	No	Fast Track Designation • Designed to speed up the transition from preclinical research to clinical testing Breakthrough Therapy Designation • Aims to expedite premarket review for treatments that are likely to treat severe life-threatening diseases Priority Review Designation • Aims to speed up FDA evaluation after completion of phase 3 trials, to enable faster access to proven drugs	Accelerated Assessment • Designed to meet urgent public health needs, especially when no alternatives exist
	Yes	Accelerated Approval Pathway • Aims to accelerate the authorization of phase 1 and 2 trials that involve patients with low life expectancy	Marketing authorization under exceptional circumstances • If the collection of large N clinical data is not possible (for example, in case of rare diseases) Conditional market approval • Cellular products can be licensed while phase 3 trial continues, if initial efficacy/safety data are convincing
Possibilities to access investigational products outside of clinical trials		Right-to-try legislation (at state level) • Offers patients the choice to use not-yet approved investigational drugs outside of the regulatory control of the FDA Expanded access/compassionate use • Provides access to investigational new treatments parallel to FDA-approved phase 2 and 3 trials	Hospital exemption scheme • Allows for provision of cellular products in hospitals under the responsibility of a doctor Compassionate use program • Allows access to investigative cellular products outside of premarket clinical trials

The different alternative pathways may or may not involve a modification in the standard of scientific evidence necessary to grant a market authorization [8a,8b]. Pathways that do not involve a change in scientific standards include *Fast Track, Breakthrough Therapy*, and *Priority Review*. *Fast Track* can be granted based on preclinical data while *Breakthrough Therapy* designation requires preliminary clinical results [9,11]. The benefits of these designations are the acceleration of review times and more support and meetings with FDA officials during the process. Applications qualified for *Priority Review* are assessed in a shorter period of time (6 instead of 10 months) [12].

The FDA created also an approval pathway that modifies the extent of the clinical data required for approval. In the *Accelerated Approval* scheme, a product may be granted market authorization based on surrogate endpoints [12]. Data showing efficacy in the clinically relevant endpoints must be submitted after marketing. If the results are not satisfying, the FDA can revoke the conditional authorization.

The pathways described above involve the realization of clinical studies in order to show the safety and efficacy of the product. The main aim of these studies is to attain generalizable knowledge and provide a scientifically sound basis for the approval. The participants enrolled in the study are involved as research subjects.

Patients may also receive experimental treatments outside clinical trials through special programs. Access through these programs is not part of the regulatory pathway to grant market approval. It is a more tailored solution where a specific doctor provides an experimental treatment to a single patient. The main aim of this intervention is not the construction of generalizable knowledge. It is medical care. In the US, FDA has created an "expanded access program," also called "compassionate use program." This program provides patients access to investigational new treatments parallel to (but outside of) FDA-approved phase 2 and 3 clinical trials [13]. The expanded use program dates back to 1987, but was revised in 2009 to ensure "broad and equitable access to investigational drugs for treatment," including access to biological drug products [14]. Another development in the USA has been growing numbers of "right-to-try" legislation, which offer patients and physicians the choice to use not-yet approved investigational drugs (including cellular medicines) entirely outside of the regulatory control of the FDA [18,19]. These right-to-try laws have now been issued in more than 30 US states [20].

More recently, the 21st Century Cure Act, which was approved by the US Congress in December 2016, has introduced further possibilities to accelerate market approval of new medicines, by offering possibilities to avoid going through rigorous, large-scale phase 3 trials [16] and by promoting methodological alternatives to the multiphase trial system such as adaptive and other new trial designs [17].

2.2 European Union

Regulatory arrangements for stem cell treatments in the EU are similar to the US model. Cells that are more than minimally manipulated and used in nonhomologous contexts are defined as "medicinal products" and are regulated under the *Advanced Therapy Medicinal Products* (ATMP) legislation, which was issued by the European Medicines Agency (EMA) in November 2007. Minimally manipulated autologous stem cells, on the other hand, are regulated under the human tissue legislations of European member states, and not centrally under EMA [21]. The ATMP regulation has harmonized regulatory approaches for clinical stem cell research in EU member states, to enable clinical collaborations and cross-country approval of stem cell products outside of the EU. As in the USA, the EMA regulation demands evidence from systematic clinical studies, typically from multiphase trials. In contrast to the USA, the EU has not experienced the emerging of a large-scale consumer market with minimally manipulated stem cells [22]. However, demands of patients to widen access to stem cell interventions have been addressed through a range of regulatory exceptions and exemptions.

In the EU, the EMA has set up nonstandard approval procedures for products that address unmet health needs. The situation has similarities with the FDA pathways and designations in the United States. If an application is granted *accelerated assessment* in the EU, the review time is reduced from 210 to 150 days. The timeframe is shorter and the process is more interactive. The preclinical and clinical data required however remain the same as in the standard procedure. Whether and under which circumstances accelerated assessment will be available for cell and stem cell treatments is at present not clear [23b]. The *conditional approval* scheme [25] is similar to the accelerated approval in the United States. A product that follows this path can be marketed provisionally based on surrogate endpoints. Complete clinical data, however, is needed for final approval. Finally, a marketing authorization *under exceptional cirumstances* is granted when the collection of the needed clinical data is not possible because the disease is rare, scientific knowledge is still uncertain, or the collection of the relevant data cannot be performed ethically. These authorizations are subject to a new evidence review each year [25a].

As in the USA, there are mechanisms to access experimental products outside clinical trials. EMA has introduced a "compassionate use" program, which allows access to new drugs and biological products (including stem cell products) outside of premarket clinical trials [23]. Unlike in the USA, however, EMA has also introduced a so-called "hospital exemption" program for stem cell interventions. This program allows the provision of cellular medicinal products to individual patients "in a European hospital under the exclusive professional responsibility of a doctor" [22]. These hospital exemptions are authorized for use by the regulatory authority in the country in which the product is applied. As a result, the hospital exemption scheme has been implemented unevenly across EU member states

[23a]. In some countries, the scheme has been used to approve large numbers of experimental interventions and has created "the opportunity for a legal market of authorized stem cell therapy products to emerge within the province of the clinical professionalism" [24].

2.3 Japan

Premarket evaluation of stem cell therapies in Japan was initially based on a similar regulatory model as in the USA and the EU. Until 2014 stem cell interventions were regulated under the *Pharmaceutical Affairs Law* (PAL) and treated either as pharmaceutical drug products, medical devices, or combination products [26]. This regulatory pathway involved systematic multiphase trials and compliance with good clinical practice (GCP) standards [26]. Then in May 2013 the Japanese National Diet passed the Regenerative Medicine Promotion Act (RMPA) [27], which formed the starting point of a radical regulatory reform. The RMPA was followed by the passing of the Amended Pharmaceutical Affairs Law (PAL), which went into effect in November 2014 [28]. Under the amended PAL the conditions for the clinical application of stem cell interventions changed significantly [26]. The amended law allowed for conditional, limited-term market approval of stem cell products after early-phase clinical trials. Conditional approval can occur after positive clinical data from as few as 10 patients [29], provided these first-in-human-trials demonstrate that the tested cell products are safe and "likely to predict efficacy" [30]. Once approved by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), clinical trial sponsors have the possibility to seek market approval for up to 7 years [30]. Clinical efficacy is tested in this time period in postmarketing procedures [31]. This is a significant shift away from the multiphase RCT system, which has emerged as the methodological gold standard in medical research in recent decades. This break, and the possibility of time-limited conditional market approval after evidence from small numbers of patients, is likely to have repercussions for the regulation of stem cell research in other countries, and possibly also other fields of medical research.

It is also noteworthy that conditionally approved stem cell interventions are eligible for reimbursement by the Japanese health insurance system [26]. Costs for these experimental treatments are split between the state and patients in the ratio of 70:30 [30]. This is a drastic change to the financing of research and development (R&D) costs which typically require long-standing corporate or government investments before development costs can be amortized through health insurance reimbursement and consumer charges. A key driver behind this regulatory reform has been to accelerate the clinical translation of iPSCs which were first created in Japan. By shortening the clinical evaluation process, Japan's revised regulation shall increase international competitiveness and enable clinical use and for-profit applications of iPSC-based treatment at an early stage and faster than in other countries.

2.4 India

The governance of the clinical stem cell field in India started with the introduction of the *Guidelines for Stem Cell Research and Therapy* [32], a regulatory guidance document that was jointly issued by the Indian Council of Medical Research (ICMR) and Department of Biotechnology (DBT) in 2007 [33]. This regulatory guidance formally prohibited the use of stem cells in human patients, except in the context of formally approved clinical trials [33]. In practice, however, this approach was not consistently implemented and India became one of the countries in which unproven or nonsystematically tested stem cell interventions flourished on a large scale [1]. In order to address these problems, the Indian authorities issued a revised regulatory approach in 2013, laid down in the *Guidelines for Stem Cell Research* [34].

These guidelines reconfirmed the prohibition of nonapproved commercial applications with stem cells and stated that all clinical trials with stem cells had to be approved by The Drug Controller General India (DCGI). In 2014, the DCGI announced that stem cells were treated as a drug product and that clinical trials and premarket approval had to conform to the Indian Drugs and Cosmetics Act, which included a new section on stem cells [35]. With these adjustments, the regulation of clinical stem cell research was formally put under statutory law.

At the level of clinical practice, however, the situation remained diverse. Stem cell trials continue to be conducted outside of DCGI control and unapproved or nonsystematically proven stem cell interventions are still offered in many hospitals [36].

As a result of this uneven implementation, the current regulatory situation in India can best be described as flexible, and as serving multiple interests and stakeholder groups simultaneously [5]. On the one hand, the DCGI's requirement for multiphase trials and international best practice standards facilitates formal approval and marketization of stem cell–based medicinal products at a national and international level. This is exemplified by the DCGI's approval of the first stem cell product in May 2016, which shall soon also be marketed in the EU, in the context of the EMA's orphan designation scheme [37]. On the other hand, the lack of coherent regulatory enforcement and the continued toleration of unapproved clinical applications [35] enable physician-based forms of innovation and localized forms of profit-making outside of the regulatory system.

2.5 China

The development of a regulatory framework for clinical stem cell applications in China has been an ongoing process and much slower than in the EU or USA. As in India, a large market for experimental for-profit interventions with stem cells emerged in the early 2000s. Following an initial attempt to control the provision of these unproven or nonsystematically tested interventions in

2009, which failed [38], the Chinese health authorities introduced a regulatory white paper, in 2013, which formed the basis of a more comprehensive regulatory framework for clinical stem cell research that was publicized in August 2015 [39]. The 2015 *Regulation for Clinical Stem Cell Research*, jointly issued by the National Health and Family Planning Commission (NHFPC) and the Chinese Food and Drug Administration (CFDA), states that the clinical translation of stem cell–based approaches must occur through systematic clinical studies, which must follow from sound preclinical evidence. The core of this regulation is that stem cell trials can only be conducted in specifically authorized research hospitals and that for-profit applications of experimental stem cell interventions are legally prohibited. If this rule is implemented, this would mean the delimitation of clinical stem cell interventions to a small number of elite hospitals. It would also mean the systematic shutting down of numerous for-profit stem cell clinics [39]. While this evolving regulatory approach indicates an important step toward the improved review and governance of clinical stem cell research and applications in China, there are still numerous unresolved questions with this framework. A first set of questions concerns implementation: Will the Chinese authorities have the political will to mobilize sufficient resources and administrative infrastructures to consistently implement this new regulatory model? In particular, will this regulation be equally implemented across the different Chinese provinces, as well as civil, military, and private institutions? At present this does not seem the case. Private and military (as well as armed police and marine) hospitals continue to offer experimental for-profit stem cell interventions on the Internet. This suggests that regulatory standards are implemented unevenly and that unapproved for-profit applications continue to be tolerated in China also, after the introduction of the national regulatory framework in 2015 [39]. A second set of questions concerns the exact methodological requirements that will be required in premarket evaluations. For instance, will the Chinese health authorities regulate stem cells as a pharmaceutical product or a medical technology? And which types of clinical studies will the NHFPC and CFDA require before approving stem cell treatments for routine clinical use? While the 2013 white paper mentioned mandatory phase 2/3 trials, the 2015 regulation only speaks of "clinical studies" that shall be conducted according to "scientific principles" [39]. In the 2015 guidelines, a more detailed explanation of these points remained undefined. This could well mean that China's health regulators leave this question deliberately open so as to have the flexibility to follow the current Japanese model rather than the more costly USA or EU model.

2.6 Argentina

The clinical use of stem cells is currently regulated under the Ministerial Resolution No. 610/2007 from the Argentinean Ministry of Health. This

resolution states that the use of human cells falls under the authority of the Unique Central Institute for Ablation and Implantation (INCUCAI). By falling under the authority of INCUCAI, stem cell interventions are not governed as a medical product (as in the EU, India, and the USA), but as a medical procedure, which are managed by the Argentinean Transplant Act. With the exception of hematopoietic cell transplants from human bone marrow, all types of stem cells are considered experimental and require evaluation of safety and efficacy through clinical research [40,41]. In the late 2000s, a dispute emerged among Argentina's regulators whether stem cells should also be regulated as a medical product. As a result, Argentina's National Administration of Drugs, Food and Medical Technology (ANMAT) started to play a major role in regulating the use of stem cells. A first step in this direction was achieved in 2011 by ANMAT regulation 7075/2011, in which more than minimally modified cellular products were classified as advanced therapeutic medicinal products (ATMP). At present, however, ANMAT has no legal authority to enforce the approval of stem cell treatments under its rule, and it has not been decided in which situation researchers should apply at ANMAT or INCUCAI. Because INCUCAI's regulation does not discriminate between different cell types, specific procedures of cell manipulation, or different levels of risks, the regulation could be considered broadly so as to include even human embryonic stem cells [40]. However, a new regulatory approach that will provide clarity on these issues is currently being drafted by the Ministry of Health (MOH), together with Argentina's Advisory Committee on Stem Cells and Regenerative Medicine [42].

In practice, the legal reach of both INCUCAI and ANMAT is limited. Argentina is a federal country in which national regulatory authorities have legal power only when medical products cross provincial borders or are involved in foreign trade. As a result, federal regulations are not applicable at the provincial level as long as medical treatments or services are applied exclusively within the geographic jurisdiction of a province [40]. A situation exists where there is no effective control over stem cell–based clinical applications if these interventions are not offered or shipped across multiple provinces. According to estimates of policy experts and representatives of patient associations, this undefined regulatory gray area has resulted in the increase of experimental for-profit interventions with stem cells, which have been provided by at least 10 private clinics in the country [43].

2.7 Brazil

The development of a regulatory framework for clinical stem cell research in Brazil has been challenging for two reasons: religious opposition to stem cell research and a constitutional prohibition that bans the commercial use of human cells and tissues [44]. Religious protests first flared up in 2005, when

the Brazilian Congress approved Law #11,105, which legitimized the use of human embryonic stem cells (hESC) for research, including in clinical trials. According to this law, the regulation for the production and clinical use of hESC and other types of stem cells (with the exception of bone marrow transplants) fell under the responsibility of Brazil's National Agency for Health Surveillance (ANVISA), the country's national drug regulatory authority [43]. Yet, following a complaint by the Catholic Church at the Brazilian Supreme Court, the authorization of the use of embryos for research purposes was suspended for 3 years. In 2008, a final verdict confirmed that the 2005 law was valid, and that hESC research could go ahead [45]. According to officials of ANVISA this 3-year deliberation delayed the development of effective regulation for other types of stem cells [44]. A first regulatory step for the clinical use of stem cells was issued by ANVISA in March 2011, in the form of ANVISA Board Resolution #9. However, this regulation specified solely the technical standards for the harvesting, derivation, processing, storage, and quality controls for clinical use of stem cells. It did not address standards for clinical trials and market authorization. The reason for this was that the Brazilian constitution prohibits the commercialization of human body materials, including human cells and their derivates [45]. As a result, market approval and commercial distribution have until this moment not been permitted. Regulatory debates on this issue within ANVISA and the Brazilian MOH are ongoing. However, because ANVISA has since 2013 worked on a draft regulation for clinical trials for advanced cell products, it is expected that commercialization of stem cell products will ultimately be approved in Brazil [44]. One consequence of this constitutional prohibition is that the number of for-profit providers of experimental stem cell interventions has been much lower than in other countries [1].

3. THREE DYNAMICS OF REGULATORY DIVERSIFICATION

The data from our comparison suggest that the regulatory landscape for nonhematopoietic stem cell research and applications is characterized by three dynamics of regulatory diversification.

3.1 The Emergence of a Growing Number of Regulatory Exceptions and Exemptions

The first dynamic is the emergence of a growing number of regulatory exceptions and exemptions, which have been introduced by regulatory authorities in high-income countries, especially in the EU and the USA [8,23a]. Examples from the EU are the "hospital exemption scheme," which has evolved as part of the EMA ATMP regulation, the "conditional approval scheme," and the "compassionate use program" [23a,46]. According to Salter, Zhou, and Datta, these schemes have provided "the opportunity for a legal

market of authorized stem cell therapy products to emerge within the province of the clinical professionalism" [24]. While the hospital exemption scheme is unique to the EU, as we have shown above, the US FDA has introduced a range of similar regulatory exceptions, such as the "fast track approval" scheme, the "accelerated approval" scheme, and the "compassionate use program" [8]. More recently, the 21st Century Cure Act, has introduced further changes and additional possibilities to avoid going through rigorous, large-scale phase 3 trials [16]. What this growing number of regulatory exceptions and exemptions share is that they either allow to shortcut the clinical trial process, or in some cases permit possibilities for clinical innovation and sometimes commercial clinical applications outside of the multiphase trial system, but still within the confines and review procedures of the national regulatory agencies. Another development in the USA, as mentioned in section I, has been a growing number of "right-to-try" laws, which have now been signed in more than 30 US states [20]. These regulatory exceptions allow for the use of experimental treatments for patients in an accelerated way, by removing requirements to go through rigorous multiphase trials. The underlying rationale, as articulated, for example, in the 21st Century Cure Act, is that less far-reaching regulatory controls allow to address "unmet needs," however vaguely defined [46a]. Many healthcare providers, however, are concerned that these regulatory exceptions and expedited approvals could compromise patient care by exposing patients to greater risks, irresponsible interventions, and high costs for potentially ineffective treatments [46b].

3.2 The Flexible Enforcement of Regulatory Standards

A second process of regulatory diversification is the flexible enforcement of regulatory rules in some countries that enables the continued provision of experimental for-profit interventions with stem cells outside of the review and control structures of regulatory agencies. This has happened for various years in India and China, where governments responded only gradually to a flourishing gray-area market of stem cell therapies [5,47,48]. Unapproved for-profit therapies continue to be tolerated in these countries even after the introduction of national regulatory frameworks, which formally prohibit stem cell interventions outside of formally approved clinical trials. As mentioned further above, in China, the 2015 *Regulation for Clinical Stem Cell Research* has explicitly stated that the clinical translation of stem cell–based approaches must occur through systematic clinical studies, which must follow from sound preclinical evidence [39]. The core of this regulation is that stem cell trials can only be conducted in specifically authorized research hospitals and that for-profit applications of experimental stem cell interventions are legally prohibited [39]. Also in India, the 2013 *Guidelines for Stem Cell Research* (and previously in 2007 the *Guidelines for Stem Cell Research and Therapy*)

have formally prohibited the use of stem cells in human patients, except in the context of clinical trials approved by India's health authorities [33,34]. Despite these formal regulatory prohibitions, however, large private hospitals and medical corporations have continued to offer their services on the Internet in both countries. In China, various private clinics and companies continue to advertise stem cell treatments on the worldwide web, including on English language websites that aim to attract international patients. Also in India, numerous stem cell clinics have an online presence and advertise stem cell–based interventions for a broader range of conditions.

However, the toleration of unapproved stem cell therapies has by no means been restricted to middle-income countries, but can also be observed in the USA. In the USA, the FDA is taking a surprisingly relaxed approach to clinics that are offering autologous stem cell interventions to patients; these clinics have sprouted all over the country during the last 8–10 years. According to research conducted in 2015, there are at present more than 350 US private clinics and businesses offering direct-to-consumer stem cell interventions to medical consumers, which have not been authorized by the US FDA. These interventions did not only include autologous stem cell treatments, but also interventions with autologous stem cells from multiple sources, and at least one clinic claimed to offer even human embryonic stem cell–based interventions [49]. With a growing number of right-to-try laws in the USA, recent regulatory changes introduced by the 21st Century Cures Act, and further changes announced by the current Trump government, this large number of clinics can be expected to expand rather than to be clamped down.

3.3 The Abandoning of the Multiphase Trial System

A third process of regulatory diversification in the stem cell field is characterized by the complete abandoning of the multiphase trial EBM system. This has recently happened in Japan and steps in this direction have, with the 21st Century Cure Act, also been initiated in the USA. In Japan, as outlined in section I, regulators introduced since 2013 a far-reaching regulatory reform that has allowed the conditional, limited-term market approval of stem cell products after early-phase clinical trials, with as few as 10 patients [29] provided these first-in-human trials do not generate adverse effects and are "likely to predict efficacy" [30]. According to Sipp [30], this evolving regulatory model in Japan has dramatically relaxed the need to demonstrate the clinical utility of cellular products prior to marketing, and raises critical questions regarding the testing of safety and treatment efficacy. As Sipp has pointed out, with this new approach "Japan clearly hopes to compete and succeed in the race to build a regenerative medicine industry by flattening a few hurdles" [30]. It is not unlikely that other countries will follow the Japanese regulatory model, or at least create additional types of regulatory exceptions in which (conditional) market approval of stem cell therapies can

be granted without preceding phase 1–3 trials. In fact, exactly this has now happened in the USA. The passing of the 21st Century Cure Act in December 2016 has introduced various steps into a postRCT world in the stem cell field, and in other emerging areas of medicine research. As Kesselheim and Avorn have stated, advocates have praised the Act as a "means of speeding drug development" and to decrease "the cost and duration of drugs and devices development" [16]. This has involved the implementation of various provisions that have been designed to "reduce the amount and rigor of clinical testing before new drugs and devices can be approved for use" [16]. These include the use of alternative, less rigorous forms of evidence, such as observational data and self-reporting of "patient experience" that were previously deemed as too subjective and unacceptable in the context of FDA approval procedures [16,17]. Many of the regulatory changes introduced by the 21st Century Cure Act will also apply to stem cell treatments, but it remains to be seen how applications for specific types of stem cell–based interventions will be handled in practice.

4. THE ADVANTAGES AND DISADVANTAGES OF DIFFERENT REGULATORY APPROACHES

Each of the different regulatory approaches and the different modes of regulatory change that have been discussed in this chapter is likely to have specific advantages and disadvantages. It is important to note that these advantages/disadvantages differ between different stakeholders. For instance, what is likely to be a benefit for pharmaceutical or biotech companies can potentially be a disadvantage for patients, and what is likely to be a plus for regulatory agencies can possibly create new challenges for researchers and corporations. I will now discuss the advantages and disadvantages of the use of the EBM and multiphase trial system that follows from the pharmaceutical model of drug development and that centers around the ideal of EBM, GCP, and the use of large-scale RCTs as its central methodological instrument. This will be contrasted with the three dynamics of regulatory diversification that have been discussed in the previous section: (1) a growing number of regulatory exceptions and exemptions, (2) the toleration of nonsystematically proven stem cell interventions outside of the regulatory system, and (3) the complete abandoning of the multiphase trial system.

4.1 Advantages and Disadvantages of the EBM and Multiphase Trial System for Stem Cell Research

Endorsement for the use of rigorous large-scale clinical trials for the clinical evaluation of stem cell–based therapies has come in particular from the International Society for Stem Cell Research (ISSCR) and for a long time (despite recent changes and the acceptance of a growing range of regulatory

alternatives) also by regulatory authorities in the European Union and the USA. The ISSCR, for instance, has argued in its 2015 *Draft Guidelines for Stem Cell Science and Clinical Translation* (ISSCR 2015) that "stem cell based medical innovations" outside of the formal clinical trial process are justified only if "exceptional circumstances" apply and in "some very limited cases." Most importantly, "providers [of experimental stem cell interventions] should under no circumstances" be allowed to "promote, advertise, attempt general recruitment of patients, or commercialize such interventions" [50].

Even though in practice, the provision of commercial clinical stem cell interventions outside of clinical trials has flourished in many countries, various advantages have been cited to support this slow and scientifically rigorous approach. A first reason, which has been cited by the ISSCR, is that the use of multiphase trials is considered as the most prudent and scientifically rigorous approach to realize clinical applications [50]. The staged process of clinical testing seeks to systematically identify potential risks and adverse effects for different sub-groups of patients, and to assure that treatments that reach the market are effective [18]. For this reason, multiphase RCTs have for a long time been seen as the pinnacle of an evidence hierarchy [51]. Despite criticism and examples where RCTs failed to deliver reliable evidence [52,53], the use of phase 1−4 RCTs is still the most important methodological instrument in pharmaceutics research, and despite a growing number of exceptions that aim to accelerate the trial process, a mandatory requirement by drug regulators in most countries [8]. Because multiphase trials can be conducted in a standardized way across multiple medical institutions in different countries, and studies can be replicated, they facilitate approval and marketing of a new drug in multiple countries, which increases both access to new medicines and possibilities for profit making [54].

On the other hand, however, there are also various disadvantages related to the use of EBM and multiphase trial methodologies. A first point is that the multiphase trials are a lengthy and expensive process. In average, the duration of the development of a new medicine from initial preclinical research to market approval is now 10 years, and costs 1.2 billion US dollars [55]. These high costs are partly driven by frequent and expensive failures in clinical development and result in high drug prices, once a new product or therapy has been approved for market use [56]. While the development costs for stem cell treatments do not necessarily have to reach this level, expenses can be high. As reported in a previous article, in case of the Geron human embryonic stem cell trial (hESC) that was launched in the USA in 2011, the preclinical development costs of Geron's hESC program was about 200 million US dollars, and was conducted over nearly a decade [4]. As stated by Edward Wirth, the chief scientist of the hESC program at Geron at the time, "to test biodistribution, dosing, delivery, toxicity, tumorigenicity, and immune rejection the company conducted 24 preclinical studies before an IND application could be filed at the FDA in March 2008. These studies included in total 1977 rodents. The IND

application that the corporation submitted was 21,000 pages long, with more than 90% consisting of data from the preclinical studies." According to Wirth, this was the longest application the FDA had received at that time [4]. While the development costs for Geron's groundbreaking hESC program may have been higher than in subsequent hESC trials, the development and clinical evaluation costs for stem cell treatments—through the phase 1–3 RCT pathway are for many researchers and small to midsize biotech companies that invest in stem cell medicine a challenge. Public funding for the clinical translation and development of stem cell treatments is highly limited. It is typically insufficient to cover the long way from preclinical development to the market, without additional support from either charitable organizations or the private sector [4]. A problem for the stem cell field has been, in particular, that pharmaceutical and many larger biotech companies have for many years hesitated to invest in clinical stem cell research [57]. One reason in this respect is also that in particular autologous stem cell treatments that use cells from patients' own bodies, which are then processed and reinjected, do not offer a viable business model for the pharmaceutical industry, and that as a result, industry support for these treatments cannot be expected [58].

But there is another disadvantage related to the use of standardized, large-scale multiphase trials in the stem cell field. Large-scale trials, and in particular multicountry trials, that are often necessary to recruit sufficient numbers of patients especially in the context of phase 3 trials, require highly standardized clinical infrastructures that allow for the exact replication of the clinical trial protocol, to generate methodologically sound clinical data. While in more established fields of medicine well-functioning research platforms have emerged over the course of several decades, in the stem cell field such well-established infrastructures are typically lacking. New alliances between researchers, hospitals, universities, corporations, and government institutions have to be formed, and unified coordination structures must be established. These processes are complicated by regulatory demands for good manufacturing practice (GMP) labs and the development of specialized surgical and injection procedures, which requires cooperation between experts from highly divergent disciplines and backgrounds [4,58,59]. The formation of such standardized multicenter clinical trial infrastructures is time- and labor-intensive, and requires additional costs—in addition to the actual costs for the trial itself. This includes tasks and responsibilities for which most medical researchers have not received training nor have time to set up or implement [4,58,59]. As a result, regulatory approaches to stem cell research that have been constructed around the conducting of multiphase clinical trials, such as regulations in the EU and the USA, favor industry-sponsored clinical trials above investigator-sponsored (academic) trials, because large companies have both the financial and administrative resources to implement large-scale trials [23a]. Moreover, because autologous stem cell treatments, as mentioned above, do not typically offer a profitable business model for the pharmaceutical

industry, this type of regulation is also biased toward the use of allogeneic stem cells that can be scaled up and used as a standardized cellular product, which can be sold as a batch treatment similar to other drugs and medicinal products [58].

4.2 Advantages and Disadvantages of the Growing Number of Regulatory Exceptions and Exemptions

The medical sociologists Salter, Zhoum, and Datta have interpreted the growing number of regulatory exceptions and exemptions for cellular (and other advanced) medicine research that have emerged in recent years in the EU and the USA as a strategy through which national governments have altered regulatory frameworks and clinical methodologies to enable greater responsiveness to health consumer needs [24]. These health consumer needs, as has been reported in various publications from the EU and USA, have especially (1) accelerated and widened access to investigational treatment, (2) shortened the drug development and approval process, and (3) provided more affordable medicines [16,19,23a,49]. A fourth outcome has been the initiation of clinical studies, as well as patient access, for orphaned and rare diseases [23a,49]. Indeed, a disadvantage of the large-scale RCT system, not mentioned in the previous section, is that it is often not possible to conduct large phase 3 trials for treatments that target rare or orphaned diseases because sufficient number of patients cannot be recruited [60]. Regulatory schemes such as the "hospital exemption scheme" in Europe or the "compassionate use" schemes that have been issued by regulatory authorities in both the USA and the EU do partly fulfill these demands. They allow access to investigational drugs and biological products, including stem cell–based therapies, outside of the formal clinical trial process. Other exceptions such as the US "fast track approval" and "accelerated approval schemes" and in the EU the "conditional market approval" scheme allow a shortened clinical trial process, delivery of treatments to patients at an earlier stage, and potentially reduced costs.

However, there are also a number of disadvantages related to this growing number of regulatory exceptions. The EU hospital exemption scheme, for example, has been criticized because it has been implemented in very uneven ways across EU member states [24]. In some countries, the scheme has been used to approve large numbers of experimental interventions and has created "the opportunity for a legal market of authorized stem cell therapy products to emerge within the province of the clinical professionalism" [24]. There are various downsides to this growing space of clinical application outside of systematic clinical studies. If investigational treatments are more long term and applied to patients on a larger scale without more rigorous clinical evaluation in parallel, patients are potentially exposed to experimental interventions whose clinical utility is likely to be limited, and in the most extreme case to interventions that are ineffective and unsafe. A similar situation also applies to

the increasing number of right-to-try laws in the USA. If these laws result in the long-term availability of unproven or nonsystematically proven cellular interventions on a large scale and over longer periods of time, patients are potentially exposed to risky treatments and likely to invest their hopes and money into ineffective therapeutic strategies. But also the above-mentioned "fast track approval," "accelerated approval," and "breakthrough designation" schemes are likely to increase risks to patients, and to expose patients to adverse effects after market approval, which have not been identified in the process of clinical testing [30,61].

4.3 Advantages and Disadvantages of Tolerating Nonsystematically Proven Stem Cell Interventions Outside of Regulatory Systems

Tolerating nonsystematically proven stem cell interventions as found in various countries in Asia, but more recently increasingly in the USA [49], has enabled a large market of gray-area applications [62] that were provided to tens of thousands of patients worldwide [1]. The lenient and sometimes hesitant approach toward regulation, increased controls, and probation to these gray-area interventions has enabled a large number of physicians, hospitals, private clinics, and companies to pursue medical experimentation with stem cells, and in most cases on a for-profit basis [1]. A potential advantage of this leniency or flexible regulatory approach has been the stimulation of local innovation and economic opportunities, especially among researchers and clinics for whom adherence to the multiphase trial process and adoption of international norms such as GCP or good laboratory practice (GLP), and in some cases GMP, would be too expensive [5]. It is important to note in this regard that the mandatory use of international standards such as GCP, GLP, GMP, etc., creates new forms of social stratification [63]. While these standards create unity and order, which enables the coordination of large-scale clinical studies across multiple institutions and countries, they also create new boundaries of inclusion and exclusion. Indeed, in stringently regulated countries where regulatory rules are implemented consistently across institutions—researchers, hospitals, or companies who do not possess the resources to comply with these international norms are typically excluded from the development of new treatments. Especially in low and middle-income countries this situation is often seen to prevent domestic innovation and business opportunities, and favor scientists and companies from high-income countries [5]. Sleeboom-Faulkner has interpreted this "flexible" or "dual" regulatory approach that can be observed in various countries as a strategic attempt of national governments to serve the interests of less funded local researchers and hospitals on the one hand (by tolerating gray-area clinical applications and business practices outside of formal regulations) and the interests of domestic and international elite scientists and corporations on the

other hand (by introducing regulatory frameworks that comply with EBM and international best practice standards) [5]. Many companies and private clinics that have provided such gray-area applications have catered to the large demand of healthcare consumers who—often out of desperation—were willing to try and pay for these interventions [1].

However, there are disadvantages to tolerating unproven or nonsystematically proven experimental stem cell interventions outside of regulatory controls. A first challenge is, of course, that this situation has resulted in so-called "snake oil" applications, where patients have been subjected to false hopes, lies, loss of money, and sometimes severe adverse medical effects resulting from irresponsible applications. However, as Sleeboom-Faulkner has argued, most stem cell treatments offered to patients outside of clinical trials and the review of regulatory agencies, fall into a gray area between irresponsible "quack" applications and "bona fide" science [62]. Most of these clinical applications are at the very least intended to help patients, and contain at least some element of data collection, even though in many cases the boundaries between medical care and profit-making are closely intertwined [1,49,62].

Be this as it may, most of these gray-area applications do not offer reliable forms of treatment and are similar to "right-to-try" applications in the USA and stem cell interventions provided under hospital exemption schemes; the efficacy and safety of these treatments are typically far from established and reports of serious adverse effects have emerged [1,18]. The provision of these gray-area applications also risk harming the reputation of countries as science nations, and reduce the public's trust in science, medicine, regulatory controls, and the government in countries in which such interventions are provided on a large scale. This is especially the case when serious clinical accidents occur and in theory has the potential to undermine trust in stem cell medicine as a whole and reduce public support and funding, similar to the effects of the death of Jesse Gelsinger in the gene therapy field [64].

4.4 Advantages and Disadvantages of the Complete Abandonment of the Multiphase Trial System

Japan's radical shift away from the multiphase trial system has been widely interpreted as an effort to increase international competitiveness and to create an edge that would allow researchers and companies in Japan to translate Shinya Yamanka's creation of iPSCs into new treatments and economic profits before other countries. By radically shortening the clinical evaluation process and allowing conditional market approval after small number of patients, Japan's regulatory reform has enabled profit-making at a very early stage of the development process. By abandoning the need for costly multiphase trials, it has also drastically reduced the development costs for stem cell–based interventions. The Japanese model, no doubt, will appeal to researchers and companies in many countries, and these are likely to increase pressure on

regulatory authorities in their countries, which could lead to similar regulatory reforms also in various other parts of the world, including in the USA, Europe, as well as possibly in China, India, and other Asian countries. Another aspect of the Japanese approach to cell-based therapies is that it enables patients to access these interventions at a very early stage, instead of having to wait to a later stage of the clinical trial process, or even many years until a new medicine is formally approved and legally available on the market.

A problem with the Japanese model is that, as Sipp has commented, it "dramatically relaxes the requirement to demonstrate the clinical utility" of stem cell–based interventions prior to marketing [30]. Another problem is how to reliably assess efficacy during the conditional approval period [30]. This is a clear disadvantage. But also reliable testing of efficacy is a problem. How can safety reliably be proven in phase 1 trials, especially if adverse effects of stem cell treatments are likely to have long latency [30]. Another disadvantage arises from the fact that conditionally approved stem cell interventions are eligible for reimbursement by the Japanese health insurance system. While this model is seen as an alternative to traditional R&D payments (the reimbursed money shall provide revenues for companies to bridge the much feared "Valley of Death" between early phase trials and full market approval), to pay large amounts of money for medical products that lack solid evidence of efficacy and safety is likely to be a losing proposition [30,65].

The recently introduced 21st Century Cures Act in the USA has been met with similar concerns. By encouraging alternative forms of evidence outside of the multiphase trial, the Act will have a "profound effect on what is known about the safety and efficacy of medical products, as well as which ones become available for use" [66]. While certain aspects of the Act improve access to new drugs and biological products, including stem cell–based therapies, and are likely to reduce development costs, various challenges can be expected concerning the validation of clinical utility. As Kesselheim and Avorn point out: "among the most concerning sections of the new law are components that address the types of data that manufacturers will be able to use to gain FDA approval for new products" [16]. Aside from forms of evidence such as biomarkers and surrogate measures, which have been accepted by the FDA as supplementary evidence for some time, other forms of evidence have previously been seen as unacceptable, and indeed were ranked low on the evidence hierarchy of the EBM system. These include, for instance, the use of data from "patient experience" and "real world evidence" that comprise "information learned from observational studies, patient input, and anecdotal data" [67]. Kesselheim and Avorn state that the use of these forms of evidence has "the potential to expose patients to poorly effective treatments or unanticipated adverse effects" [16]. The US Public Citizen's Health Research Group and the National Center for Health Research who campaigned against the Act put it in even more drastic terms. The two organizations believe "the Cures Act, as it stands, will endanger public health by weakening FDA standards" [67].

However, while a previous version of the Act included a provision that would have allowed the FDA to approve stem cell treatments conditionally, without a final-stage phase 3 trial, this provision was not part of the final legislation. The signed Cures Act does not allow stem cell–based therapies and other regenerative medicine products to skip phase 3 trials [67]. However, the bill clearly promotes alternatives to the multiphase trial system and provides the possibility for accelerated approval for stem cell therapies (in the process of a phase 3 trial), if an investigational treatment indicates that it works [67].

5. ROADBLOCKS TO THE CLINICAL TRANSLATION OF NONHEMATOPOIETIC STEM CELL–BASED THERAPIES

A more general set of challenges for the clinical translation and use of stem cell–based therapies arise from the complexities of using living cells as therapeutic agents. This has various implications for the assessment of efficacy and safety of cell-based therapies [60]. The potential of stem cells for tumorigenicity, contamination, loss of viability, undesired cell migration, as well as immunogenic and autoimmune rejection by graft recipients, continues to be a challenge for both regulators and researchers conducting clinical studies. Another problem is the lack of knowledge around mechanisms of action. This is especially a handicap "for modifying clinical strategies to improve their actions" [68]. These scientific roadblocks have been summarized by others and will not be repeated in this chapter [68–70]. I mention these factors, however, because they are one of the reasons why the development of regulations for stem cell research has turned out to be challenging. Regulators across the world have addressed these challenges in different ways and set different priorities. Decisions had to be made, for example, about how much variation in cell behavior is acceptable, and in which ways and to what extent procedures for tracking cell behavior and migration should be applied [71]. This is one important reason why different regulatory responses have evolved across the world [72]. But what are the roadblocks and challenges that emerge from the increasing level of regulatory disunity and from other practical challenges that affect the clinical testing and application of nonhematopoietic stem cell therapies? This question will be answered now. Four roadblocks that affect the clinical translation of stem cell–based therapies will be introduced.

5.1 The Challenge of Navigating a Complex and Changing Regulatory Environment

The rapidly changing regulatory environment for stem cell therapies is cause of uncertainty and often confusion, which requires research, time, and specific skills to navigate. As Gardner and colleagues explain with the EU as an example, there are a myriad of legal instruments in the EU alone, which include not only the above-mentioned ATMP framework, but also guidelines on GMP and various

other aspects of the market evaluation process [60]. Then there is variation between EU countries. The hospital exemption scheme, as mentioned above, is implemented differently by different national level regulatory authorities, which offers opportunities in some EU countries that do not exist in others. In addition, the growing number of exceptions and exemptions in the EU also poses many questions to researchers, whether and when particular schemes can be used and whether these schemes also apply to stem cell–based treatments [60]. And it is only within the EU, where a harmonized regulatory environment for advanced cellular therapies exists. In the context of multicountry trials that involve institutions in countries with nonharmonized regulatory frameworks an even more complicated situation exists.

As we have noted elsewhere, the high level of regulatory variation in the stem cell field necessitates ongoing in-depth research from the earliest stages of preparing a clinical study. What is required is a long-term, comparative engagement with the regulatory frameworks and institutions in all countries in which a trial shall be conducted [73]. Differences between regulatory specifications in these countries must be identified early on, so as to develop trial protocols that comply with the demands from multiple jurisdictional frameworks. This process takes time, specialist knowledge, staff, and sometimes money for consultancy. It is complicated further by cultural differences, language barriers, and differences in the ways in which regulatory rules are implemented and enforced [58]. A related problem is that operation in contexts where regulatory rules are still evolving or are inadequately defined can result in long drawn-out delays, uncertainties with regard to the planning, execution, and successful completion of clinical trials and unexpected costs [4].

5.2 The Challenge to Develop Stem Cell Therapies in the Absence of Industry Funding

Seventy percent of all trials conducted in 2014 in the cell therapy field were investigator-initiated trials (i.e., trials conducted by academic researchers that received public funding) [68]. Only 30% of trials were sponsored by companies. The majority of these corporations were small to midsize biotech companies, who do not possess the same resources as large pharmaceutical companies. Investment by the pharmaceutical industry has remained at a low level, because even though significant achievements have been made in preclinical research, in the context of clinical trials "only a modicum of success" has been achieved [68]. This does not encourage a climate of intensive corporate investments.

For academic researchers, however, the dependency on public funding is a challenge. As the stem cell researcher Stefanie Dimmeler and colleagues have pointed out: "The lack of public funding for academics to work effectively in translation and the scarcity of venture capital finance for these relatively expensive studies have been, and will continue to be, major barriers to progress, unless public investment increases by recognition of the role of

academics and private capital returns to support life-sciences opportunities" [69]. The lack of corporate funding is a problem in particular, because well-established clinical trial infrastructures typically do not yet exist in the stem cell field. While in older research areas well-functioning research platforms have emerged over decades, in the stem cell field the development of clinical infrastructures is often still in its initial stages [4]. The formation of such infrastructures is cost- and labor-intensive, and the time required to build and organize these networks is not typically recognized by public funding schemes [69]. For stem cell trials, this also includes the building of standardized infrastructures for cell processing and manufacturing, including a logistical infrastructure for the transportation of cellular products from the manufacturing lab to the clinic, which can often include long distances [60]. For academic investigators and smaller- or mid-size biotech companies, it is particularly difficult to meet these requirements and costs, especially in the context of phase 3 trials. For researchers and corporations in low- or middle-income countries, this is even more of a challenge.

A closely related problem is that the existence of regulatory differences between countries often increases costs, especially for phase 2 and 3 trials that are conducted in two or more countries. To counterbalance regulatory gaps and to implement clinical research protocols in multiple institutions and countries in a standardized and trustworthy way requires intensive forms of capacity building, the training of clinical staff, as well as changes of locally evolved practices, medical equipment, and conditions in participating trial sites [58,59,73]. Unless sufficient funding for these forms of capacity building, training, and the preparation of trial institutions is set aside, the execution of larger trials remains a risky undertaking [73].

5.3 The Challenge to Demonstrate Clinical Utility of Stem Cell–Based Therapies

A more general challenge, as already indicated above, is that with the adoption of alternative methodologies and forms of evidence it may become increasingly difficult to determine the safety and efficacy of an investigational stem cell product or treatment. As Trounson and McDonald have stated: "The new regulatory pathway established in Japan, where products may enter the marketplace with provisional approval if [small-scale] studies show efficacy, will test the robustness of the entire global regulatory system. If products become available without testing for sufficient benefit then patients will not be served well by the evolving cell therapies" [68]. As mentioned in section III of this article, challenges with regard to the clinical utility of a treatment, can also be expected with other regulatory changes. If right-to-try laws in the USA, or the hospital exemption scheme in Europe, for example, results in the long-term

availability of nonsystematically proven cellular treatments, patients are exposed to increased risks and to invest their money in potentially ineffective treatments. But also accelerated approval programs, that cut short phase 3 trials, are likely to increase risks to patients and to approve therapies whose clinical utility may be contested and insufficiently proven.

5.4 The Challenge to Evaluate Stem Cell Therapies for Health Insurance Reimbursement

Another challenge, which is closely related to the previous point, is the challenge to evaluate health insurance reimbursement. While various stem cell–based therapies are gradually approaching market authorization, "such authorization is not determinative of whether the resulting technology represents a good investment from either commercial or health system perspectives" [56]. However, various reports have stated that current health technology assessment methods may be inappropriate for regenerative medicine products [60]. Assessment methods for health insurance reimbursement of a new treatment require a clear understanding of "what signifies value to payers of health technologies and services" [56]. These conceptions of healthcare value are typically based on solid clinical evidence that testifies to the efficacy and safety of a new treatment, and that demonstrates that the treatment creates a significant advantage to another existing treatment (if available) and can be offered to patients at an acceptable cost [23a]. These data were mostly provided from multiphase clinical trials. In light of the current process of regulatory diversification in the stem cell field that has been outlined and discussed in section II and III of this chapter, and the increasing shift away from multiphase RCTs and the introduction of new, alternative forms of clinical methods and forms of evidence, the standardized evaluation of the healthcare value of stem cell treatments is likely to become increasingly difficult. Possibilities to reliably assess efficacy and safety in the context of conditional market approval following small-scale trials as in Japan, accelerated (and shortened) phase 3 trials as in the EU and the USA, and the use of the new forms of evidence promoted by the 21st Century Cures Act are decreasing. The requirement to demonstrate the clinical utility of stem cell treatments prior to market approval is reduced with these regulatory changes, albeit to a varying extent.

The potential lack of reliable forms of evidence will likely pose a dilemma for insurance companies and government health insurance schemes. This is also a significant challenge for researchers and companies who invest in stem cell treatments themselves. If it is not certain what types of evidence are required to assure health insurance reimbursement, there is a chance that approved stem cell treatments will only be available on the private market and that private funding for investigational stem cell therapies is likely to be withheld.

6. CONCLUSIONS

The regulatory changes and developments introduced in section III of this chapter represent a gradual shift away from a pharmaceutics-oriented model of drug development that was based on the EBM and multiphase RCT system and has shaped the regulation of stem cell research in its initial phase, at least in the context of the EU and the USA, but also in many other countries. Alternative methods and forms of evidence are now accepted stepwise in many parts of the world and are likely to partly replace the multiphase trial model for the approval of stem cell–based interventions, as well as approval procedures in other evolving fields of medicine research. Whether this development will be to the ultimate benefit of patients, as many advocates of the 21st Century Cure Act in the USA (and advocates of similar changes in various other countries) have claimed, remains to be seen. Some argue that it is not, and that the current politics of alter-standardization, which is shaped by powerful economic and political interests, does misuse the desire of patients for more affordable and more rapid access to cures, by justifying potentially dubious research and irresponsible business practices [18]. Others have said that the growing acceptance of less rigorous standards and data do in fact increase health risks for patients, as well as risks for potential forms of financial exploitation [61]. This in turn could undermine trust in science and medicine at a broader level. Still others reason that many of the regulatory changes that have been introduced in this paper diminish hard-won ethical and methodological achievements, which have aimed to safeguard patients from potential misuse by the medical profession [66]. No matter where one stands in these debates, it seems safe to say that the line between the realization of new opportunities for patients and the emergence of new risks, dangers, and regulatory flaws is thin. Long-term monitoring of the regulatory changes described in this paper is required to obtain a clear idea of their implications for patients and healthcare systems.

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