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Global Diversification in Medicine Regulation: Insights from Regenerative Stem Cell Medicine

Achim Rosemann^{a,b}, Federico Vasen^{c,d} and Gabriela Bortz^{c,e}

^aDepartment of Sociology, Philosophy and Anthropology, University of Exeter, Exeter, UK; ^bCentre for Bionetworking, School of Global Studies, University of Sussex, Brighton, UK; ^cNational Council of Scientific and Technical Research (CONICET), Buenos Aires, Argentina; ^dInstitute of Education Sciences, School of Philosophy and Letters, Universidad De Buenos Aires (UBA), Buenos Aires, Argentina; ^eInstitute of Science and Technology Studies, Universidad Nacional de Quilmes (IESCT-UNQ), Buenos Aires, Argentina

ABSTRACT

Medicine regulation worldwide has undergone a process of regulatory diversification. The evidence-based medicine (EBM) paradigm, centered on multi-phase randomized controlled trials, is increasingly contested and replaced by new models of clinical validation. To explain these changes, STS research has cited just a few factors, e.g. growing pressure from health consumers; the role of pharmaceutical companies to lobby for fast, affordable drug development; the influence of neoliberal ideas and libertarian advocacy of deregulation; and the agency of national governments to enable domestic innovation opportunities in the context of global competition and inequalities. Those factors individually cannot account for the increasing variation in medicine regulation at both national and global levels. Instead it is helpful to integrate elements of existing explanations into a framework with four pairs of conflicting regulatory choices, which play a central role in the formation of medicine regulation. We use this framework to compare regulatory changes in the USA, European Union, China, India, Argentina, and Japan. Across these jurisdictions, the case studies illustrate four dynamics of diversification. Key regulatory concepts such as evidence, risk, safety, efficacy, responsibility and accountability acquire different meanings, reshaping medicine innovation in far-reaching and often contradictory ways. The boundaries between medical research and healthcare provision, commerce and humanitarian service, as well as state control and medical self-regulation are re-defined.

KEYWORDS

Science policy; regulatory conflicts; evidence-based medicine; clinical trials; health care provision; unequal development

Introduction

The regulatory landscape for the clinical testing and approval of new medicines is in the midst of a phase of change and global diversification. Calls for

CONTACT Achim Rosemann  a.rosemann@exeter.ac.uk

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deregulation and the introduction of more flexible and typically less costly regulatory requirements are now commonplace in many countries. The multiphase randomized controlled trial (RCT) system, for many years considered the gold standard of evidence-based clinical research, has increasingly come under pressure and is partly replaced by more affordable, less lengthy but often also less rigorous methodological alternatives.

Japan, for example, introduced a new regulatory framework in 2015 that radically shortens the drug development process. As a result of this change, investigational medicinal products, gene therapies and regenerative medicine product can be sold on the market on a conditional basis after an initial stage of clinical testing in as few as ten patients (Sipp, 2015). In the USA the *21st Century Cures Act* (2016) aimed to accelerate the approval of new medicines, by lowering requirements to go through rigorous, large-scale phase III trials (Hogle and Das, 2017; Kesselheim and Avorn, 2017) and by promoting methodological alternatives such as adaptive and other new trial designs (Montgomery, 2017).

Similar developments can be observed in other countries. India, for instance, eased rules for clinical research in 2016 and has reportedly halved the time for the approval and conduct of clinical studies, with further regulatory reforms to fast track clinical research currently underway (Raghavan, 2016). Also China is trying to speed up approval for innovative drugs and medicinal products. In order to develop its pharmaceutical sector, regulators initiated reforms in 2016 that aim to expedite the clinical research process and to accelerate market approval of urgently needed drugs (Deere, 2016). In both countries there has also been widespread support for the provision of innovative medical approaches outside of state controls and without preceding clinical trials (Rosemann and Chaisinthop, 2016). Regulatory changes in the European Union, on the other hand, have been less extensive, but health authorities have introduced a growing number of regulatory changes and exemptions in recent years, that have aimed to limit the duration and scale of phase III trials and to broaden access to investigational medicines (Faulkner, 2017).

These developments indicate substantial changes in the culture and politics of biomedicine today. In this paper we introduce an analytical framework to analyze and make sense of these regulatory changes in a comparative perspective. For this purpose we discuss four pairs of conflicting regulatory choices that play a central role in the formation of medicine regulation. The individual components of this framework are based on a survey of relevant STS and medical anthropology literature that provide theoretical perspectives on medicines regulation. We have focused in particular on texts that examine the drivers, interests and stakeholders that shape the regulation of new medicines, as well as writings that explore the role of global inequalities, international competition and frictions between internationally harmonized regulatory standards and local practices.

We use this framework to analyze recent regulatory developments in stem cell medicine. Controversies and calls for the use of alternative regulatory models in

the stem cell field have been at the forefront of regulatory debates also in other areas of medicine. In the USA, Europe, Japan, India and China, for instance, think tanks and lobby groups have used the case of stem cell medicine to campaign for regulatory reform, deregulation and the partial abandonment of the multi-phase controlled trial system in medical research at a wider level (Cooper and Waldby, 2014). Regulatory controversies in the stem cell field, in other words, provide an important analytical window into the global reshaping of regulatory and clinical realities in medical research.

This article compares regulatory developments for the clinical translation of stem cell-based treatments in six jurisdictions: Argentina, China, the European Union, India, Japan and the USA. The following questions underlie our analysis: How do recent regulatory changes in stem cell medicine diverge from the conventional model of EBM and the use of multiphase randomized controlled trials in international medicine research, and how do these changes vary across countries? Which tensions and consequences arise as a result of these changes?

In order to shed light on these questions we, first, introduce the heuristic framework. Then, in the empirical section we analyze the regulatory conditions and trends in the above-mentioned jurisdictions. In conclusion we wrap up the findings by answering the main questions and reviewing the theoretical contribution of this article.

Analytical Perspectives: Beyond EBM Models

To understand the broader process of global diversification that is currently taking place in medicine research, we have developed a heuristic framework that is structured around four pairs of conflicting regulatory choices that underlie the formation of medicine regulation. These conflicting choices, which become apparent especially in emerging technologies, require the weighing between diverse options that represent different benefits, risks, interests and values in terms of economic competitiveness and business profit, safety and efficacy control, and widening/restricting people's access to healthcare goods and services:

- International integration and access to global markets vs. the facilitation of local innovation and business opportunities
- Rapid development of and early access to new medicines vs. the systematic testing of safety and efficacy
- The realization of affordable medicines vs. the generation of corporate profits
- State led forms of regulatory controls vs. deregulation and scientific self-regulation

The development of new regulatory options requires strategic compromises between these conflicting demands, which result from complex negotiation

processes between stakeholders (e.g. firms, scientists, regulatory authorities, lobby groups, physicians, patients, investment groups, health insurances, etc.) that promote different visions of the future and bioeconomy-based development pathways.

International Integration and Access to Global Markets vs. the Facilitation of Local Innovation and Business Opportunities

The creation of a regulatory environment that facilitates participation in international research projects and that provides access to global markets is a high priority in many countries. International integration and the use of harmonized regulatory standards have been associated with the creation of new economic opportunities and possibilities for joint innovation (Van Zwanenberg *et al.*, 2011), increased availability of health related products and services, and the uncomplicated circulation of (biological) materials, patients and professionals (Parry *et al.*, 2015).

A problem arises, however, in that adherence to internationally harmonized standards is not always conducive to the realization of domestic innovation and business opportunities. Historically, large biotech corporations and pharmaceutical companies have welcomed regulatory harmonization. These large companies are well-resourced and benefit most from unified regulation (Petryna, 2009). For smaller companies or academic researchers, on the other hand, compliance with international scientific standards and regulatory requirements is often impracticable and unaffordable, especially in low-to-middle income countries (Sleeboom-Faulkner *et al.*, 2016). Hence, smaller entities in the biomedical sector as well as competitors in less wealthy countries often experience the adoption of internationally unified standards as a hindering factor, which impedes local innovation rather than generating benefits (Sleeboom-Faulkner, 2016; Hauskeller *et al.*, 2017).

The integration of local stakeholders into a standardized international biomedical sector, thus, gives rise to new forms of stratification that generate new patterns of inclusion and exclusion (Timmermans and Epstein, 2010; Knaapen, 2014). Locally evolved forms of innovation and value production that do not conform to these international standards are delegitimized and as a result often shut down (Birch, 2012). There is thus an inherent tension between the realization of international integration and access to global markets, which requires harmonized regulation, and the development and protection of domestic market and innovation opportunities, which necessitates a regulatory environment that corresponds to local needs, ambitions and available resources (Mikami, 2015).

Most governments seek to strike a compromise between these two aspirations, by creating a regulatory environment that seeks to facilitate participation in global projects and markets on the one hand, and the stimulation of domestic

innovation and business opportunities through flexible or locally specific standards on the other hand. Sleeboom-Faulkner *et al.* (2016) speak in this regard of ‘national home-keeping policies,’ a concept that refers to regional or national-level regulatory strategies that aim to revert and resist the exclusionist effects of international medicine regulations, by enabling localized approaches of medical research and commercialization that correspond to local ambitions, circumstances and available resources. This perspective enables the analysis of regulatory change as a response to the effects of dominant international standards in medicine regulation, and in relation to a variety of contextual factors that range from resource inequalities to differences in national development strategies, health care needs and regulatory cultures.

Rapid Development of and Access to New Medicines vs. the Systematic Testing of Safety and Efficacy

Another tension that underlies the formation of regulatory policies for medicine research emerges from the demands of citizens and patients to realize novel medical solutions rapidly. Health social movements have sought to influence the clinical research process in numerous countries (Rabeharisoa *et al.*, 2014). Many of these movements have organized around the issue of earlier and more far-reaching access to investigational products, often in the name of personal autonomy (Blasimme and Vayena, 2016) and social justice (Reardon, 2013).

These claims contradict the slow process of drug development, which requires the need to generate legitimated scientific evidence for the safety and efficacy of new treatments. A growing movement for right-to-try medicine (Jacob, 2015) – which demands early access to experimental treatments outside of the clinical trial system and before formal market approval – has put increasing strain on regulatory authorities. This has resulted in regulatory adjustments, and in some countries far-reaching revisions of drug policies (Salter *et al.*, 2015; Hogle and Das, 2017).

Salter *et al.* (2015) have argued in this regard that the global political economy of medicine research has been shaped by ‘biomedical hegemony’ based on the legal enforcement of evidence-based medicine standards and multi-stage trials by state agencies. However, this hegemonic system, which is closely intertwined with the global expansion of pharmaceutical research, is facing increasing tensions. While the mandatory use of EBM standards ensures the systematic evaluation of safety, efficacy and clinical utility, mounting pressure from consumer groups has given rise to calls for regulatory adjustments. Due to this pressure, Salter, Zhou and Datta suggest, governments have started to amend national regulatory frameworks, which has given rise to new models of medical innovation that stress informed consumer choice, earlier access to experimental

medical interventions, and the shortening of clinical evaluation procedures (2015, p. 156).

Demands for the acceleration of the drug development process have also come from the pharmaceutical industry, often in coalition with patient organizations and in the name of ‘patient empowerment.’ As Davis and Abraham (2013) point out, the pharmaceutical industry has been a driving force behind the adoption of fast track and accelerated review and marketing approval mechanisms in the USA and Europe, and this shift toward deregulation does not always coincide with patients’ interests.

Realization of Affordable Medicines vs. the Generation of Corporate Profits

The development of medicines that are affordable to people and national health insurance systems, is a requirement to achieve wide-ranging access to new treatments (Rawlins, 2010). This contrasts with the necessity of biotech and pharmaceutical companies to generate profits from new drugs that can be re-invested into research and development (R&D) or paid out to shareholders. At the same time, the costs of the drug development process have continually increased over the last few years, which has made it more difficult for corporations to amortize costs (Rawlins, 2010). But the rising costs of new drugs also clash with the fact that health insurance systems in many countries are under pressure. Highly constrained financial resources and demographic transformations – in particular, the expansion in ageing populations – have resulted in cuts in healthcare budgets and cost-containment measures (Kaplan and Porter, 2011).

While pharmaceutical companies have shaped, in important ways, drug regulations in high-income countries over the last three decades (Davis and Abraham, 2013), in recent years there has been increasing criticism from both healthcare regulators and the industry that the costs of clinical testing and market approval have become disproportional and that more affordable regulatory alternatives are needed (Rawlins, 2010; Montgomery, 2017). These demands have resulted in advocacy for alternative clinical trials, especially the use of adaptive trial designs, that allow for a greater level of flexibility and reduced costs and which have become increasingly common in mainstream drug research (Hogle and Das, 2017; Montgomery, 2017).

Thus there exists a tension between a commitment to the development of safe and efficient medicines that are affordable to patients and national healthcare systems, on the one hand, and the generation of sufficient corporate profits, on the other hand. It is noteworthy that regulatory responses to this problem are also influenced by differences in healthcare expectations. As Peters *et al.* (2008) have shown, patients’ expectations of healthcare vary considerably across societies. In high-income countries with well-established health care systems patients expectations for widely available, high-quality healthcare

services are usually much higher than in countries with less well-established healthcare systems. In most low-and-middle income countries, for example, the expectations of medical services are often lower on average and the acceptability of private payments as well as potentially ineffective and unsafe drugs is higher (Peters *et al.*, 2008). These factors influence regulatory decision-making, including the decisions taken by healthcare providers, companies and biomedical entrepreneurs (Sleeboom-Faulkner, 2016).

State-led Forms of Regulatory Control vs. Deregulation and Scientific Self-regulation

Regulatory controls for market approval of new medicines have in the last decades primarily lain in the hands of the state. Co-developed with the pharmaceutical industry, state-led regulatory procedures have stabilized product approval pathways and created a route to the market that has sought to protect the interests of patients, trial participants and drug producers (Roman, 2014). In recent years, however, calls for increased choice among patients and more affordable drugs have resulted in growing demands for deregulation and new forms of regulatory exemption and scientific self-regulation (Darrow *et al.*, 2015; Hogle and Das, 2017).

New alliances and networks of patient organizations, researchers, private clinics and small-to-mid size biotech companies have sought to maximize experimental and clinical freedoms, and to minimize the controls of drug regulatory agencies and the high costs and restrictions that characterize the formal drug approval process (Rosemann and Chaisinthop, 2016). These demands go beyond the pharmaceutical industry's attempts to lobby for accelerated review and market approval (as referred to above), in that they seek to legitimate profit-oriented experimental medical intervention independent of the review procedures of drug regulatory agencies and outside the EBM paradigm.

Patient organizations, free market health advocates and professional lobby groups that include private clinics and smaller biomedical enterprises have advocated for access to experimental medicines on the basis of a market-driven logic of supply and demand, under new forms of scientific and professional self-regulation (Turner and Knoepfler, 2016). For example, in more than 30 US States these claims have resulted in right-to-try laws that enable access to investigative medical strategies after preliminary forms of safety testing. Patients are liable for all costs and consequences of these experimental treatments, including expenses from negative adverse effects (Darrow *et al.*, 2015).

Similar developments can be observed in other countries (Rosemann and Chaisinthop, 2016). Many experts and government agencies are critical of these developments, however, and states and state-led regulatory authorities have a sustained interest in continuing to regulate and control access to new medicines. That being said, the debates and types of regulatory responses

through which a balance between state and market-led forms of medicine regulation is sought to be realized differ widely between countries.

Four Dynamics of Regulatory Change: Comparative Study

Integrating previous STS explanations, this section analyses plural divergences from the EBM model through regulatory changes in six jurisdictions: Argentina, China, the European Union, India, Japan and the USA.

Pharmaceutical-oriented Model of Cellular Therapy Development¹

The first regulatory frameworks for cell and stem cell therapies evolved in the USA and the European Union in the mid-2000s. Regulatory authorities in both the USA and the EU initially opted for a ‘cells-as-drugs’ approach for stem cell treatments, which has been modeled on a pharmaceutical-based model of clinical testing and market approval. This approach is committed to the evidence-based medicine system and the use of multi-phase clinical trial system, with the randomized controlled trial (RCT) as gold standard. It also involved compliance with international best practice guidelines such as GCP (good clinical practice), GTP (good tissue practice), and GMP (good manufacturing practice). These guidelines were initially designed to control the authorization and licensing of drug products by the pharmaceutical industry (Carson and Dent, 2007).

The USA was the first country to issue a formal regulation for the clinical use and market approval of stem cell interventions. FDA regulations went into effect on 25 May 2005 with the interim rule *Human Cells, Tissues, and Cellular and Tissue-Based Products: Donor Screening and Testing, and Related Labeling* (FDA, 2005). On 19 June 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) (FDA, 2007). This regulatory framework introduced a risk-based, tiered approach that regulates stem cells as biological products within two categories: ‘351 products’ and ‘361 products’ (FDA, 2007).

The ‘361’ category refers to minimally manipulated stem cells that are applied for homologous use. ‘361’ cells are considered as low-risk and are exempt from pre-market approval by the FDA. They can be used in patients under compliance with the US human tissue regulation (Sipp and Turner, 2012). The ‘351’ category, on the other hand, refers to cells that are more than minimally manipulated and to cells that are used in a non-homologous manner. These cells are classified as a biological drug product and they are subject to US Food and Drug Administration (FDA) pre-market approval. ‘351’ biological products (which comprise the majority of stem cell interventions) must ‘by law [...] go through the multi-phase drug pipeline approval process starting after pre-clinical studies with an Investigational New Drug (IND) application

and proceeding to Phase I trials' and then to Phase II and III trials (Knoepfler, 2015). With this commitment to rigorous EBM principles and the methodological standards of industry-sponsored drug trials, US regulators have prioritized a slow development process that requires systematic evidence for safety and efficacy.

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 non-homologous 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 (EMA, 2015). 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.

Salter, Zhou and Datta have interpreted the emerging of these regulatory models in the EU and the USA as a 'hegemonic [...] science-based paradigm of stem cell innovation,' that is grounded into the scientific, regulatory and economic history of high-income countries (2015, p. 156). This 'biomedical hegemony of expertise, governance and values' (Salter *et al.*, 2015, p. 156) has also informed the adoption of a 'cells-as-drugs' regulatory approach in other countries.

In India, for example, the Drug Controller General India (DCGI) announced in 2014 that stem cells were to be treated as a drug product and that clinical trials and pre-market approval had to conform to the Indian Drugs and Cosmetics Act, which included a new section on stem cells (Tiwari and Raman, 2014). With these adjustments, the regulation of clinical stem cell research was put under statutory law and – at least on paper – subjected to the same methodological requirements as pharmaceutical research (Tiwari and Raman, 2014). In practice, however, regulatory requirements are not implemented evenly. As we show below, a highly flexible situation exists; stem cell trials continue to be conducted outside of DCGI control and unapproved for-profit interventions with stem cells are offered in many hospitals (Bhagavati, 2015).

In Argentina, on the other hand, stem cell interventions have until now not been regulated as medical products but as a medical procedure, which are managed by the Argentinean Transplant Act under the authority of the Unique Central Institute for Ablation and Implantation (INCUCAI), a subunit of Argentina's Ministry of Health. However, and as in the USA and the EU, all types of stem cell therapy (with the exception of hematopoietic cell transplants from human bone marrow) are considered investigational in Argentina and therefore require evaluation of safety and efficacy through multi-phase

trials (Arzuaga, 2013). At present, the clinical use of stem cells is regulated under the Ministerial Resolution No. 610/2007 from the Argentinean Ministry of Health. However, this situation is gradually changing (Arzuaga, 2013). In 2011, regulation 7075/2011 of Argentina's National Administration of Drugs, Food and Medical Technology (ANMAT) decided that more than minimally modified cellular products should be classified as Advanced Therapeutic Medicinal Products (ATMP). This is a clear shift toward the adoption of the US-European model. At present, though, ANMAT has still no legal authority to enforce approval of stem cells treatments under its rule, and it has not been decided in which situation researchers should apply at ANMAT or INCUCAI (Arzuaga, 2013; MSTIA, 2016).

In China a different situation exists. The development of a regulatory framework for clinical stem cell applications has been a long and ongoing process in China, and considerably slower than for instance in the EU or USA. As in India, a large market of experimental for-profit interventions with stem cells emerged in the early 2000s, which were offered to patients outside of state control (McMahon, 2014). After several attempts to address this situation (Sui and Sleebloom-Faulkner, 2015), the Chinese National Health and Family Planning Commission (NHFPC) and the China Food and Drug Administration (CFDA) jointly issued the *Regulation for Clinical Stem Cell Research* in 2015. This regulation states that the clinical translation of stem cell-based approaches must occur through systematic clinical studies, which must follow from sound pre-clinical evidence.

With this evolving regulatory approach the Chinese authorities have taken a vital step toward international integration and compliance with regulatory requirements in the USA and EU; a step that is conducive for international trial collaborations and multi-country approval of stem cell treatments developed in China. At present, there are still numerous unresolved questions with this framework. A first set of questions concerns the exact methodological requirements that will be required in pre-market evaluations. In the 2015 guidelines, this point remained undefined, and updated information has so far not been published (Chen, 2017).

It is still unclear whether stem cells shall be regulated as a pharmaceutical product or a medical technology or procedure, and also which types of clinical studies the NHFPC and CFDA require before approving routine clinical use. The 2015 regulation only speaks of 'clinical studies' that shall be conducted according to 'scientific principles,' but the precise nature of these 'principles' remains undefined (Rosemann and Sleebloom-Faulkner, 2016). A second set of questions concerns implementation; it is at present not clear whether the Chinese authorities have the political will to mobilize sufficient resources and administrative infrastructures to consistently implement this new regulatory model (Rosemann and Sleebloom-Faulkner, 2016; Chen, 2017; Zhang, 2017).

Research on the Internet suggests that unapproved for-profit interventions continue to exist next to formally approved clinical trials.

In Japan, pre-market evaluation of stem cell therapies was initially based on a similar regulatory model as in the USA and EU. Until 2013, stem cell interventions were regulated under the *Pharmaceutical Affairs Law* (PAL) and treated either as pharmaceutical drug products, medical devices or combination products (Azuma, 2015). This regulatory pathway involved systematic multi-phase trials and compliance with good clinical practice (GCP) standards (Azuma, 2015). Then in 2013, in order to capitalize on the therapeutic promise of induced pluripotent stem (iPS) cells, the Japanese government abandoned its commitment to the EBM multi-phase trial approach by introducing a radical regulatory reform that allowed for conditional, limited-term market approval of stem cell products after early-phase clinical trials (Cyranoski, 2013).

The adoption of a pharmaceutical-oriented regulatory model for cellular therapy development in the USA, EU, India, Argentina and initially in Japan has formed a basis for international harmonization, which facilitates multi-country trials and cross-border marketing. Efforts 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 (ISSCR, 2016) or by the ATMP Cluster of the US Food and Drug Administration (FDA), EMA and Health Canada (Arcidiacono *et al.*, 2012). With its commitment to the EBM system, the use of multiphase controlled trials and the adoption of industry standards (such as GCP, GMP and GTP), the ‘cells-as-drugs’ regulatory approach favors a slow development process, which prioritizes long-term safety and systematic evidence of the efficacy of stem cell-based treatments (Knoepfler, 2015; Hogle and Das, 2017).

However, as regulations for the market approval of pharmaceutical products, a ‘cells-as-drugs’ approach favors the commercial interests of large companies, above the interests and possibilities of academic investigators (Faulkner, 2017). Large companies have both the financial means and the administrative resources to implement large-scale trials, while academic researchers and smaller biotech companies do typically struggle or fail to fund such trials and to comply to the regulatory requirements that a ‘cells-as-drugs’ approach entails (Hauskeller *et al.*, 2017). However, by seeking to serve the commercial interests of large commercial stakeholders, a pharmaceutical-based regulatory model for cellular therapy does not only disadvantage and exclude smaller stakeholders, it also increases the costs of the development process of cellular treatments (Savage, 2015). Considering the high developments costs of many stem cell treatments, it is still uncertain whether and what types of therapies will eventually meet the cost-effectiveness criteria of public health care systems in different countries and to what extent patients will be able to access these treatments on the private market (Tabar and Studer, 2014).

Emergence of non-standard pathways for market approval

The second dynamic of regulatory diversification that we describe in this article is the surfacing of an increasing number of exceptions and exemptions (Faulkner, 2017) in the regulation of stem cell and regenerative medicine. These non-standard pathways for market approval have emerged either as alternatives to or as adjustments of the ‘cells-as-drugs’ regulatory approach. These complementary regulatory strategies have been designed and are implemented by national-level drug regulatory authorities. By lowering regulatory standards and by enabling alternative forms of clinical testing, these strategies seek to integrate a wider range of stakeholders into the innovation process, and also to increase access to investigational treatments at an earlier stage and to a larger group of patients (Salter *et al.*, 2015; Faulkner, 2017).

In the USA, the FDA has introduced three types of non-standard pathways since 2012, which can also be granted to human cell and tissue products (Knoepfler, 2015). These regulatory exceptions aim at: (1) speeding up the transition from preclinical to clinical testing (‘fast track approval’) (FDA, 2017a); (2) accelerating the authorization of phase I and II clinical trials that involve seriously ill patients with low life expectancy (‘accelerated approval’) (FDA, 2017b); and (3) more rapid clinical testing of ‘breakthrough therapies’ that have the potential to treat a serious or potentially life threatening disease (‘breakthrough therapy designation’) (FDA, 2017c).

In addition to these recent regulatory exceptions, the FDA also operates a ‘priority review’ procedure, which was introduced in 1992. Priority review aims to expedite the duration of the evaluation process that precedes market approval of a new drug (six instead of ten months), after the completion of the clinical trial period (FDA, 2017d). A fifth exception is the ‘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 II and III clinical trials (FDA, 2017e). 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 (FDA, 2017f).

In the EU, the EMA introduced a similar range of non-standard pathways. For example, the EMA has also introduced a ‘compassionate use’ program, which allows access to new drugs and biological products (including stem cell products) outside of premarket clinical trials (EMA, 2017a). More recently, the EMA has introduced a ‘conditional market approval’ scheme (EMA, 2017b), which can be used also for stem cell interventions. According to this scheme, a stem cell product can be licensed at a later stage of a phase III trial, when data collection for efficacy and safety has almost been completed.

Unlike in the USA, however, the EMA introduced a so-called ‘hospital exemption’ program for stem cell interventions. This program allows for the

provision of cellular medicinal products to individual patients ‘in a European hospital under the exclusive professional responsibility of a doctor’ (MacGregor *et al.*, 2015). 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 (Faulkner, 2017). 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 authorised stem cell therapy products to emerge within the province of the clinical professionalism’ (Salter *et al.*, 2015, p. 165).

Salter *et al.* (2015) explain the rising number of regulatory exceptions and exemptions in the EU and USA as resulting from the growing influence of health consumers, who challenge ‘the hegemony of the science-based paradigm of stem cell innovation through the exercise of their demand in a global market’ (p. 162). This challenge, according to the authors, has resulted in gradual forms of ‘hegemonic adaptation,’ through which governments have amended national regulatory frameworks to ‘enable greater responsiveness to health consumer needs’ (Salter *et al.*, 2015, p. 162). Faulkner (2017) has also pointed out that the ‘hospital exemption scheme’ in the EU has been designed to enable more localized, physician-based forms of clinical innovation, so as to counter the ‘industry bias’ that underlies the EMA’s ATMP regulation.

While these explanations account for the situation in the USA and EU, they do not necessarily apply to the emerging of regulatory exceptions and special rules in other countries. In Argentina, for example, regulatory exceptions that have enabled the provision of stem cell interventions outside of multi-phase trials (which are required by the country’s national-level regulatory authorities) have emerged for a different reason. Because Argentina is a federal country in which national regulatory authorities have legal power only when medical products cross its provincial borders or are involved in foreign trade, federal regulations are not applicable at the provincial level. This means that as long as medical treatments or services are applied exclusively within the geographic jurisdiction of the different Argentinean provinces, federal regulations have no legal power and only provincial regulations apply (Arzuaga, 2013, p. 41). As a result, there is currently no effective control over stem cell-based clinical applications within the different Argentinean provinces, as long as these interventions are not offered to patients from other provinces, or are not shipped across provincial or state borders (Krmpotic, 2011).

Non-standard pathways that aim to accelerate the clinical innovation process have also emerged in China and India. The Drug Controller General of India (DCGI) eased its rules for clinical research in 2016, and has reportedly halved the time for clinical testing and market approval; further regulatory reforms to fast track the clinical development process are currently underway (Raghavan, 2016). China has also tried to speed up the approval of innovative drugs and medicinal products. In order to develop its domestic pharmaceutical sector, in

2016 Chinese regulators initiated reforms aimed at expediting the clinical research process and speeding up market approval of urgently needed drugs (Deere, 2016).

Regulatory exceptions and exemptions have played an important role in the growing availability of stem cell-based treatments outside the multi-phase trial process in the USA, EU, and, for different reasons, Argentina. In contrast, in India and China the widespread availability of unproven or non-systematically proven stem cell treatments can be explained through the flexible implementation, and at times complete disregard, of existing regulatory rules.

Flexible Enforcement of Regulatory Standards

A third dynamic of regulatory diversification that can be observed in the stem cell field is the flexible enforcement and non-observance of regulatory requirements, which has enabled the long-term provision of experimental for-profit interventions with stem cells outside of the review and control structures of regulatory agencies. This has happened for several years in India and China, where governments responded only gradually to a flourishing grey-area market in experimental stem cell interventions (Sleeboom-Faulkner *et al.*, 2016). These developments are not only restricted to the stem cell field, but exist also in other areas of experimental medicine (Holdaway *et al.*, 2015).

Unapproved for-profit therapies continued to be tolerated in these two countries even after the introduction of national regulatory frameworks that formally prohibit stem cell interventions outside of formally approved clinical trials. As mentioned 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 pre-clinical evidence (Rosemann and Sleeboom-Faulkner, 2016). 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 (Rosemann and Sleeboom-Faulkner, 2016). If this rule would be implemented, it 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 (Rosemann and Sleeboom-Faulkner, 2016).

In India, the 2013 *Guidelines for Stem Cell Research* (and previously the 2007 *Guidelines for Stem Cell Research and Therapy*) have formally prohibited the use of stem cells in human patients, except in the context clinical trials approved by India's health authorities (Viswanathan *et al.*, 2013). Despite these formal regulatory prohibitions, however, large private hospitals and medical corporations have continued to offer their services on the Internet in both countries.

Of interest here is the fact that the toleration of unapproved stem cell therapies is by no means limited to middle-income countries, but can also be

observed, more recently, in the USA. In recent years, the FDA has taken a more relaxed approach to clinics that have offered autologous stem cell interventions to patients, which have sprouted all over the country over 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 (Turner and Knoepfler, 2016). This large number of clinics is expected to grow further, with a growing number of right-to-try laws in the USA and recent regulatory changes introduced by the *21st Century Cures Act*, which will be discussed in the next section.

Salter (2008) has interpreted the lenient regulatory environment for stem cell research and therapies in China and India as a deliberate strategy to situate these countries in a new and competitive global market, in which these countries had traditionally little or no experience. Sleeboom-Faulkner (2016) has in this regard pointed out that both India and China have sought to pursue a ‘flexible’ or ‘dual’ regulatory strategy that aims to serve the interests of scientific and corporate elites in these countries (by providing possibilities for formal regulatory approval that would allow for international trial collaborations and cross-border marketing), and less well-funded local researchers, hospitals and corporations (by tolerating gray-area clinical applications and business practices exterior to formal regulatory rules).

Linear logics of bench-to-bedside translation strategies are, as a result of this flexible and regulatory approach, often reversed (Chen, 2017). Promising approaches with new cell types are often tested first in patients, then explored further in the laboratory, and subsequently back to the clinic, either as for-profit experimental interventions, or in the context of more systematized pilot studies or clinical trials (Rosemann and Sleeboom-Faulkner, 2016; Prasad, 2017).

However, the flexible enforcement and sidelining of regulatory requirements comes at a cost. While it enables localized clinical innovation among less well-funded researchers and corporations, and provides rapid access to potentially helpful treatments for patients, these treatments mostly do not result in conclusive evidence of efficacy and safety (Zhang, 2017). Even though real ‘snake oil’ applications may in fact be rare, the risk of exposure to ineffective and unsafe interventions, and also the risk of financial exploitation of patients increase in such an environment (Lysaght, 2017). Other risks of the flexible implementation of regulatory rules are reputational risks (Salter, 2008), as well as a loss of trust in the regulatory capacities of the government, including among scientific elites and corporations in these countries (Zhang, 2017).

Abandonment of the Multiphase Trial System

The fourth and most far-reaching process of regulatory diversification that is currently taking place in biomedical research is characterized by the complete abandonment of the multiphase trial EBM system. This is exemplified most drastically in Japan's regulatory reform of the translational pathway for investigative medicines, devices, gene therapies and regenerative medicine products, as well as in the introduction of the *21st Century Cure Act* in the USA.

In May 2013 the Japanese National Diet passed the *Regenerative Medicine Promotion Act* [RMPA] (Government of Japan, 2013a), which formed the starting point of a radical regulatory reform. The RMPA was followed by the passing of the *Amended Pharmaceutical Affairs Law*, which went into effect in November 2014 (Government of Japan, 2013b; Sipp, 2015). Under the amended PAL the conditions for the clinical application of stem cell interventions changed significantly (Azuma, 2015). 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 ten patients (Cyranoski, 2013), provided these first-in-human-trials demonstrate that the tested cell products are safe and 'likely to predict efficacy' (Sipp, 2015). Once approved by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), clinical trial sponsors have the possibility to seek market approval for up to seven years (Sipp, 2015). Clinical efficacy is tested in this time period in post-marketing procedures (Miyata, 2013).

This is a significant shift away from the multiphase RCT system, which has emerged as the methodological gold standard in medicine 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 medicine research.

It is noteworthy that conditionally approved stem cell interventions are eligible for reimbursement by the Japanese health insurance system (Government of Japan, 2013a). Costs for these experimental treatments are split between the state and patients at a ratio of 70:30 (Sipp, 2015). This is a significant change to the financing of research and development (R&D) costs for medicine research, which typically requires long-standing corporate or government investments before development costs can be recouped through health insurance reimbursement and consumer charges.

According to Sipp (2015), this evolving regulatory model in Japan has 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 (2015) points 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.' It is likely 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 I-III trials.

In fact, exactly this has now happened in the USA. 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 III trials (Kesselheim and Avorn, 2017) and by promoting methodological alternatives to the multi-phase trial system, such as adaptive and other new trial designs (Montgomery, 2017). The passing of the Act in December 2016 has the potential to lead to a transition into a post-RCT world, which will impact the development of stem cells and many other medical treatments.

As Kesselheim and Avorn (2017) state, advocates have praised the Act as a ‘means of speeding drug development’ and to decrease ‘the cost and duration of drugs and devices development. This has involved various provisions designed to ‘reduce the amount and rigor of clinical testing before new drugs and devices can be approved for use’ (Kesselheim and Avorn, 2017). 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 (Kesselheim and Avorn, 2017).

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 are handled in practice. A related development in the USA has been ‘right-to-try’ legislation at the State level, which offers patients and physicians the choice to use not yet approved investigational drugs (including cellular medicines) entirely outside of the regulatory control of the FDA (Darrow *et al.*, 2015).

Japan’s shift away from the multi-phase trial system has been interpreted as an effort to increase international competitiveness (Lysaght, 2017) and to create an edge that would allow researchers and companies in Japan to translate Shinya Yamanka’s discovery of iPS cells into new treatments and economic profits before other countries (Mikami, 2015; Sipp, 2015). By shortening the clinical evaluation process and allowing conditional market approval after small numbers of patients, Japan’s regulatory reform enables profit making at a very early stage of the development process (Lysaght, 2017). By abandoning the need for costly multiphase trials, it also reduces the development costs for stem cell-based interventions.

The Japanese model, no doubt, will appeal to researchers and companies in many countries, which will likely increase pressure on other national regulatory authorities to make similar regulatory reforms. Moreover, as with the *21st Century Cure Act*, the Japanese approach to cell-based therapies enables patients to access these interventions at a very early stage, instead of having to wait until

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.

Discussion

This article asked firstly: How do recent regulatory changes there diverge from the EBM model, and how do these changes vary across countries? And secondly, what tensions and consequences arise as a result of these changes? These are discussed below in turn.

Divergences from EMB Model

Regarding the first question, our findings indicate that the regulatory conditions that lead to the routine clinical use and commercialization of new medical interventions are subject to far-reaching changes. Although the EBM model is still influential, it is increasingly contested and being partly replaced. While our empirical analysis has focused on regulatory developments for stem cell-based medical treatments, the described changes represent a wider process of diversification that is currently taking place in the regulation of medicine research at a global scale.

In the six jurisdictions we analyzed, four different dynamics of regulatory change could be observed with reference to stem cells. The first is the emergence of a pharmaceutical-oriented model of cellular therapy development, with the multi-phase trial system remaining at the core. The origins of this model lie in the USA and EU, where regulators in the mid-2000s developed a regulatory approach for stem cell medicine modeled on the clinical evaluation of pharmaceuticals. In the early 2010s, this ‘cells-as-drugs’ approach was adopted by regulatory bodies in Argentina, Japan, and, at least at the level of intent, in India and China. With the exception of Japan, where regulators initiated a different regulatory approach in 2013, the ‘cells-as-drugs’ model remains influential in these jurisdictions for corporate-sponsored research, which targets the development of ‘off-the-shelf’ stem cell products.

A second process of regulatory change was the emerging of a growing number of non-standard pathways for market approval that accelerate and shorten clinical evaluation procedures, and in some cases enable clinical innovation and for-profit applications without the use of multi-phase trials. These regulatory exceptions and exemptions have emerged especially in strictly regulated high-income countries such as the EU and USA. New rules to fast-track clinical testing have more recently also been issued in India, China and Argentina. These non-standard pathways are partly the result of pressure from the pharmaceutical industry to ease regulatory rules for drug development (Montgomery, 2017), partly the outcome of pressure from patients and consumer organizations to increase access to investigational treatments (Salter *et al.*, 2015), and partly the effect

of criticism from professional medical organizations that seek to enable more localized, physician or hospital-based forms of innovation (Cooper and Waldby, 2014; Faulkner, 2017).

A third regulatory development was the flexible enforcement of regulatory standards, which allows local clinics and companies to circumvent regulatory rules. The toleration of clinical for-profit interventions that disregard regulatory requirements has emerged especially in low-to-middle income countries, with India, China, and Argentina, at a provincial level, as examples. Salter (2008) argues the flexible handling of regulatory controls in such rapidly developing countries is a way to increase competitiveness in an environment where regulatory conditions are mainly shaped by transnational corporations and regulatory authorities of high-income countries.

In a related argument, Sleeboom-Faulkner (2016) stresses that for many researchers in low-to-middle income countries participation in highly expensive 'bona fide' projects remains out of reach. Participation in 'grey area' research and applications is, for many stakeholders, the only feasible way to take part in the innovation process. From this perspective, the adaptable enforcement of regulatory standards simultaneously facilitates international integration and local innovation practices that would be delegitimized if (inter)national rules were strictly enforced (Timmermans and Epstein, 2010; Sleeboom-Faulkner *et al.*, 2016).

The fourth type of regulatory change that this article has described was the abandonment of the multi-phase trial EBM system. This has happened with Japan's regulatory reform in 2013, in which the translational pathway for investigative therapies, devices, gene therapies and regenerative medicine products is shortened and conditional market approval is permitted after clinical tests in small numbers of patients. More than three years after the introduction of Japan's regulatory reform, the *21st Century Cures Act* in the USA has introduced similar changes that enable commercialization before large-scale phase III trials, and permit the use of alternative, less rigorous forms of clinical evidence that was previously unacceptable for FDA approval procedures. Moreover, with the continuing expansion of 'right-to-try' legislation in the USA, growing numbers of patients can now gain access to investigational medical interventions at an early stage of the clinical testing process, outside of FDA controls.

As pointed out by Hogle and Das (2017), these changes disrupt long-held beliefs about what counts as credible data and the methodological procedures through which evidence is constructed. Nevertheless, the drivers that underlie these changes in the two countries vary. In Japan, on the one hand, regulatory hurdles have been flattened to facilitate the clinical development and commercialization of induced pluripotent stem cells (a domestic discovery) and to position the country as a global leader in this field and for other innovative treatments (Mikami, 2015). In the USA, on the other hand, the shift away from the EBM/multiphase RCT system has been driven by long-term advocacy for deregulation and free market healthcare and pressure from patient

organizations (Cooper and Waldby, 2014), as well as lobbying by the pharmaceutical industry, in an attempt to reduce drug development costs and to sell drugs to consumers faster (Montgomery, 2017).

Tensions and Consequences

Which tensions and consequences arise as a result of these changes? To answer this question we draw on the analytical framework introduced earlier, which discussed a set of conflicting choices that play key roles in the formation of medicine regulation. In each of the four regulatory developments that this article has described, the research process and regulatory rules that lead to commercialization and routine clinical applications vary significantly. Key regulatory concepts such as evidence, safety, risks, efficacy, responsibility and accountability acquire different meanings. This is reflected in the adoption of conflicting methodologies and regimes of evidence, differing processes of audit and peer review, and the use of divergent ethical and safety standards. These differences result in tensions between different types of practices and stakeholders and have implications for knowledge producers, national governments, health care systems and patients.

The ‘cells-as-drugs’ approach, which is based on the EBM/multi-phase trial system, favors especially the interests of large biotech and pharmaceutical companies as well as well-funded researchers, mostly in high-income countries. Because multi-phase trials can be conducted in a standardized way across multiple institutions in different countries, this approach facilitates international integration, collaboration and market approval of new medical interventions in multiple jurisdictions.

However, and as Timmermans and Epstein (2010) point out, international harmonization of regulatory standards stratifies social systems and can result in new forms of exclusion. The global diffusion of the standardized EBM/RCT system, for example, has threatened the autonomy of individual practitioners, which has precluded and delegitimized physician-based forms of experimental medical practice (Knaapen, 2014). In the stem cell field, this has resulted in a power struggle between different professional groups, which has driven processes of regulatory diversification at both national and international levels.

At a national level a struggle exists between the regulatory needs of large corporations and academic elite researchers who benefit from participation in the EBM/RCT system, and researchers, clinics and smaller corporations who do not have the means to conduct multi-phase trials. The growing number of regulatory exceptions that this article has discussed and the use of new clinical methodologies as introduced by the *21st Century Cures Act* in the USA and the conditional approval system in Japan all seek to address and solve this tension; for example, by allowing new types of practitioners (individual

physicians, academic researchers, small-to-mid size companies, private hospitals) to take part in the clinical innovation process.

At an international level, a conflict of interest exists between medical researchers and companies in low-to-middle income countries and high-income countries. This explains why opposition to the international EBM/RCT system has been especially pronounced among innovators in less wealthy countries, whose business practices, livelihoods and clinical interventions are threatened by regulatory standards from high-income countries.

Both, the creation of new regulatory exceptions/exemptions and the flexible enforcement of regulatory standards indicate a shift towards deregulation and increased self-governance. The hospital exemption scheme in the EU and the growing number of right-to-try laws and more independence for individual medical practitioners in the USA suggest that – outside of the regulation of pharmaceutical drugs – state intervention is downsized and partly replaced by more market-oriented medical interventions and self-regulation by medical institutions and associations.

A consequence of deregulation is, however, that the oversight of experimental medical interventions are shaped and enacted by professional networks with vested interests, which can undermine scientific credibility and public trust. For patients, deregulation and the acceptance of less rigorous methodological standards creates a tension between earlier and more widespread access to potentially helpful treatments and higher risks of adverse effects and financial as well as psychological exploitation. Less regulatory oversight and the acceptance of less reliable forms of clinical evidence mean also less certainty regarding the efficacy and clinical utility of new treatments.

Conclusion

This article has analyzed regulatory developments in stem cell medicine, especially divergences from evidence-based medicine (EBM) paradigm, centered on the multi-phase RCT system. It compared changes in and across six jurisdictions (USA, EU, China, India, Argentina, and Japan). Summarizing answers to our main questions: Amidst far-reaching regulatory changes, the EBM model is still influential but is being partly replaced. Across the six regulatory jurisdictions, the case studies illustrate four dynamics: pharmaceutical-oriented models of cellular therapy development, non-standard pathways of market approval, flexible enforcement of regulatory standards, and replacement of the multi-phase trial (EBM model). These changes involve tensions around four pairs of conflicting regulatory choices (see previous sub-section for details).

In informing debates on the changing politics of evidence and legitimization in medicine research, this article has wider implications for the Science and Technology Studies literature on medical regulation. A first point is that, in order to understand the process of global diversification that is currently

taking place in medicine regulation, more comparative research is needed that can account for different regulatory approaches and that is able to explain why some countries choose one approach and others another. Single-country studies, or a primary concern with developments in high-income countries, fall short in this regard because they highlight factors that are significant within individual countries, but may overlook aspects that are relevant in other countries. A comparative framework also enables the identification of transnational patterns and developments and analysis of legislative and regulatory strategies in different countries, and how these influence each other.

A second point is that many studies that have analyzed recent changes in medicine regulation have used a relatively limited set of explanatory factors. This is reflected in various studies we have cited and discussed in this article. Montgomery (2017), for example, has particularly focused on the role of the pharmaceutical industry in trying to replace the RCT as methodological gold standard in medicine regulation. Salter *et al.* (2015) have interpreted the ongoing process of regulatory diversification in the EU and USA as a form of 'hegemonic adaptation,' through which governments respond to new demands from patient and consumer organizations. Cooper and Waldby (2014), alternatively, have pointed to the influence of neoliberal ideas and libertarian advocates of pharmaceutical deregulation in explaining the continuing increase of regulatory exemptions and the relaxation of pre-market testing. Sleebom-Faulkner *et al.* (2016), by contrast, have analyzed conflicting global developments in medicine regulation through the concept of 'national home-keeping.' This enables them to investigate how national regulatory bodies in different world regions respond to the exclusionary effects of international standards in medicine regulation.

While each of these studies makes an important contribution to understanding current processes of regulatory change, individually they provide key pieces of a broader puzzle, but fail to account for the complexity of reasons that underlie the ongoing process of global diversification in medicine regulation. In order to facilitate a more comprehensive understanding of the current pluralization of regulatory models in medicine research and to provide a basis for international comparisons and the analysis of transnational patterns, we have combined insights from these studies in an analytical framework that has explored regulatory developments through the use of four pairs of conflicting regulatory choices. Work with this framework has enabled us to foreground both the conflicts of interests and the tensions between different regulatory aspirations that are relevant in the context of specific countries, and in the emerging of broader global developments.

A third point is, that an analytical concern with medical innovations that are not amenable to the business model of Big Pharma (i.e. the development of scalable, mass-produced medicinal products that can be stored long-term and shipped across long distances) is of increasing importance to understand

processes of regulatory change. With the advent of novel medical approaches that are based on the use of personalized tissue and gene products, which are biologically fragile and whose storage life is limited, new types of research and profit-making have emerged, that differ from conventional forms of drug development in important respects. The key stakeholders in this emerging innovation landscape are not large, transnational corporations, but small-to-mid size companies, academic researchers and hospitals, and sometimes private clinics. These stakeholders have fewer resources and different regulatory needs compared to pharmaceutical companies, and seek to influence medical regulations in new ways.

Moreover, many advances in regenerative medicine, gene therapy and tissue engineering are now developed in rapidly developing countries in Asia and to a lesser extent South and Middle America and the Middle East. In this changing innovation landscape, global competition and inequalities have become important factors that drive diversification in medicine regulation. International standardization and harmonization, the hallmark of the Big Pharma model of drug development is less important in these new areas of medicine. With the significance of these emerging medical approaches growing, and health care systems at a global level coming increasingly under pressure, a further shift towards deregulation and regulatory diversification can be expected in the future. However, as medicine regulation diversifies, the boundaries between medical research and healthcare provision, commerce and humanitarian service, as well as state control and medical self-regulation are re-defined. The implications of this are only just coming into view.

Note

1. Some of the data in the empirical section of this article are also published in Rosemann *et al.* (2016). However, the data presented here include updates on regulatory developments from the last two years, are more in-depth, and have been analyzed in the context of a completely different argument and theoretical discussion.

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Notes on contributors

Achim Rosemann has interdisciplinary background in science and technology studies, medical anthropology as well as China and East Asian studies. Currently, he is a research fellow at the Department of Sociology, Philosophy and Anthropology of the University of Exeter and an associate researcher at the Centre for Bionetworking of the University of Sussex. His work has examined the socio-cultural, economic and regulatory dimensions of technology developments in regenerative medicine, genetics, gene editing and synthetic biology.

Gabriela Bortz has a PhD in Social Sciences, is a Political Science graduate (Universidad de Buenos Aires, Argentina) and has an MA in Science and Technology Studies (Universidad Nacional de Quilmes, Argentina). Currently, she is a postdoc research fellow at the Institute of Science and Technology Studies (UNQ) and CONICET, focusing on public policies, knowledge production and innovation in biotechnology for inclusive and sustainable development. She is a lecturer in graduate and postgraduate courses at UNQ and other higher education institutions.

Federico Vasen is CONICET Assistant Researcher at the Institute of Educational Research (IICE) and Academic Coordinator of the Master in S&T Policy and Management, Universidad de Buenos Aires. He has a background in Science and Technology Studies, science policy, regulatory science and environmental politics.

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