

# Regulatory brokerage: Competitive advantage and regulation in the field of regenerative medicine

Social Studies of Science  
2019, Vol. 49(3) 355–380

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DOI: 10.1177/0306312719850628

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## Abstract

This article concerns the roles of entrepreneurial scientists in the co-production of life science research and regulation. Regulatory brokerage, defined as a mode of strategic planning and as the negotiation of regulation based on comparative advantage and competition, is expressed in scientific activities that take advantage of regulatory difference. This article is based on social science research in Japan, Thailand, India and the UK. Using five cases related to Japan's international activities in the field of regenerative medicine, I argue that, driven by competitive advantage, regulatory brokerage at lower levels of managerial organization and governance is emulated at higher levels. In addition, as regulatory brokerage affects the creation of regulation at national, bilateral and global levels, new regulation may be based on competition in regulatory advantage rather than on ethical and scientific values. I argue that regulatory brokerage as the basis for regulatory reform bypasses issues that need to be decided by a broader public. More space is needed for international and political debate about the socio-political consequences of the global diversity of regulation in the field of the life sciences.

## Keywords

Japan, regenerative medicine, regulation, regulatory brokerage

## Introduction

The translation of life science into clinical applications, especially in the field of regenerative medicine (RM), has led to fierce scientific and industrial competition, and a push to accelerate the development of innovative medical intervention (Doudement and

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Uppal, 2014; Dutton, 2007). As a result, the regulation of this important field is influenced by diverging, and often contradictory, pressures and knowledges to protect patients, to safeguard scientific development, and to facilitate the translational process ‘from bench to bedside’ (e.g. Blasimme and Rial-Sebbag, 2012; Faulkner and Poort, 2017; Kahn, 2015). Thompson (2013) has characterized the ethical procurement and procure rhetoric driving innovation and investment in California’s human embryonic stem cell research hub (p. 29).

Although biomedical ideologies and pro-curing framings are at the heart of activities to attract both financial and regulatory support for research in the field of RM, I am here interested in pragmatic activities that seek both to strategically utilize differences in regulatory regimes and broker advantageous regulation in support of both scientific and commercial enterprises. This two-fold meaning of ‘regulatory brokerage’ (further defined below) is important, because the latter usually builds on experience with or on awareness of the former. In my exploration of regulatory brokerage, I am concerned with the pragmatics of strategies followed by entrepreneurial scientists in creating the conditions expedient to their research and industrialization plans.

This article draws on data about regulation and regulatory brokerage in India, Thailand and the UK, in relation to Japan. Although my focus on Japan is particularly helpful in illustrating regulatory brokerage, this does not imply that regulatory brokerage is particular prevalent in that country, or that the creation of regulation does not entail concerns for ethical issues. Japan has been an important player in developing regulation for RM and its science community is highly respected globally. Though relatively early in its encouragement of human embryonic stem cell research, its regulation of research materials and clinical trials was conservative until the ‘Japanese’ discovery of induced pluripotent stem cells (iPS), when regulation became considered as permissive, leading the USA and EU to reconsider their regulation. A comparison of regulatory brokerage at different points on this, albeit winding, trajectory can help us understand how and why regulatory reform is undertaken.

### *Scientist entrepreneurs*

The encouragement of life scientists to collaborate with industry in marketing their products has led to an increase in entrepreneurship among scientists (Jones et al., 2011). Entrepreneurship in the world of business refers to the capacity and willingness to develop, organize and manage a business venture along with any of its risks in order to make a profit. Although entrepreneurial activities by scientists can be traced back to at least the 19th century, today’s complex university–firm networks took shape in the mid-1980s (Etzkowitz, 1983; Mirowski and Sent, 2002), when the Bayh-Dole Act in 1980 and the Federal Technology Transfer Act in 1986 were introduced in the USA. These acts devolved the right to patent the fruits of federal-funded research from the federal government to recipient institutions (Murray, 2004). European countries have followed suit, and, as a result, the share of public research organizations (universities and public research laboratories) in patent application has increased (Nesta and Mangematin, 2002, cited in Oliver, 2004: 585). A Japanese version of the Bayh-Dole Act (‘Law of Special Measures for Industrial Revitalization’) was enacted in 1999. The law facilitated the

trade of intellectual property rights (IPR) derived from publicly funded research (Edgington, 2008: 11), and became a novel way of tackling healthcare costs and stimulating economic growth.

Science-company collaborations, according to Etzkowitz and Leydesdorff (2000), follow the 'triple helix model' of university-industry-government relations. The authors describe how most *countries and regions* try 'to realize an innovative environment consisting of university spin-off firms, tri-lateral initiatives for knowledge-based economic development, and strategic alliances among firms' (Etzkowitz and Leydesdorff, 2000: 112). Another strategy of transnational entrepreneurship embedded in the organizational culture of firms seeks to generate value through the exploitation of opportunities in the international marketplace (Dimitratos and Plakoiyannaki, 2003: 189). Its significance lies in that transnational entrepreneurship combines the pathways enabled through the triple-helix model with the advantages provided by collaboration with potential partners in other countries or regions. However, unlike the authors of bioconstitucionalism, these authors do not include in their models the regulatory embedding of life science in society through 'public engagement' or publics as actors. And although some of the workings of the transnational pick-and-mix strategies have been illustrated for the global pharmaceutical industry (Angell, 1997; Petryna, 2009; Sunder Rajan, 2006), they differ in the field of RM.

### *Clinical research and entrepreneurship in molecular and regenerative medicine*

Social scientists have observed that, in addition to human capital, social capital is crucial to scientists' collaborations with industry (Murray, 2004; Stuart and Ding, 2006). It has also been observed that scientists working with the pharmaceutical industry take advantage of ethical variability regarding global clinical trials and clinical studies in low- and middle-income countries (LMICs) (Petryna, 2006, 2009). In the case of RM, differences in geographical conditions and regulatory factors are important to decisions companies make about where to locate. This is related to fundamental differences between the testing of stem cells and molecular medicine.

Compared to molecular medicinal drugs, cell products are unstable, as the state of the cell in RM is critical from the stage of harvesting to the point of implantation (Mason and Hoare, 2007). Cells, unlike drugs, have the ability to multiply. Although it is the regenerative potential that makes stem cell treatments promising, it also poses risks, as cell batches can vary over the course of a trial (Medical Research Council (MRC), 2012: 16). Furthermore, the transplantation of undifferentiated stem cells can pose considerable risk when the cells do not 'home in' or develop into the kind of tissue expected, while with allogeneic cell applications, using cells from other people, there is a risk of immunological response (Interview, Michaels). Therefore, testing on healthy volunteers (non-patient groups) is usually not an option. Nevertheless, when tested in only a few patients, scientists value the outcome of a stem cell intervention as a strong proof of principle, unlike in molecular medicine, where statistical evidence in large patient numbers is usually required (Interview, Kaketani).

The novel nature of cell therapy development has consequences for the organization and funding of clinical applications. In contrast to the clinical testing of compounds and

molecules, no internationally binding standards or harmonized regulatory framework, such as those of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH, 2016), are in place for clinical stem cell interventions. This means that regulatory conditions vary starkly across countries (Sleeboom-Faulkner et al., 2016). Regulatory frameworks for the clinical application of stem cells have been strict and drawn-out in Europe, the USA and also Japan – until recently (Blasimme and Rial-Sebbag, 2013; Kawakami et al., 2010; Rawlins, 2009) – which is partly due to the challenges involved in the evaluation of new cell products (Von Tigerstrom, 2015). The lengthy time of application and uncertainties around regulation (Roehr, 2014; Whittlesey and Witten, 2012) have added to the high costs involved in the organization of clinical trials, which in the case of RM draw relatively few investors (Doudement and Uppal, 2014; Rosemann, 2014).

Much state funding has been invested into stem cell research and its translation into clinical applications. Although some larger companies (e.g. Osiris, Genentec) have organized clinical stem cell trials in the US, and to a lesser extent in other countries, companies and researchers look to the state and NPOs for financial support (Dutton, 2007; Littman, 2014). The shortage of investment in RM means there is a great number of small biotech start-ups in academia that need to become self-sufficient, which has led to extensive licensing and to the globalization of this trade – not so much in health products, but in products or services for conducting research (Jones et al., 2008).

These differences between molecular medicine and RM have implications for the ways in which scientist entrepreneurs position themselves and move internationally. As markets for RM products and services tend to be global, they seek to derive competitive advantage from the use of resources and the sale of outputs in multiple countries. Such transnational entrepreneurship has been limited mainly to stem cell research resources, culturing services and drug screening. The testing of applications in RM is not as flexible and mobile as it is for pharmaceutical treatments, and is not targeted at LMICs. Rather than healthy volunteers, cell product testing requires access to patients with particular, often serious, conditions; these are not generally concentrated in LMICs (Earls, 2012). As such, patients have become increasingly mobile (Chen and Gottweis, 2013; Salter et al., 2015; Song, 2010), and ‘stem cell tourism’ may well be an important resource for testing in some countries (Patra and Sleeboom-Faulkner, 2009; Song, 2010). Stem cell experimentation taking place in LMICs is not so much due to a lack of local healthcare access, but to international travel by patients who are elderly and/or have serious, intractable diseases.

The number of cell therapy products is extremely limited, considering the substantial investment into the field, and it is too early to say to what extent ‘stem cell cures’ will be realized and when: Other than therapies for blood diseases, there are very few RM products that have gained market authorization (Detela, 2016).<sup>1</sup> However, the realization of successful cell therapies is thought to lead to a radical reorganization of the field of RM, including the setting of international standards, and a replacement of state and small investment by large-scale industrial funding. Hoping to influence or set the standards themselves, ambitious scientists may aim for early success and internationalization through the exploitation of variation across boundaries.

## *Regulatory brokerage*

Using examples of regulatory business strategies negotiated by Japan with India, Thailand and the UK, I illustrate various aspects of what I call regulatory brokerage. In business, a broker is a go-between who ‘supports partners in navigating their collaboration journey by helping them to create a map, plan their route, choose their mode of transport, and change direction when necessary’ (Partnership Brokers Association, 2019). In social scientific terms, brokers are individuals who have the social capital, including education, career and organizational experience, to form connections either for themselves or their organization into other domains, social networks and functional areas (Murray, 2004). In the scientific community, scientists may establish social capital in networks of collaboration on one hand (Parker et al., 2010; Shrum et al., 2007; Vermeulen, 2009), but remain bound within the distinctive practices and beliefs that constitute the knowledge community or epistemic culture (Knorr-Cetina, 1999) on the other. In RM, understanding the distinctive institutional and material settings linking collaborative networks and epistemic cultures, including regulatory conditions, can be advantageous. Various forms of legal, procedural, moral, economic and industrial knowledge (Faulkner and Poort, 2017) are mobilized in creating research/business strategies and risks are assumed to further the interest of a business or lucrative research through activities ranging from administrative management and recruitment to raising venture capital. In brief, scientist entrepreneurs in the field of RM broker regulation for the sake of competitive advantage – be it direct profit, knowledge assets or reputation, rather than being decided upon on the basis of safety, efficacy and ethical concerns. The concept of regulatory brokerage therefore does not hinge on the particular professional background of the brokers, although in this research all had scientific backgrounds. What is relevant here is that those engaging in regulatory brokers are aware that the geographical constituency to which they belong is subject to a particular regulatory regime. This regulatory subjecthood is treated as a form of ‘regulatory capital’ and commodified in the negotiation of international collaboration among science-entrepreneurs.

I use ‘regulatory brokerage’ to refer to, first, the use of regulation in brokering science collaborations at home and abroad, involving the entrepreneurial exploitation of the differences between regulatory regimes. Here, regulatory brokerage does not just take into account, but strategically bases research, the selection of research partnerships and localization tactics on the administrative-geographical regulation of science activities, including ethical-, research- and product-review. I also use the concept to refer to the role that brokers, often high-profile scientists and managers, play through their negotiation between business and regulators, officials and others involved in the creation of regulatory guidelines.

Definitions of the regulator as an autocratic bureaucrat who controls the making and enforcement of rules are misleading. Abbott et al. (2017) show that the capacity of regulators is partly dependent on intermediaries. Intermediaries, who can range from officials and scientists to company presidents and members of NGOs (Abbott et al., 2017: 7) support, monitor and advise on the implementation of regulation. The notion of regulatory brokerage, however, pertains not so much to the implementation of regulation but to its active creation or reform, and it introduces a clear strategic direction to the (self-interested) envisaged alteration in negotiations.

At stake are decisions about the treatment of human life, its value, citizenship, governance and healthcare. A main question here is whether these issues are decided by the state on the basis of bioconstitutional considerations (see Jasanoff, 2011), including public consultations, or through international competition in the life science research and industry in the form of regulatory brokerage. In this article, I explore how regulation has become an important instrument in the hands of scientist entrepreneurs in the course of the clinical translation of potentially marketable clinical applications. I intend to illustrate how taking advantage of ‘regulatory variability’ (Petryna, 2006, 2009) is no longer confined to the pharmaceutical industry, but has become a major factor in the scientific decision-making on collaboration and the geographical location of clinical applications, to the point of determining the rules of the very playing field of RM.

Some scientists engaged in regulatory brokerage are laboratory leaders without business management training; having to juggle roles, some of them engage a manager to help them run their company. Other regulatory brokers are scientists specifically hired to focus on international collaborations. They tend to focus on gathering information on other companies, negotiating between the companies and researchers they represent and their partnership targets. Still others are scientists exclusively running venture companies, raising venture capital, negotiating with industry, and communicating with regulators on the company’s behalf. I have selected cases of regulatory brokerage on the basis of organizational level and present them as cumulative; that is, the forms described first have occurred before later ones. I hypothesize that this is not coincidental. Although the cases are not directly related to one another, there are political, scientific and economic reasons for this order to be meaningful. I will also point out why regulatory brokerage is not inevitable, even where there are opportunities to benefit from regulatory discrepancies. And, finally, I will discuss how regulatory brokerage entails issues that are in need of public scrutiny.

## **Methods**

This article is based on a project on international collaboration in the field of regenerative medicine, which has been on the increase in recent decades. The project looks into the motivation and reasons for engaging in collaboration in translational research. In the cases examined, regulatory conditions play a major role in the decision to collaborate. Once collaborations were identified, interviewees were located on both sides of collaboration, with the aim of understanding the advantages and disadvantages of regulatory brokerage on each side. Analysing the cases pertaining to Japan, it became clear that regulatory brokerage took place on increasingly high levels of organization, ranging from simple bilateral to the global level.

The first four cases involve interviews and visits, while the last case involves the attendance of a conference. For cases one and two, I draw on interviews that took place in the following periods: October–December 2008; November–December 2012; March–July and October–December 2013; for cases three and four I draw on fieldwork that took place in October–December 2013 and January–March 2016. I approached scientists working in the field of RM, including induced pluripotent stem cells, human embryonic stem cell research and tissue engineering. In Japan, interviews took place with research

at the Centre for iPS Cell and Research Application (CiRA) and the Institute for Integrated Cell-Material Sciences (iCems) in Kyoto, the RIKEN Centre for Development Biology (RIKEN-CDB) in Kobe, and in Tokyo, where I visited Keio University and the Women's University of Science and Technology. In addition, I spoke with experts in the regulation, ethics and social aspects of science and science communication. Other interviews with researchers in took place in Thailand at Chulalongkorn University, in the UK at Sheffield and Loughborough Universities, and in India in Chennai.

The cases of regulatory brokerage were selected strategically on the basis of involvement in international collaboration and tactical use of regulatory conditions in the countries involved. The foregrounding of regulatory difference by the interviewees themselves was crucial. Methods of repeated close readings and coding (using notions around the key concepts of 'commercialization', 'regulation', 'financial support' and 'approval') highlighted the roles of funders, government and state authorities. The scientists interviewed varied in occupation and experience from physicians to research scientists and from administrators to consultants; they had various disciplinary backgrounds, including medicine, engineering, the life sciences and work in the pharmaceutical industry. Although most had degrees and experience in at least one of the life sciences, only a few had a business background. In most cases, the life scientists were stimulated to look for business opportunities mid-career, and were struggling to learn about marketing. All interviewees, even those who had started a venture company themselves, were looking for partners or CEOs, who could 'run the business' for them.

The materials presented draw on interviews with scientists, engineers, company managers and regulators from Japan, India, Thailand and the UK (see Appendix 1). Although many interviewees said there was no need to remain anonymous, I have used pseudonyms, as I aim to draw attention to regulatory brokerage rather than provide information on the conduct of individuals. When citations from secondary or archival sources are used, I use original names, unless they reveal the identity of my interviewees.

## **Forms of regulatory brokerage**

This section discusses five forms of regulatory brokerage. My presentation of the cases suggests that regulatory brokerage in the field of RM over time has increasingly involved higher levels of governance. The various forms should be understood together to comprehend the pressures on regulatory systems and science policy-making (Table 1).

### ***Case 1: Informal forms of regulatory brokerage***

Although Japan is known for its 'iron triangle' between government, bureaucrats and heavy industry (Johnson, 1982), until recently, Japan's government had not succeeded in pushing industry to invest substantially into RM (Umemura, 2011). In 2003, Japan was early to make stem cells the core of its national ten-year project for RM development, though scientists complained that stem cell regulation was both strict and bureaucratic (Nakatsuji, 2007; Slingsby et al., 2004). Japan's first RM product, an autologous cultured epidermis named JACE for the treatment of serious burns, made by Japan Tissue Engineering Co., Ltd. (J-TEC), took seven years before, in 2007, it received government

**Table 1.** Five forms of regulatory brokerage.

<i>Regulatory Brokerage</i>	<i>Activities</i>	<i>Level of regulatory brokerage</i>
<i>Informal</i>	Transnational collaboration out of regulatory considerations	Sub-national
<i>With state support</i>	Transnational collaboration out of regulatory considerations	Sub-national with state support
<i>Deregulation</i>	Deregulation to attract international collaborators	National
<i>International</i>	Brokering by science-entrepreneurs, officials and regulators of two countries	Bi-national
<i>Global</i>	Negation among science-entrepreneurs, industry and regulatory agencies of leading regions	International

approval to culture and sell, and another two before it was listed as an item covered by the country's national health insurance (J-Tec, 2015). But after Shinya Yamanaka's successful publication of his research on human iPS in late 2007, the government appointed the Council for Science and Technology Policy (later renamed the Council for Science, Technology and Innovation), a scientific advisory board reporting to the Prime Minister that would play an important role in the regulatory reforms. Various strategies were created to encourage the launch of government-led projects in RM, funding was increased, especially for iPS, and regulation was adjusted (see Kawakami et al., 2010; Mikami, 2015; Sleeboom-Faulkner et al., 2011). Nevertheless, many scientists continued to complain about regulatory complexities hampering the clinical translation of RM.

It was not just frustration with Japan's regulatory bureaucracy, but also the insight that it would be possible to turn the regulatory gaps between countries into an advantage, which led some entrepreneurial-minded scientists to initiate transnational biotech ventures. Sleeboom-Faulkner and Patra (2011) illustrate how the Indian-Japanese joint-venture, Japan-India Centre for Regenerative Medicine (JCRM) boasts a large scientific, political and financial network in both Japan and India, and has organized clinical stem cell application for a range of diseases, including spinal cord injury, cardiovascular diseases and cirrhosis of the liver, and immune diseases in India. Settled in Japan and established as a cardiac surgeon at a university there, Indian-born scientist entrepreneur Kumar commuted between India and Japan to overcome regulatory boundaries. In 2005, Kumar and a group of Japanese scientists and companies set up JCRM as a charitable company in Chennai, India, with Japanese equity. In 2008, Kumar reported that the company's charitable goals had led to profit in the long run:

We now have plans for a lot of years. We have proven that corneal limbal tissues taken from the same patients or person, cultivated by our method and reinserted into the eye, regenerates the normal cornea inside the person – on the basis of animal research. After having proven this, it can be applied. Corneal cells have some problems in common with the endothelium. If we do the research here, then we have ten years of research ahead of us, as there are various regulatory



complications. The Waseda people gave us the materials and our Indian guys tried the primary culture in the laboratory. Then we did the collaboration with an institute in India. There they did the basic study and animal study in the lab in India, and the tissue engineering before application in the hospital. (Interview, Kumar)

Here we find that regulatory brokerage takes place by a simple strategic use of regulatory discrepancy and avoiding regulatory clashes where possible. Although there are differences in healthcare, wealth and scientific development between the countries, it is the regulatory discrepancy that is crucial to JCRM's decision to start operating in India. Regulation for stem cell application had not been put into place until 2007 (Department of Biotechnology (DBT) and Indian Council of Medical Research (ICMR), 2007), from which time JCRM managed to avoid having to apply for ethical permission by providing stem cell isolation/expansion services to Indian hospitals (Sleeboom-Faulkner and Patra, 2011). Formally, hospitals need to follow the guidelines of the Institutional Ethics Committee and Institutional Committee for Stem Cell Research and Therapy (IEC/IC-SCRT), stipulated by the ICMR. The guidelines permit the use of autologous stem cells in research and treatment, provided the protocols are approved by these committees, and registered with the National Accreditation Committee for Stem Cell Research and Therapy (DBT and ICMR, 2007). But, as there is no adequate supervision over the ethics committees, and, as the National Accreditation Committee had not yet been formed, regulation did not stand in the way of research and therapeutic applications. The Consul General of Japan, frequently present at JCRM's public events, seemed to imply formal endorsement of JCRM's activities. By definition, its omissions of regulatory requirement in both India and Japan has ethical and health implications for patients in India and reputational implications for Japan's RM community. Public awareness of these omissions would enable both patients and scientists to ask why.

### *Case 2: Regulatory brokerage with official support*

In the 2010s, Japan's life sciences underwent various changes, including the legalization of clinical research on cells differentiated from pluripotent stem cells, and policy strategies, such as the 'Highway for the Realization of RM', the Japan Revitalisation Strategy, and the Plan for the Promotion of Medical Research and Development (Headquarters for Healthcare Policy, 2014). The strategies aimed to increase coordination among the ministries and to enhance Japan's global competitiveness in the pharmaceutical and medical equipment industries, including the areas of medical products and equipment, RM, and personalized medicine. The final aim was to strengthen competition in the Euro-American market in the field of drugs and devices through technological innovation and to create the infrastructure for regenerative and personalized medicine abroad and at home.

In February 2012, the Minister of Health, Labor and Welfare's outlined the five-year strategy intended to serve as the core driver of Japan's economic growth (MoHWL, 2012). It emphasized the bridge-building between industry and academia [*hashi-watashi*] by stimulating venture capital to invest into biomedical science, and it allowed the outsourcing of cell processing and promoted joint research. Another emphasis was on improving the infrastructure for clinical trials and creating an environment that uses

Japanese-made devices and instruments, making Japan the hub for clinical trials in Asia for the first time. A new funding body, the Japan Agency for Medical Research and Development (AMED), was to combine the budgets of three ministries – the Ministry of Health, Labor and Welfare, the Ministry of Education, Culture and Sports and the Ministry for International Trade and Industry. Japan's Department of New Energy and Industrial Technology Development Organization (NEDO, 2016) were to support industrial applications, both domestically and overseas.

NEDO, established as a semi-government organization in 1980 to promote the development of technology and new energy, in response to 'a recent increase in open and global innovation' has been promoting the establishment of world-standard technology, as well as market development, by drawing on established research networks in collaboration with foreign governments and relevant organizations. NEDO's 2015 budget for the support of international expansion was 20.8 billion Yen (US\$190m; £129m). One example of a collaborative network supported by NEDO is that between Kawasaki Heavy Industry (KHI) in Japan with Bangkok, where NEDO has an office. In Japan, the processing of cells had to be done by the doctor or university involved in the clinical application. KHI, which was developing an automatic cell-processing robot for stem cell applications, wanted to show that marketable products could result from clinical trials using the robotic machine. It regarded Japan's regulation, however, as too slow and onerous.

After negotiation with various universities in Thailand, Chulalongkorn University decided to allow KHI's robotic machine on the premises and to collaborate in a clinical trial. The parties signed a memorandum of understanding in June 2012. When asked why, the Thai scientist who had first received the Japanese delegation explained:

Especially in the beginning we have been wondering why they came to Thailand. They did not go to China, which is understandable. Political relations are not good. But they did not go to Singapore either. This is because they are potential competition. We were skeptical in the beginning. There is no such thing as a free lunch and all that. They now just want to have [Thai] FDA [Food and Drugs Administration] approval or a license. (Interview, Wattanapanit)

Here, KHI strategically chose Chulalongkorn University as a collaborative partner, being confident that it would receive permission for conducting a clinical trial using the robotic machine. Chulalongkorn University, on the other hand, accepted the collaboration because the use of advanced equipment would help it both scientifically and financially. Although NEDO's official support and the involvement of officials in Thailand had been encouraging factors in bringing about the collaboration, a leading Thai scientist said in 2013, the final year of the project, that KHI had been too optimistic about gaining permission for a clinical trial: The Thai government was expected to maintain the high reputation of its elite laboratories, and none of the scientists involved thought that Thai regulation was going to show favoritism (Interview, Wilipana).<sup>2</sup> This Japanese–Thai collaboration illustrates how the difference between regulation in Thailand and Japan was the main resource for KHI to broker collaboration with the Thai laboratory. It raises questions about the use of Thai patients to prove the processing ability of a robotic machine, and it raises questions about the authority of state organizations to evade their own regulation.

### Case 3: Deregulation as regulatory brokerage

The Office of Medical Innovation, a cabinet-level advisory organization set up in Japan in 2011, played an important role in the development of regulation by reducing sectionalism among the science, health and trade ministries, and by bringing industry and science closer together in developing more effective intellectual property and regulatory frameworks in the field. The Japanese Society of RM (JSRM) and the Forum for Innovative RM (FIRM) played major roles in directing the development of regulation in RM. In this ‘triple helix’ set-up, the prominent role of Professor Teruo Okano of Tokyo Women’s Medical University, well-known for his innovative ‘cell-sheet’ therapy, played a major role. Made of human cells grown on temperature-responsive sheets, these cell-sheet products were used in various clinical applications, including for heart failure, which Okano was intent to market. The triple helix around Professor Okano embodied the link between regulation, science and industry. Okano was acting head of the Office of Medical Innovation, President of JSRM, and a co-founder of FIRM. The JSRM, established in 2001, had been campaigning for the relaxation of Japanese government regulations concerning studies, clinical trials and clinical applications related to RM. Its 2012 ‘Yokohama Declaration’ made RM a priority in the Cabinet Secretariat’s Five-year Healthcare Innovation Strategy and has been instrumental in the creation of the new Act for the Promotion of RM, the Revised Japanese Pharmaceutical Law, and the Act to Ensure Safety in RM, which were approved in 2013 (JSRM, 2016). Okano’s collaboration with Osaka University Hospital’s cardiovascular surgeon Yoshiki Sawa, has been crucial to the success of CellSeed, a company set up by Okano in 2001. In 2007, Sawa announced the successful application of Okano’s cell-sheets into a patient with cardiomyopathy (Okano et al., 2015). Sawa is President of JSRM’s Board and led the publication of the Osaka Declaration (17 March 2016), which announced Japan’s role as world leader in universalizing RM and finding evidence for its safety (JSRM, 2016). Okano and Sawa are active representatives of the companies they work closely with, CellSeed and Terumo respectively, while their networks spread widely. Counting a membership of over 180 companies, FIRM was set up to promote the commercialization of RM in Japan. It aims to establish industry-led partnerships with governments, academia, research institutions and the private sector to promote a stable and welcoming international business environment.

In 2013, a well-known leader in RM had severe complaints about Japan’s regulatory policies, which were widely shared by those interested in the commercialization of cell products. The leader explains the regulatory challenges and his role in the subsequent regulatory change:

Sheets cannot sell in billions like molecules in drugs; we cannot do it, as they need many improvements. Only a small number can be transplanted. We require a new law for treating large numbers of patients. We have started clinical research on the cornea, the heart and the esophagus. I went to Congress many times – I had to start teaching the committee – the Diet member alliance for the promotion of RM (‘zai seiiryō suishin giin renmei’) - in 2008, when we had this building built. In 2007, 9–10 professors had formed a study meeting. They submitted an opinion paper about autologous application. The Diet responded with the creation of the committee: they had to learn how clinical application is progressing. It took 5–6 years for the

Diet and the Cabinet Office (Naikaku-fu), the three Ministries and the Legislation Office (hōsei-yoku) to understand that we needed different regulation. To reach a decision on the situation took many years. Medical doctors only think of publications. I had to yell to them: 'Patients are waiting!' The JSRM needed to create new circumstances for regulation. Without efforts, there would be no law. (Interview, Asada)

Financial inability was not the only factor that stopped scientists from taking their products through clinical trials and to industry. In RM, the 'product is the process', which means that the product requires a continuous track of developmental steps. It was argued that, as Japan did not have experimental spaces or 'expanded-access related mechanisms', such as hospital exemption, compassionate treatment in Europe or investigational new drugs (INDs) in the USA, scientists felt that testing opportunities were particularly limited in Japan. Other scientists and regulators have pointed out, however, that Japan's Medical Practitioners' Act or Advanced Medical Care B gave Japanese PIs similar or more spaces to 'test' their products (Tsuyuki et al., 2016).

Nevertheless, some leading scientists urged the government to concede the regulatory demands of the Yokohama Declaration. RM needed infrastructural support that the government alone could not supply. Industrial investment was needed for clinical trials in RM, but industry was holding off. It was not that the Japanese market was not big enough; it was because infrastructural and regulatory conditions were unfavourable. One scientist explained in March 2013:

The government has tried to give them funding, but to them it's peanuts. If they decide they are interested, they pay themselves! ... How are they [life science industry] going to collaborate with us? *Their strategy is not to take any funds from the government*, as it can put restrictions on them. For instance, when companies would like to collaborate with Shimadzu or other [state] subsidised companies, Shimadzu has to say 'we cannot collaborate with you, as we have government funding', 'we have a non-disclosure agreement (NDA), we cannot show any data', or 'Five years later, when the NDA expires, we are willing to disclose.' Too late! (Interview, Kaketani)

According to this scientist, industry is willing to work in a country that builds the platform and provides workable regulatory conditions: 'That is why they try the UK first' (Interview, Kaketani).

Another reason for regulatory reforms was that the Japanese government needed to wean scientists from government funding. In 2013, for example, the Japanese government invested US\$150 billion into the science innovation budget, which was only about 10% of that of the NIH (Interview, Sonoda), while the availability of venture capital in Japan was much lower than in the USA and Europe (Interview, Kato). It was hoped that deregulation would get Japanese and foreign companies interested in paying for clinical trials, as they would now be less costly and would require fewer subjects before any products would be eligible for licensing. Apart from stimulating industrial investment into Japanese products, the plan was to attract foreign researchers and companies to test their products in Japan. This would, first, strengthen Japan's ability to organize clinical trials, second, increase the purchase of Japanese products through joint-ventures, and,

third, increase the need for international regulators to recognize Japanese procedures and systems of permission.

In 2012, it was decided to speed up the examination of medical devices and therapies through investment into the Pharmaceuticals and Medical Devices Agency. In May 2013, the Law for the Promotion of RM was passed, obliging subsequent governments to support the field. Two other acts followed: the ‘Act to Ensure Safety in RM’ (RM Act) and the ‘Revised Pharmaceutical Affairs Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act’ (PMD Act), both of which were enacted in November 2013 and became law in November 2014 (Azuma, 2015). The RM Act uses a three-tiered system based on risk assessment to determine the level of research oversight required. The PMD Act defines an expedited approval system for regenerative medical products, whereby a product is given conditional, time-limited marketing authorization.

In short, Japan’s deregulation has created new regulatory relations between Japan and other countries, with Japan’s regulation being perceived as permissive. But the policy raises important ethical issues that, according to critics, require public discussion. Thus, a well-known legal scholar explains that safety and efficacy studies required before clinical trials are reduced to mainly safety studies and some presumptions about efficacy: ‘This is because iPS is *expected* to be effective; the regulation therefore is about “regenerative therapy” [saisei-chiryō] as “RM” is not a correct expression: We do not know yet if it is regenerative’ (Interview, Ito). Similar comments about this ‘expectation’ bias have been made by Japanese researchers (Interview, Takeuchi), and were commented on by an editorial in *Nature*, which pointed out that patients and the taxpayer will be paying for what are in essence unproven stem cell interventions (*Nature*, 2015: 163–164; see also Sipp, 2015).

#### **Case 4: International regulatory brokerage**

Regulatory brokerage at the higher level of government has laid the regulatory groundwork for international collaborations. One policy related to the new regulation stipulated the creation of comprehensive special zones (CSZs) for industrialization in 2013, of which the Life Innovation in Keihin Coastal Areas CSZ for International Competitiveness is one example. It was set up to stimulate the innovation in RM and cell therapies (Kantei, 2019). These CSZs play an important role in the facilitation of international collaboration.

Before the promulgation of the PMD Act in November 2014, only two products, J-Tec’s aJACE and JACC (Autologous cultured cartilage cells for cartilage defects and knee joints) had been approved. Shortly after the Act, two new cell therapy products obtained approval for marketing: Heartsheet, autologous skeletal myoblast sheets for cardiac regenerative therapy (Terumo, 2015) obtained conditional approval in September 2015 and Terumo has started production in the Keihin CSZ (Nikkei, 2016), and Temcell – formerly Prochymal – an allogeneic mesenchymal stem cell product for graft-vs-host disease prevention, a Mesoblast/JCR Pharmaceuticals product (Meldrum, 2014) for which Mesoblast had acquired licensed-in technology from Osiris (Bersenev, 2015) and for which it obtained unconditional approval. Under the new RM Act, all four products are eligible for National Health Insurance reimbursement.

The regulatory changes in themselves led to a flurry of purchases and collaborations, including regulatory brokerage on an international level. Japan's pharmaceutical and industrial sectors have RM on their agendas, and industry groups estimate the domestic market for these therapies could top ¥3 trillion by 2050 (Kahn, 2015). Deregulation has made Japan attractive not only to Japan's pharmaceutical and related industries – some major players include Takeda, Astellas, Sumitomo Dainippon, Fujifilm, Kyowa Kirin, Healios, Terumo, and Eisai – but also to foreign companies. Interest in Japan by foreign companies exploded to such extent that one scientist referred to it as *kusakariba* or 'cutting from the hay-meadow commons' (Interview, Takeuchi), implying a place from which numerous people hope to profit.<sup>3</sup>

The encouragement of rapid commercialization and internationalization has led to a rift within the academic community and an atmosphere of secrecy. One scientist, who left academic research, maintained that 'stem cell therapy is overrated, especially treatment for the elderly' (Interview, Yamamoto), while according to another, 'regulation should not put up barriers, but offer clear traffic lights at least' (Interview, Takeuchi). Others feel pressurized and overwhelmed by the burden of commercialization, preferring to collaborate with other academics, while some scientists feel isolated from their colleagues, as non-disclosure agreements have made many scientists secretive about their research. Some academics are keen to commercialize their work, but the need to market internationally leads them to think in terms that illustrate regulatory brokerage. Dr Hirogawa, a researcher in Kyoto explained:

There is a lot of secrecy here. No one talks. I never speak with Kumamoto, even though he is my neighbour. I am unhappy here. There is much competition and everyone is careful. There is much Venture Capital available now. (Interview, Hirogawa)

He is caught between two senior entrepreneurial scientists, who follow their own business agendas. So he decided to work out his own entrepreneurial strategy:

We need to compare the conditions regarding the FDA and the PMDA. The American government also wants change. The final aim is commercialization, and it is feared that full permission will be very hard to get from the PMDA. I have to study the situation in the US and in Japan, and then decide where to go ahead and apply for IND [investigational new drug] approval or for PMDA permission. The main achievement for me will be commercialization. (Interview, Hirogawa)

In early 2016, this researcher decided to move to a smaller university where he would be left to develop his own commercial network.

Regulatory brokerage has thus taken on international proportions among wealthy, advanced industrial countries. The negotiations that take place in the Keihin Coastal Area Comprehensive Special Zone (CSZ) in Kanagawa Prefecture illustrate how the particular regulatory features of countries can be combined in international strategies. With the support of FIRM, Keihin Coastal Areas is doing its utmost to attract industry. In 2017, ten companies within FIRM (Fujifilm, Astellas Pharma, Janssen Pharma, Regience, Rohto Pharmaceutical, Cell Seed, Wako Pure Chemical, Takara Bio, Tella, MediNet), initiated a taskforce called RM Industrialization Task Force (RMIT) to establish a RM

development centre in Kawasaki city, in the Keihin Coastal Area. The group is inviting overseas biotech companies to join them, to pool technologies and to provide treatments using cultured cells. The major areas of the development are cell processing and culturing, cell sheets, materials, equipment, reagents and pharmaceuticals (Ogawa, 2015).

Representatives of Kanagawa/Keihin – like those of the UK's Cell and Gene Therapy Catapult – list the advantages of their respective science parks in a self-congratulatory dance of mutual grooming. Kanagawa/Keihin is pictured as close to Haneda airport, allowing one-day round trips to Asian countries and offering deregulation, subsidies and tax advantages. Located at a distance from conglomerated areas, it allows for R&D using blood or bacteria. It has a local government open to industrial applications in RM. Its closeness to Tokyo Metropolitan area, with over 40 million people ('one-third of Japan') makes for access to many patients in a super-ageing society. It has a Life Innovation Centre (LIC) with a large hospital network counting fifteen hospitals and 7,900 beds, and possibilities for integration with other advanced medical technologies. Finally, the Kanagawa Centre for Clinical Research and Strategy boasts connections with the PMDA that can facilitate early permission, and a number of memoranda of understanding, including with interested organizations in Singapore, various states in the US, France, Germany, Finland, the UK and the World Health Organization.<sup>4</sup>

One prominent British delegate from the regenerative medicine community at the UK-JAPAN Life Innovation Symposium 'Opportunities for UK-Japan Collaborations in Cell and Gene Therapy' in Kawasaki in early 2016 recommended combining aspects of the regulatory systems of Japan and the UK. Identifying a gap between science and patient needs, he proposes the Academia, Business and Clinical approach, whereby both Japan and the UK score high on government and public support, infrastructure and R&D in academia, life science–industry collaboration, manufacturing, commercial support, cell automation and banking in business and hospitals and translational research in the clinic. From a regulatory point of view, according to the speaker, the countries differ: The regulation and reimbursement for cell and gene therapies (CGTs) – a European term for regenerative medical products – in Japan is both sensible and pragmatic. The question, then, is: 'How can your and our regulation push cell therapy along the long development pathway?' Typically, the pathway is ten to twelve years, but venture capital funds only invest in years five to seven. The financial gap and the risk of no reimbursement by health insurers are the main problems. According to the speaker, the EU and the US have tried to accelerate the regulatory pathway and reimbursement, but these are still not advantageous in the EU. Working together, he argues, can overcome various problems, also for Japan, through a trick: combining the Japanese and European systems. The problem with current international regulation, the speaker argues, is that it is inappropriate for CGTs:

The MHRA are holding discussions with Japanese regulators to discuss harmonization. Conventional regulation is an incredibly long process. It was for drugs; it has been adapted for biologicals, but it is inappropriate for CGT. Efficacy of CGTs is incredibly high: They work! We do not need many patients to show this. We have many therapies that only need two phases. We only need proof of concept in patients: We don't need many patients. The first in human application in a few patients is crucial. Then we need post-marketing studies.

According to the scientist, the plan involves only two steps:

There are challenges with the regulation internationally. In Japan, there are great conditions for approval; it is a big improvement compared to the UK/US. If we start a clinical trial in the EU, you start with a first-in-man in the UK; then you need to do a bridging study – six patients – to get to Japan. In Japan, you get a conditional and time-limited approval, which means you get reimbursement. It also helps clinical experience in Japan and getting economic data. The trick is to have a parallel study in Europe: It would be a randomized control study in the UK, which is much better in Europe. The advantages are, first, you get quicker approval internationally, second, you do not need to wait as long for approval, and, third, you get higher reimbursement.

From the point of view of life scientists knowledgeable about various regulatory systems and aware of the importance of becoming international early on, this ‘trick’ is an attractive strategy of regulatory brokerage and conforms entirely to formal regulatory provisions in place in both countries. Nevertheless, we also see that this form of international regulatory brokerage, ageing populations are offered as testing material for products that are only presumed to work, a notion that calls out for public discussion. And as pointed out by various scientists, Japan should not use its tax money to pay foreign companies to experiment, even if experiments yield some successful products. Different camps of scientists have come about, whereby some feel that the quality of science suffers from the demands of Japan’s international ambition, while others ride high on the wave of opportunities it has created.

### *Case 5: Global brokerage and regulatory ‘harmonization’*

The previous case points at some difficulties at the heart of Japan’s deregulation. The expected efficacy requirements for conditional and time-limited marketing permission differ from those of the authoritative International Society for Stem Cell Research (ISSCR). The ISSCR, an organization widely (but not necessarily correctly) thought to only represent scientists from ‘Western’ elite laboratories, propagates standards of safety and ethics through its website, affiliation to elite research centres, representation on the boards of journals and funding agencies, and its widely attended conferences. The difference between Japan’s and ‘international’ standards entails at least two major challenges:

- Gaining international acceptance of cell therapy products licensed in Japan to access the global market
- Maintaining the reputation of Japan’s science, if inferior products are licensed without internationally accepted evidence

To address these challenges, regulators and scientists have tried to gain international acknowledgement of the validity of the new Japanese regulation. They have done this by first, persuading other governments to follow Japan’s regulatory model, which would turn Japan into a leading example, second, lobbying with global regulatory agencies, industry and scientists to involve them in discussions about regulation, and, third, pushing for international regulatory standards for cell therapy producers.



Deregulation both encourages and requires a prioritization of scaling up and international industrialization; only off-the-shelf products are regarded as affordable and in the long run the only way to recoup the large investments into cell therapy products. In Japan, clinical trials are unaffordable for academic institutions, which is why IND-led clinical research may be done ‘under GMP- (good manufacturing practice) like conditions’ (Interview, Hirogawa).<sup>5</sup> And, without state support for quality control for clinical trials, RM clinical studies, which cost roughly ¥50 million (US\$500k), are beyond the budgets of academia. One researcher argues that, regardless of the new ‘deregulation’, the way forward in RM requires clear industrial standards for companies to manufacture therapies that are affordable and safe. This involves the scaling up of production and the creation of international agreement on a ‘smart’ form of cell processing – a form of process monitoring and validation, whereby raw material, process, facility and manufacturing may be variable – which in turn requires scientists to work in tune with the manufacturing process. Regulation modeled after the ICH guidelines would enable the development of therapies attractive to industry. This idea is now on top of the agenda of the PMDA (Interview, Kato), and, indeed various stakeholders are working towards this purpose (JSRM, 2015: 2–5).

AMED, the PMDA and FIRM work closely together to achieve this. In February 2011, the Stem Cell Evaluation Technology Research Association, a system for the evaluation of marketing and post-marketing, was founded, which in 2015 was reorganized under AMED and FIRM (SCETRA, 2016). AMED, with a budget of ¥121 billion (US\$1.27 billion) in 2014, is tasked to maintain an efficient and better environment for R&D. Funding and managing projects with 330 staff, it negotiates the coordination and insurance of clinical trials and clinical research with Asia (Japan, China and South Korea), and has established overseas offices in the United States (Washington DC), the United Kingdom (London), and Singapore (AMED, 2019). The PMDA has created the ‘PMDA International Strategic Plan 2015’ to establish inter alia a Regulatory Science Centre, and to launch the ‘Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs’ (PMDA, 2015); it invites regulators from other countries to international conferences to discuss and propagate Japan’s regulatory system (PMDA, 2016).

FIRM especially engages with global industry, and according to FIRM Chairman Yuzo Toda, FIRM ‘strives to promote Japan’s novel regulatory system to the world’ (Okano et al., 2015). It also does so in Asia through the Asia Partnership Conference of RM Associations (QLifePro, 2018) and in the West through the Alliance for RM (ARM, 2016), the international organization representing RM and advanced therapies in the West. In March 2015, the Alliance for RM announced its memorandum of understanding with Japan’s FIRM. The Alliance’s Chairman, Edward Lanphier said:

Our collaboration with FIRM is an important step towards ensuring the continued growth and support of this field. ... With the recent changes in Japan’s regulatory environment, FIRM is uniquely positioned as a vital partner in promoting the success of RM and advanced therapies worldwide. (ARM, 2015)

With a similar mission to accelerate research, development and commercialization of RM and advanced therapies products, the two organizations seek global regulatory

harmonization. One question that arises here, is how regulatory harmonization fueled by international regulatory competition can internalize human concerns.

## **Discussion**

Compared to molecular medicine, the ‘lively’ nature of RM makes it unsuitable for global clinical trials, which is why new regulation was developed. This article explores the role of regulatory brokerage in such regulatory change. If regulatory change is largely driven by regulatory brokerage, important issues related to social and cultural values and human rights may be bypassed. I define regulatory brokerage as a form of science-entrepreneurship that takes advantage of regulatory variability in the negotiation of collaborative scientific research and in the shaping of regulation. Exemplifying forms of regulatory brokerage at various levels of organization and governance, I have shown how regulation is used commodified and used as regulatory capital in negotiations. Differences between relatively permissive and prohibitive regulation are utilized to broker transnational collaboration to gain a competitive edge. What the five cases here have in common is that, rather than complying with regulation in terms of such goals as safety, efficacy and ethics, regulation is commodified and utilized as ‘regulatory capital’. Here, it is notable that the five cases show that the commodification of regulation occurs at different levels of international collaboration and governance. Regulatory brokerage at the global levels of negotiating and shaping regulatory regimes is just as driven by competitive advantage as is regulatory brokerage on the lowest level of international science-collaborations among companies.

In what follows, I suggest that lower levels of regulatory brokerage precede higher levels of regulatory brokerage for political, scientific and economic reasons. I argue that regulatory brokerage as the basis for regulatory reform bypasses issues that need to be decided by a broader public. Last, I point to examples of transnational collaboration that are not driven by competitive advantage to show that regulatory brokerage can be resisted, when other considerations trump.

Tracing forms of regulatory brokerage in Japan has helped to generate understanding of the pressures and drivers behind regulatory reform. Forms of regulatory brokerage have changed radically over time, starting out with relatively prohibitive regulation in the early 2010s, and becoming increasingly permissive after Japan started to focus on translation of iPS in the late 2010s. The first case of regulatory brokerage by a science-entrepreneur in JCRM revealed a simple unilateral strategic use of the regulatory gap between companies and organizations in India and Japan, and the utilization of infrastructural, economic and scientific differences since 2005. The second case, of Japan-Thai collaboration initiated by Kawasaki Heavy Industry, describes the bilateral use of regulatory differences regarding the permissions for conducting clinical trials and marketing in 2011. The collaboration was brokered using regulatory capital on the Thai side, even though, as discussed below, the regulatory capital was contingent upon decision-making by Thai regulatory bodies. As KHI wanted to test the robotic processes through a successful clinical trial, and as Chulalongkorn University hoped to benefit from using it and the scientific training accompanying it, the agreement was explicitly bilateral. Interestingly, the venture was financially supported by state organizations in both

countries, which made the evasion of regulatory hurdles a state-supported undertaking. Despite the presence of officials and royals, the collaboration was emphasized as one between academic and commercial institutions. The third case shows how the push toward deregulation and the reconfiguration of rules in Japan by some industrial and professional organizations constitutes a form of regulatory brokerage, as the deregulation aimed to attract investment and industrial companies to Japan, reformulating criteria for safety, efficacy and ethics. The fourth case exemplifies a case of international regulatory brokerage. It described an openly proposed 'trick' for industry in Japan and the UK to accelerate the commercialization of RM with the support of regulatory agencies in both countries. This form of regulatory brokerage was advertised as combining the advantages of both regulatory systems. The last case illustrates how Japan, to gain acceptance of its cell therapy products and to maintain its scientific reputation, engaged in regulatory brokerage through overseas offices in Asia and in the West to create international industrial alliances and to lobby for deregulation. Minimizing global regulatory differences became advantageous both to the Japanese (who saw themselves as setting the standard, and wanting the world to accept it) and to ARM, to which liberalized regulation seemed the only way to catch up. In this case, too, regulation is being brokered in the first place as a commodity, rather than as a vehicle to ensure safety, efficacy and ethical practice.

These examples show that regulatory expedience is an economic driving force, whereby comparative advantage incentivizes research collaboration. State organizations, we saw, encourage such collaborations, violating the spirit of the country's regulation. Moreover, policies of deregulation, investment in infrastructure and legal measures in Japan clearly assumed that they would accelerate the translation of RM in Japan, attract foreign investment, and in the end lead to more affordable healthcare provision for Japan's rapidly ageing population. The ensuing regulatory discrepancy with other countries attracted foreign industrial capacity and investment from abroad and Japan. Deregulation was also the reason for foreign scientists and official representatives to broker a situation in which science and industry could take advantage of features of both country's regulation. Japan's perceived regulatory permissiveness put pressure on other countries to take similar measures, now at the level of international harmonization and competition. At the same time, Japan had to do groundwork to persuade other countries that deregulation must not be equated with allowing the marketing of inferior products. As international industry is already under pressure to deregulate, international alliances were formed to lobby with governments to liberalize regulatory standards. It is clear, then, that regulatory reform efforts in the field of RM described here have taken place for political, scientific and economic reasons: through regulatory brokerage.

We have seen, then, that regulatory brokerage may evade state regulation (case 1), evade state regulation with state sponsorship (case 2), create comparative advantage vis-à-vis other states (case 3), provide a setup for bilateral advantages among states (case 4), and facilitate global powers to reform international regulation (case 5). But whatever the motivation given for regulatory reform, such as the acceleration of translational research, scientific advance and savings on healthcare, regulatory brokerage is always about competitive advantage, regardless of any specific motivation.

There is a need for public discussion about the issues bypassed by regulatory brokerage as the basis for regulatory reform. In particular, transnational collaboration for reasons of regulatory advantage avoid responsibilities associated with ethical and legal behaviour 'at home', and so raise interrelated bioconstitutional, socio-economic and ethical issues. As shown in cases one and two, regulatory brokerage entails important socio-economic issues concerning whether transnational collaboration with countries with scarce resources justifies the investment into it by the host countries (India and Thailand here), especially when its advertised values depend on regulatory discrepancies in the first place. There are also ethical issues related to whether experimental service providers should be allowed to import and export health risks to patients at home or abroad. Regulatory brokerage becomes especially problematic if it is treated as a proxy for public healthcare in the country importing experimental clinical applications. This issue becomes especially poignant in the case of the brokerage of regulatory regimes (cases 3–5). Pushing regulation that undercuts international competition as a policy of economic expansion in the area of testing RM entails unknown risks, as I discussed in the introduction.

On a *national level*, we see that international brokerage in Japan has involved the political rigging of public resources in support of RM, and pressure to accelerate clinical translation and marketing. Despite concern given to ELSI issues, it has ethical consequences for patients, if they are required to contribute to treatment that is expected to work rather than proven to work. At the same time, international companies are attracted to test their products on Japanese patients and indirectly subsidized by both Japanese patients and insurance companies. Strategic regulatory changes that have the potential to affect the quality of science and internalize the financial and risk burden for patients require public consideration.

On an *international or bilateral level*, taking advantage of each other's regulation as a strategy of entrepreneurial scientists to accelerate clinical translation, as we saw in case 4, violates the spirit of the regulation in both countries. Should members of the government bureaucracy be obliged to report to the public cases that contradict a country's regulation or its spirit?

On a *global level*, we need to ask whether regulatory issues in RM should be decided by industry. Considering the fundamental disagreement on the state of the art among scientists, there needs to be far more transparency on regulatory reform with involvement of independent outsiders, both from wealthy countries and LMICs. Discussion on regulation should consider scenarios of regulatory brokerage when formulating regulatory reform.

Considering the socio-economic consequences, insights into the role of regulatory brokerage give a worrying impression of competition as the basis for regulatory change. However, the examples above also show instances where regulatory brokerage was rejected, even when it could have yielded short-term benefit. In the second case, Thai scientists from Chulalongkorn University were concerned with the quality of their science and their reputation, and did not support the early marketing or premature clinical trials. Similarly, the ISSCR regarded clinical trials based on 'probable evidence of efficacy' as problematic (ISSCR, 2016). Such stances show that a slippery slope of regulatory brokerage is not inevitable, even though there might be an uphill struggle. The

current procurement focus depoliticizes the field and needs further bioconstitutional considerations. Research on regulatory brokerage needs to further explicate how international regulatory decision-making and national regulation interact, and how conflicts of interest between industry and science regulators affect the regulatory decisions that shape the international development of RM.

### Acknowledgements

I would like to thank Alex Faulkner and the anonymous reviewers for their helpful comments. Many thanks also to the anonymous interviewees for their time and efforts. Due to ethical concerns, supporting data cannot be made openly available.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This article has benefited from research support provided by the European Research Council (ERC: 283219) and the Economic and Social Science Research Council ESRC: ES/I018107/1).


### Notes

1. For instance, as of 16 March 2016, EMA has approved only 6 products: three tissue engineering products (ChondroCelect [2009]; Maci [2013] and Holoclar [2014], the last of which is approved only conditionally), two gene therapy products (Glybera [2012] and Imlygic) and one somatic cell medicinal product (Provenge [2013]), which has been withdrawn (Detela, 2016).
2. Indeed, permission for using ‘mesenchymal stem cells’ processed by the robotic machine in a clinical trial on knee cartilage deficiency was not given until late 2016 (Kawasaki, 2016). Though this shed positive light on the automaton, what KHI needs to show that its processed cells are used in a product with marketing permission.
3. Some collaborations announced in recent years include: Athersys with Healios KK for novel cell therapy treatments, including MultiStem for ischemic stroke (Athersys, 2016), Avita Medica with INDEE Medical for their ReCell® device for autologous cell treatment for burns, reconstructive and cosmetic procedures (Densford, 2016), Cynata (Australia), and Regience KK to develop and commercialize Cynata’s therapeutic mesenchymal stem cell (MSC) technology for Japan and for certain Asian countries (Cynata Therapeutics, 2016), Mesoblast (Australia) with JCR Pharmaceuticals to market Prochymal®, an allogeneic MSC product for graft-vs-host disease (GVHD). Cytori (USA) announced first patient enrollment/treatment in their Japanese physician-initiated ADRESU trial for Cell Therapy™ (Cytori, 2015); Pluristem (Israel) reached agreement with the PMDA on the design for a 75-patient phase I/II trial in Japan for PLX-PAD for the treatment of CLI (Pluristem, 2016); Replixel (Canada) collaboration with Shiseido for their RCH-01 therapy (Replixel, 2013); and, Regeneus (Australia) announced targeting Japan for their allogeneic adipose-derived mesenchymal stem cell (MSC) off-the-shelf product, Progenza (Regeneus, 2017).
4. For comparison, the British counterparts showcase the attractions of the Cell and Gene Therapy Catapult – an independent non-profit organization, set up in 2012 – listing its advantages for transport, industry and R&D. Other benefits that are emphasized include: government support for the first eight of the nine phases of clinical translation in product development, the advantages of the Stevenage incubator planned to be in operation from 2017, with its cluster development housing many industrial players, a world leading Good

Manufacturing Practice manufacturing center, viable logistics, a gateway to Europe, and a highly skilled workforce.

5. A GMP cell-processing facility can be expensive, with requirements for air filtration, barriers to contamination, oversight and certification. In some cases, laboratories just follow GMP practices and specify the grade of cell processing facility used.

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### Author biography

Margaret Sleeboom-Faulkner is Professor of Social and Medical Anthropology at the University of Sussex (Brighton, UK). Her work concerns processes of nation-state building in China and Japan and biotechnology and society in Asia. See: <http://www.sussex.ac.uk/profiles/192052/publications>. Margaret's research projects concern international life science networks in the fields of biobanking and biomaterials, and stem cell therapies and experimentality (funded by the ERC and ESRC respectively). In these projects, she combines anthropological approaches and social studies of science.

### Appendix I. Cited interviewees.

Pseudonyms	Background	Case	Place	Date
Prof. Asada	Scientist/engineer	3	Tokyo Uni	27-11-2013
Prof. Sonoda	Scientist	3	Kyoto Univ	05-11-2013
Prof. Ito	Lawyer	3	Kyoto Univ	09-03-2013
Dr Yamamoto	Scientist	4	Kyoto Univ	28-03-2013
Dr Hirogawa	Scientist	4	Univ in Kyoto	12-02-2016
Prof. Takeuchi	Scientist	4	Univ in Kyoto	22-11-2013
Prof. Kato	Scientist	3	Hospital in Tokyo	27-02-2016
Prof. Kaketani	Scientist	3	Biomedical Institute, Kobe	27-01-2016
Dr Hata	Scientist		Hospital, Tokyo	26-11-2016
Dr Kumar	Scientist	1	JCRM, Japan-India	05-11-2008;
Dr Wilipana	Scientist	2	CU, Bangkok	25-6-2014
Dr Wattanapanit	Scientist	2	CU, Bangkok	27-6-2014
Prof. Michaels	Scientist	2	Univ. of Loughborough	13-8-2014