A view against the grain? The role of regulation in Argentine and Indian bioscience innovation

Conference or Workshop Item

REGULATION AND INNOVATION AND REGULATORY INNOVATION: A VIEW AGAINST THE GRAIN FROM ARGENTINA AND INDIA

Shawn H.E. Harmon[*]
Dina Kale[†]

Abstract: This paper engages with the complex relationship between innovation and human health and the role of regulation in bringing the two together, and, in doing so, facilitating sustainable development in emerging economies. After outlining the contested role of regulation in fields reliant on innovation, we provide two case studies derived from our empirical research into regenerative medicine regulation (in Argentina) and medical devices regulation (in India). While these case studies examine different scientific sectors in different jurisdictions and therefore have very different contextual foundations, they both demonstrate the important link between regulatory policies and the successful promotion of innovation. Through these case studies we challenge the oft-repeated complaint that regulation stifles innovation. We demonstrate that both a lack of regulation (Argentina) and poorly conceived regulation (India) are equally damaging to innovation, to actor wellbeing, and, ultimately, to human health. We go on to argue that devising new forms of regulation could facilitate increased innovation and thus improved thus technological (and economic) competitiveness (ie: social/regulatory innovation can lead to improved technological/scientific innovation).

Keywords: biotechnology, regenerative medicine, medical devices, innovation, regulation, Argentina, India

I. INTRODUCTION

Biotechnologies are a group of technologies, a range of activities, and a cluster of sectors that 'enable' other sectors (eg: environmental, food and health), and they are increasingly important for translating scientific knowledge into instrumental products, including medical ones delivered 'at the bedside'. Biotechnologies are seen as contributing to the 'bioeconomy', which, while somewhat amorphous, is increasingly important to developmental ambitions. Perhaps unsurprisingly, biotechnologies and the bioeconomy are tangled up with the concept of 'innovation'. Sometimes defined as 'the successful application of new idea to use' (Kaplinksy and Morris, 2008), innovation is the lode-stone of the 'creative destruction' claimed by Schumpeter (1934, 1942) to be necessary for development.[1] Biotechnologies like stem cell

[*] Lecturer in Regulation and Risk, School of Law, University of Edinburgh; Research Fellow, Innogen, ESRC Centre for Social and Economic Research on Innovation in Genomics, University of Edinburgh.
[†] Lecturer in International Development and Innovation, School of Social and Political Science, Open University; Research Fellow, Innogen, ESRC Centre for Social and Economic Research on Innovation in Genomics, Open University.
[1] Innovation can be 'path-breaking' (revolutionary changes deemed to be radical or disruptive), or, more commonly, 'path-following' or 'incremental' (small developments in products or processes within a firm, sector, region, or globally). Transistors and integrated circuits are examples of innovations which caused creative

research techniques and pre-natal genetic diagnostics processes are examples of innovations which are realigning healthcare and pharmaceutical industry practices. Successful innovation requires:

1. appropriate linkages between the diverse (and often networked) actors;

2. effective nodes for consideration of the myriad social and technical hurdles/concerns; and

3. space to forge unique or alternative practices and processes that are necessary to transform a new idea into a safe and effective product.

Governments often seek to address these requirements (and innovation stimulation more generally) through industrial policies and infrastructure investment, taxation, and regulation. While concentrated public investment and attention has proven successful in the past,[2] it is relatively rare in the absence of intense pressures. And while regulation is often *not* the main driver (Wolf and Delgado, 2003), regulation can have profound impacts on stakeholder ambitions and activities, and therefore on innovation trajectories. Indeed, regulation can determine company strategies, types of companies that can succeed, and the structure and dynamism of whole sectors (Tait, 2007).

Regulation can include international treaties, agreements, and declarations, national legislation and/or derivative statutory instruments, and national, regional or professional guidelines or codes, as well as the evolving norms of established and newly emerging networks, and in the life sciences, often includes all of the above. The courts are also important regulatory institutions, with the ability to shape innovation (and sectors). For example, the US Supreme Court's decision in *Diamond v Chakrabarty* has been credited with the rise of the biotechnology industry.[3] Regulation often has one or more of the following objectives:

1. to establish incentives and constraints aimed at stimulating growth;

2. to create sustainable institutional modes that are flexible enough to accommodate sectoral evolution; and

3. to develop products that are safe, effective and supportive of public health.

As a result of the expansion, transformation and intensification of risks associated with developments in the biosciences, the regulation of the biosciences (and biotechnologies) has become extremely important. However, concerns abound about the regulation that prevails and

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destruction and shifted how actors provide products, pursue processes, and offer services.

[2] The impact of government investment and regulation can be observed in the case of the pharmaceuticals industries. In 1880, Germany and Switzerland were at the forefront of drug development and manufacturing. The outbreak of World War II, however, prompted the US to foster massive chemical analysis and commercial production techniques (Henderson et al., 2007). The resultant system significantly improved productivity and provided the platform for the US to leapfrog European pharmaceutical companies.

[3] That case involved a patent claim on a genetically modified, oil-eating bacterium. The US Patents and Trademarks Office (USPTO) rejected the claim on the basis that subject matter (a living organism) was a discovery, not an invention. The Court reversed that ruling and granted the patent, thereby establishing the practice of making very broad patent claims which positively encouraged investment (Merges and Nelson, 1994).

about their effect on the bioeconomy. The form, scope, and stringency of regulation have been, and continue to be, much discussed and much maligned. Many of these regulatory efforts, particularly the formal or command-and-control ones, have been reactionary. As noted by Wolf and Delgado (2003), and Schellekens and Moors (2010), the unfortunate consequence is that they have been largely cumulative, rarely cooperative/integrated, and often fragmentary and complicating of innovation systems and product pathways.

Perceptions of 'regulation overdose' (Espein, 2006) or 'overregulation (Havighurst and Richman, 2006) together with changing regulator attitudes and behaviours (ie: both the FDA and EMA have gradually shifted from post R&D evidence evaluators to more active participants in the scientific process) have contributed to the advancement of several widely agreed criticisms of regulation. For example, Curtis and Schulman (2006) argue that regulation affects service delivery costs by demanding excessive documentation. Moreover, increased intervention in one area (or aspect) of innovation may (and frequently does) conflict with regulatory requirements in another, resulting in uncertainty and duplication of effort, and therefore increased costs (PWC, 2002; Reed et al., 2006; Munos, 2009; Schellekens and Moors, 2010). Another criticism is that regulation quickly becomes obsolete as technologies evolve, so rules designed to protect subjects may have unintended consequences such as preventing quality low-cost alternatives from reaching the marketplace. It is also claimed that regulation often stifles creativity by erecting barriers to 'out-of-the-box' or 'blue sky' thinking (ie: it prevents disruptive technological improvements). Drawing on Christensen (2007), Curtis and Schulman (2006) argue that disruptive innovation is more likely in weakly regulated markets because lower standards allow the introduction of experimental products that cannot meet the standards in markets where products are expected to meet 'ideal standards'; 'ideal' rather than 'optimal' standards hamper disruptive innovation.[4]

In short, the oft-repeated view is that regulation hampers innovation and the development of strong and competitive industries (Zerhouni, 2005; Reed et al., 2006; Munos, 2009). This view, combined with counter-veiling concerns around risk, have pushed governments to oscillate between tight regulation and deregulation. While we do not dispute the potential of regulation to serve undesirable ends, that is not the whole story. Regulation can have many salutary effects, some of them surprising, so neglecting to regulate, or deregulating where frameworks already exist, is not necessarily the way forward, a fact not always appreciated in jurisdictions with sophisticated (or burdensome) regulatory infrastructures.

This paper examines some of the difficulties caused by regulatory vacuums. Examining two emerging jurisdictions over which there has been limited attention – Argentina and India – it offers some preliminary observations about the negative impact of such vacuums. The first case study focuses on Argentine regenerative medicine research regulation and the second focuses on Indian medical devices regulation. Both demonstrate that regulation can be a boon rather than a burden for a host of reasons only peripherally relevant to risk, and both support the conclusion that these jurisdictions (and others which have pressures and concerns quite different from those in developed countries like the UK, US, Canada, Japan) should make every effort to avoid

[4] The information and communication technology sector is a good example of this. In the last two decades, the lightly regulated ICT sector has experienced much greater growth and product (and technical) evolution than the much more heavily regulated life sciences sector, and innovations have often emerged from small start-up companies which are able to build resources and upstage existing industry players by innovating in ways that challenge the status quo. In short, less burdensome regulation has permitted new and dynamic players to drive the sector forward. By contrast, the life sciences sector is dominated by a relatively small group of multinational companies with the capacity to navigate the regulatory forest. See Tait (2007) and Tait et al. (2007).

recreating the 'should we / should we not' regulate debate. A failure to avoid this dualism could result in missed opportunities to explore (wholly) new and smarter forms of regulation which might better generate improved bioscience (and medical) innovation.

II. REGULATORY NEEDS AND AMBITIONS IN TWO DEVELOPING COUNTRIES

While both case studies were undertaken within Innogen, the ESRC Centre for Social and Economic Research in Innovation in Genomics (with one – 'Governing Emerging Technologies: Stem Cell Research and Social Values in Argentina' (GET: Social Values Project) – being separately funded by the ESRC), they were not designed or conducted as a 'pair'. However, they are appropriately considered together because they both investigate healthcare research and medical product settings in emerging jurisdictions, they both have a regulatory focus, and they are both informed by Innogen's concern with overarching innovation frameworks. The following analysis is structured to highlight shared insights and points of comparison. The quotes used were chosen as representative of the evidence on the particular issue explored.

1. Argentina: Regulatory Boundaries and 'Cover' in Regenerative Medicine

a) Aims and Methodology

This case study was designed to gather qualitative data around key issues of regenerative medicine research governance in Argentina. While the GET: Social Values Project captures important and heretofore largely untapped qualitative evidence concerning various facets of this field (and specifically stem cell regulation), the opinions of the broader (lay) public were not solicited and the data generated cannot be said to represent 'the Argentine view'. Those originally viewed as most likely to influence the nature and content of bioscience regulation (generally) and stem cell research regulation (specifically) were targeted. Ultimately, twenty-two respondents falling into two broad categories took part. Approximately half were regenerative medicine clinicians and/or researchers, many of whom also held policy advising positions, and the other half were national regulators, jurists, and politicians, many of them either scientifically or legally trained.

The interviews were semi-structured and lasted from 50 to 90 minutes. For the most part, open-ended questions and a relatively informal interview schedule were used to encourage participants to speak in their own words about their experiences, observations, opinions, and desires. Nonetheless, some structure was observed insofar as the PI and Co-I ensured a consideration in each case of certain broad topics, and topics were consistently broached in the same order, unless a particular exchange intervened to make an issue's immediate exploration more appropriate/convenient. The scope of evidence-gathering was limited by access to the participants; interviews were scheduled to fit as un-disruptively as possible into the participants' schedules, and time availability varied. The transcripts and interviewer notes were coded and analysed for emergent themes, the most relevant of which for present purposes address public debates and public understanding of science and opinions about hurdles to achieving regulation that is morally grounded (Theme 2 – Social Context), and opinions about the necessity of government regulation (Theme 3 – Regulatory Ambitions).

b) Background

Argentina faces a collection of healthcare and bioscience innovation challenges, some of them common to developing countries, and some of them rather unique. With respect to the former, access to healthcare is uneven, healthcare standards are neither uniformly defined nor universally applied, researchers struggle for enough funding to be internationally competitive, and basic research has no explicit domestic boundary-setting regulation (Arzuaga, 2011). With respect to its unique challenges, Argentina experiences significant medical tourism, enjoys relatively high levels of regenerative medicine research, and suffers from unclear boundaries between (1) clinical practice and research and (2) accepted therapies and experimental therapies (Arzuaga, 2011).

Despite these challenges, some of which have a profound effect on how actors within the regenerative medicine 'industry' behave, Argentina aspires to make biomedical research a pillar of sustainable development, and it is pursuing a host of activities in the health innovation setting. This might be expected given the very strong bioscientific heritage enjoyed by Argentina and the generalised esteem to which scientists are held by Argentineans (Kramer, 1996; Stekolschik et al., 2010). However, close examination of the Argentine regulatory scene suggests that, as of January 2012, its regulatory regime remained sub-optimal (Harmon, 2008; Harmon, 2011). Relevant regulatory instruments are as follows:

- The *Transplantation Act* (Law 24.193), as supplemented by Ministry of Health (MOH) Resolution 610/2007, establishes the INCUCAI, which oversees the transplantation of organs and tissue into human patients. The INCUCAI must approve all stem cell projects, but its capacity to do so has been questioned, as well as its expertise, and it has no effective enforcement mechanism when approved projects fail to comply with expected standards.

- The *Medicines Act* (Law 16.463) establishes the ANMAT, which licenses medicinal products for market. Cellular therapies are considered medicinal products, not transplants, if they are manipulated, but there are no agreed good manufacturing practices for cellular products.

- MOH Resolution 1490/2007 sets out good practices for biomedical research.

Argentina's federal character means that these instruments and institutions have limited reach into the provinces, which have primary responsibility for health but which are unequal in both financial capacity and attention to research and healthcare demands.

c) Findings

Obviously, then, there are a range of gaps or bases on which to draw a conclusion of sub-optimal regulatory frameworks in Argentina.[5] For present purposes, the GET: Social Values Project uncovered two widely held views (amongst the respondents) that support the thesis advanced, namely that regulation can have positive consequences. The first reiterates the previously

[5] Although note that some of these are being addressed through ongoing legislative efforts of the Ministry of Science, Technology and Innovative Production (MOST).

mentioned (and widely held) risk-based perception of regulation, and so will not be dwelt on. Basically, many respondents opined that the prevailing dearth of regulation left improper scientific practices unmonitored, unchallenged, and unpunished. While it would take a bold (and misinformed) person to suggest that regulation guarantees 'good science', and while it was acknowledged (at least by some) that consistently achieving 'good science' requires systemic approaches, it was generally held that regulation is important for discouraging 'bad science' (eg: falsification of results and fraudulent behaviour) (Kreutzberg, 2004). A common aim of regulation is, after all, to alter or shape behaviour according to defined standards (Black, 2002).

By way of example, a consequence of the prevailing Argentine setting, as identified by the respondents, is that there is ample scope for actors to behave in ways that are detrimental to the scientific undertaking and patient safety. R5, a stem cell researcher, observed that clinical trials have been undertaken (and published in international journals) without the consent of authorities:

> So the scientific community should be much more strict on asking, for example, for the authorisation to do the clinical trial … because if that paper gets published then, for us in Argentina, it is more difficult to tell the patient, 'This clinic is doing something wrong'. Because the clinic then shows the scientific paper saying this clinical trial is validated.

This, this respondent felt that more comprehensive coordination is warranted. R6, a public health physician and policy advisor, stated:

> You have problems in the academic institutions [with] investigators [and] with ethics committees. Ethics committees don't have training … . They need training, starting with specific knowledge. They don't have it. And they don't have government support for this. That is a big problem because you can't approve or refuse something you don't know about. Then you have problems with investigators. I [know an] Argentinean investigator, he knows nothing about the international regulations.

R19 added:

> You know that we have some places in Argentina – like St Nicholas in the province of Buenos Aries – that are using cellular therapies for everything. And that is, they have protocols that … don't have the approval of the Ministry of Health, and they don't have the approval of INCUCAI. And they publish papers in the international level, because, I don't know why, because … in the paper they have the institutional review boards in their institution. And so they have the informed consent of the patient because the patient is blind. And of course, the journals accept the papers.

More interestingly, respondents felt that regulatory lacunae hampered innovation insofar as researchers operating in potentially high-impact but controversial fields (such as regenerative medicine) were offered no 'regulatory cover'. In short, researchers by-and-large wish to (1) pursue their science, and (2) where appropriate, engage with the public around their science and

its trajectories and potential outcomes. The former is the natural desire that pushes researchers to enter and then excel in their chosen field. The latter comes from the realisation (by some) that both public understanding and acceptance of science *and* science outcomes are improved when science is approached democratically, or pursued in an open and participative manner.

The ideas of openness and discursiveness are particularly daunting in Argentina because of the perceived antagonism of certain institutions toward science generally and regenerative medicine more specifically. Perhaps unsurprisingly, one such institution is the Catholic Church. While there is a risk of broad-brushing away the diversity of opinions toward science within the Church, it can be said that it has acted suspicious of, and resistant to, many aspects and aspirations of regenerative medicine (Macklin and Luna, 1996; Acreo, 2006; Luna and Salles, 2010). It is also reflected by the dominant view of respondents in the GET: Social Values Project, many of whom viewed the Church, or at least its formal, public positions, as antagonistic. Respondents felt that rigid Church positions and dogma made it impossible to have reasoned and rational public discourses on any aspect of science that implicates reproduction or the embryo, including regenerative medicine. One respondent, R4, a stem cell researcher, said:

> [Y]ou will see that the debates [about] abortion; there are still people who are against abortion and they go to the hospital and try to convince very poor people that they shouldn't abort. It is the claim that God and angels will come and will lead them. I don't know. There is still a lot of work to do.

With respect to stem cell research related dialogues, R16, a physician, stated:

> Just within the specific scientific community. In that group we agree this kind of research is important, but there is a problem in Argentina with religion. … People are confused, confused ideas from church [about] science. …

R19, a physician, health administrator, and policy advisor, noted:

> I am sure that if we put the [issue of embryonic stem cell research] on the face, it's very probable the Catholic Church would take a position against that. And the Church influences, probably not the population, but the politicians.

In settings where powerful institutions are oppositional, and are perceived as such, the science culture and the individual researchers' place in it become negative and embattled, sometimes even untenable. In Argentina and similarly polarised environments researchers are confronted with challenges and concerns that are not necessarily experienced to any comparable degree by colleagues in competing and collaborating jurisdictions. Many of the Argentine respondents harboured serious concerns around such basic matters as their 'freedom to research', which they felt was jeopardised by working openly, or publicising their work (of which they were rightfully proud). This perceived need to conduct science 'behind closed doors' was articulated by R14, a lawyer, who stated that scientists remained reluctant to announce their findings to the people and this reluctance meant that people formed decisions about science based on partial evidence; the scientific voice was not heard so people sometimes formed false impressions about research. R15, an academic scholar and bioethicist, stated:

> There [was] some buzz … when the Obama position about accepting research with stem cells was brought up by the [Advisory Commission on Regenerative Medicine and Cellular Therapies], but it's more like isolated voices. I think that behind the scenes, the root of the problem is the position of the Catholic Church. And that's why everybody tries to be cautious about what they say and how to deal with this issue. ... It is like everybody is afraid of the Church … . And so people that are doing assisted reproduction will save embryos and they will not destroy embryos and they will not accept that they do anything. … And even the abortions that are accepted by law, they are not performed. … I think there is really a silence about it. … The researchers are not saying anything. We have really high quality centres for assisted reproduction, and people come to Argentina to do these treatments because they are cheap and very good. But at the same time, nobody will accept what they are doing. … [N]obody is willing to go upfront and say, 'Well, we do this because it is important,' and it is difficult continuing to work with embryos.

This position was echoed by a member of the Advisory Commission on Regenerative Medicine and Cellular Therapies, who stated that the Commission tried to encourage an open debate on stem cell research in 2007/08, but many of the key actors were reluctant to do so because of concerns about negative attention.

Ultimately, researchers are not comfortable exposing their research or announcing their findings publicly because of anticipated reactions from institutions like the Church, and because of potential reactions from publics labouring under misunderstandings of science which are, at least in part, encouraged by the Church. Unsurprisingly, Argentine researchers – at least those who participated in the GET: Social Values Project – wish to be more open in the pursuit of their science. R2, a researcher and regulator, stated that proper scientists are tired of listening to the claims of those who are working unethically, and would like to have better and safer opportunities to clarify the situation. R16 reiterated this, stating that attendees at recent doctors' meetings claimed that they would like to work in this area (ie: regenerative medicine) but they would like to have more contact with supportive organisations, including international ones.

While most respondents felt that past efforts at regulating science in Argentina were not particularly well conceived, or were now outdated, they almost unanimously felt that rational, evidence-based, and informed government boundary-setting was essential. R2, a regulator, suggested that the governance regime must facilitate science while demarcating forbidden pursuits and practices, thereby giving actors clear guidance. R10, a legal-ethical academic, stated:

> I think that, today, you need to regulate because the power and possibilities in the scientific field are so much, and the possible effects are so terrible … . With a lot of care … and consulting specialists [scientific and bioethical], something must be done.

R12, a federal judge, noted the quality of Argentina's science and opined that good regulation which encourages useful outcomes would be helpful.

d) Summation

Generally, most respondents either wanted or recognised the value of a regulatory framework. They considered that such would (1) set boundaries and thereby help to dissuade 'bad science', and (2) signal publics and antagonists that this research is, in the usual course and where appropriately reviewed and pursued, ethically defensible, publicly supportable, and internationally competent. In short, they want some framework with a legitimating effect, for this, it is perceived, will serve a trust-building function that will promote greater transparency, an improved working culture, better science, and therefore improved innovation. While it was recognised that regulation (or the process of regulation-making) might exacerbate opposition and polarise opinion in a way that sets the science back, it was nonetheless seen as worth the risk, and the Brazilian example served as a model outcome.[6]

2. India: Standards and Specificity in Medical Device Regulation

a) Aims and Methodology

This case study investigated key factors hampering development in India's medical device industry, exploring in particular the role of regulation in the effective diffusion of technology in this important high-tech industry. It emerged from a concern that the nature of knowledge complexities in this setting combined with a lack of appropriate regulation can create important barriers to innovation. The Medical Devices Project engaged with 4 medium sized firms and the Sree Chitra Research Institute in the Indian medical devices sector. The firms were involved in developing products such as heart valves, orthopaedic implants, and blood bags. It undertook 10 semi-structured interviews with 2 interviews per company. Interviewees were primarily the Head of R&D and the CEO or Managing Director of the firms. Interviews were also conducted with senior journalist and industry association president to collect opinions from other stakeholders. Questions focused on the current status of the medical device industry, its regulatory framework and government initiatives to promote medical device research and manufacturing, and how it compares with India's pharmaceutical/biotech industry. Open-ended questions and a relatively unstructured interview schedule were used to encourage participants to speak in their own words about their experiences, observations, opinions, and desires. Data analysis was carried out using a theoretical framework based on innovation systems literature. As in the GET: Social Values Project, while specific participants were targeted, the original sample was supplemented by further participants through a snowball technique reliant on the social/professional contacts of the original sample members.

b) Background

According to the World Health Organization (WHO), the term 'medical devices' captures both highly sophisticated computerized equipment and simple wooden tongue depressors, and much in between (eg: medical gloves, bandages, syringes, condoms, contact lenses, disinfectants, X-ray equipment, surgical lasers, pacemakers, dialysis equipment, baby incubators, and heart valves). In contrast to 'medicinal products', whose primary mode of action is metabolic,

[6] The Brazilian stem cell industry went through a very turbulent and briefly stultifying time in the last 5-8 years as the government erected a permissive regulatory framework in the face of hostile institutions, including the Catholic Church.

immunological, or pharmacological, 'medical devices' are instruments, implants, or machines intended to be used, alone or in combination, for one or more specific purposes such as diagnosis, prevention, monitoring, treatment, or alleviation of disease (Shah and Goyal, 2008).

The medical device industry (MDI) is variably regulated. In the US, medical devices can reach the market through two regulatory processes: the 'pre-market approval' (PMA) process or the '510(K)' process. The most rigorous is the PMA process, which requires scientific evidence of safety and effectiveness for a device's intended use obtained through ethically sound clinical trials. Class III devices, which support or sustain human life and include many novel cardiac devices, are subject to the PMA process. In contrast, a device that goes through the 510(K) process need only have evidence to demonstrate that it is substantially equivalent to, or at least as safe and effective as, another device that has already been cleared by the FDA (ie: the new or investigational device must be shown to be as safe and effective as a predicate device). The 510(K)'s route and evidentiary demands for 'substantial equivalence' makes it much quicker and cheaper for device makers than the PMA process, and the 510(K) process enables evolutionary changes to roll out more quickly, and it is such changes that are the hallmark of many device niches, including orthopaedic implants. Foote (1992) argues that regulation, including that around quality and safety, product liability, compensation regimes, and government funding of research, have had a significant impact on the production and diffusion of medical devices. Regulations around quality and safety (ie: risk – degree of invasiveness, duration of contact, affected body system, and local v. systemic effects) have been particularly influential, although non-harmonised legal meanings have proven problematic (Shah and Goyal, 2008). While the principle behind a device can be patented, most specific devices cannot (ie: the protected innovation often lies in the underlying principle being used in the particular application). Thus, for example, the concept of a transducer is patentable but the specific implementation of the idea into a device is not, as it is viewed merely as a matter of design.

In 2008, the global medical device market was valued at US$210 billion, and it has grown at a rate of 6% annually since 2000 (WHO, 2010). While both China and India are emerging as important markets, the USA remains the largest consumer of medical devices, with a market valued at over US$100 billion. India's market is estimated at US$2.75 billion, with growth coming from the expanding middle class of 300 million people with disposable income and heightened health expectations. The USA, Japan, and the European Union (EU) manufacture some 85% of all medical devices, and over 70% of those used in India are imported from developed countries. The USA supplies more than 28% of the approximately 14,000 medical devices used in the Indian market (worth approximately US$400 million in 2008). There are almost 700 Indian manufacturers, but most make low-value products such as needles and catheters, leaving high-tech specialist devices such as transducers and heart-valves to foreign multinationals like GE, Siemens, and St. Jude (NIPER, 2010). Kamath (2010) describes the Indian MDI as follows:

> The words India and medical technology are seldom used in the same sentence. An indigenous medical device industry has been virtually non-existent. Local players … have struggled to shed the 'low-tech, low quality' tag. For instance doctors faulted local pacemakers for being too bulky and difficult to implant, with leads (that connect the pacemaker to the heart muscle) fracturing easily.

Despite the size of its market, India failed to regulate foreign or domestic medical devices until

2005. The Medical Devices Project was designed to analyses the impact of that failure on the development of India's MDI. Three phenomena describe the current status of the Indian MDI: (1) flawed industrial policy; (2) lack of entrepreneurship; and (3) inappropriate government regulation. This paper focuses on the third phenomenon – government regulation of devices that are both imported to India and made in India – and it examines two periods, the 1947-2005 period of no regulation, and the 2005-present period of wrong regulation.

c) Findings

While the Indian government acknowledged the need for medical devices regulation in the 1980s, there was no clear understanding of how such regulation should work (ie: its mechanisms of action and its criteria for performance measurement), and no serious movement to adopt any regulation (Kamath, 2007). Indeed, the field was largely neglected by the Indian medical profession, technologists, industry, and government for many years. The consequences of this neglect were threefold.

First, there was very little reliable information on function and performance available to practitioners or government authorities. The only available information was that used by companies to market the devices. They were sold without any monitoring by a regulatory authority and without reporting by hospitals, so that when Boston Scientific and Johnson & Johnson withdrew their stents worldwide in 2004, there was no information available in India on how many of these devices had been used or how many adverse events had been reported (Harper, 2003). Lack of information, of course, opened the door for low quality devices to enter the market in force.

Second, and following on from this, the market became populated by spurious operators and counterfeit traders who used scrap material or imported goods of uneven quality from Chinese manufacturers. Small trading companies importing from China, Korea, and Taiwan mushroomed all across the country, offering generally low quality (or counterfeit) products at very low prices. One respondent in the Medical Devices Project, a leading bioengineer involved in the development of an indigenous heart valve, claimed as follows:

> … [T]he market for the lower tech disposables products is swamped by the spurious manufacture of devices without any concern for good manufacturing practices.

Another respondent, a CEO of an orthopaedic implants company, reported that his company lost more business to these spurious traders and counterfeit manufactures than to multinational corporations. Even when legitimate and conscientious domestic manufacturers entered the market, an absence of uniform standards as to quality and performance, meant that they had nothing to work toward. This contributed further to variable quality, and it also hampered their entry into international markets:

> At the time, Sri Chitra was on the cusp of developing a range of local alternatives to imported devices, but we had no clue whose approval to take to launch product. Until there's a law all decisions become ad-hoc (Kamath, 2007).

Third, as the clinical community became more and more averse to using Indian devices (because

of uncertain standards and lack of quality assurance), multinationals were able to charge high prices (and reap significant profits) for their more stringently regulated products. Murthy (2004) points out that, of the more than 11,000 valve procedures performed annually in India since 1994, only 1,000 valves developed by Sri Chitra Research Institute (a leading Indian institute) were used even though they cost less than 50% of the average imported valves. There was no transparency in the production cost of these multinationals and selling prices varied widely in the market, but were generally high, especially for the high-tech devices. In short, the regulatory lacunae skewed the market in favour of foreign multinationals who could charge a 'monopoly rent'. One respondent in the Medical Devices Project, a leading cardiovascular surgeon, commented as follows:

> We are compelled to import 90% of high-end instruments, devices, etc for our hospitals at high cost and replace them every 3-5 years at still higher cost. This pushes up the cost of specialised care in cardiology, neurology, etc and makes them inaccessible to the majority of Indians. MNCs estimate their Indian market as 200 million who can pay – they conveniently ignore the one billion who can't do it.

This creates disparities in access to these devices, not only for poor Indians but also for the poor in other developing countries. Another respondent, a leading bioengineer, argues:

> The lack of regulations, scarcity of raw materials and unrestricted import of finished products all conspired to daunt an intending manufacturer of biomedical devices.

Unfortunately, this near market monopoly by foreign multinationals did not guarantee quality. For example, in 2004 the state-run JJ Hospital in Mumbai used drug eluting stents on as many as 60 high-risk cardiac patients. The stents, manufactured by Occam, a Netherlands-based company, and marketed under the brand name Axxion, were not approved for use in the Netherlands but were marketed in (unregulated) India by a Mumbai-based trading company. After patients were harmed by the devices, the government shut down both the importer and a local stent company, who initiated a judicial review of the decision in an effort to showcase the absence of rules (Magotra, 2006).

The JJ Hospital case resulted in the High Court ordering the Indian government to set standards for the manufacture, sale, and distribution of 10 specific medical devices under the *Drugs and Cosmetics Act 1940* (D&C Act), thereby ushering in the second period under investigation, that of 'wrong regulation'.[7] The D&C Act governs the Indian pharmaceutical field; it is a national law applicable to both domestic and imported pharmaceutical products and enforced by the Drugs Controller General of India (DCGI), which is authorised to administer product approvals, clinical trials for the introduction of new drugs, and import license for new drugs. The court-stipulated standards were approved by the Ministry of Health and Family Welfare (MOH) and associated guidelines came into force on 1 March 2006. Prior to these implementing guidelines, companies were left to speculate how the regulations would be administered. Customs authorities were at a similar loss and began holding devices shipments,

[7] The 10 devices regulated were cardiac stents, drug eluting stents, catheters, intra ocular lenses, IV cannulae, bone cements, heart valves, scalp vein sets, orthopaedic implants, and internal prosthetic replacements.

thereby creating a shortfall of devices in the market. This prompted widespread debate on the legal status of medical devices, with several experts claiming that they should be excluded from the drugs listed in the D&C Act.

By mid-2008, the MDI suffered from inconsistent application of the guidelines, in part due to the multiple levels of regulators enforcing them (ie: inconsistent interpretation and application by customs officials, state drug controllers, and officials within the Central Drugs Standard Control Organization (CDSCO)). Some suppliers waited over 7 months for product licenses, even for products that had been in the market for more than 20 years and had received regulatory approval in Europe (Kamath, 2007). It was becoming evident that the regulatory framework – which had been designed for pharmaceutical products – was inadequate for governing medical devices due to the different natures of the products, their action in the human body, and their packaging. For example, 'sterility' differs between pharmaceutical products and medical devices; drug manufacturing requires 'clean room conditions' (necessitating certain flooring, air-flow, and energy deployment) whereas medical devices are often sterilised at the point of use.

One respondent in the Medical Devices Project, a leading manufacturer of diagnostic devices, explains the issue as follows:

> This industry is considered to be a pharma segment but really does not belong there. The authorities themselves are not knowledgeable about [the] diagnostics industry. A device cannot be regulated as a drug.

By 2011, it was obvious that the D&C Act was not appropriate for devices. Rather than legitimating domestic manufacturers, it was endangering their survival. It is now apparent that India requires a bespoke regulatory body for medical devices. However, there remains a lack of communication between government departments, and severe infrastructural problems persist thereby hindering implementation of any regulation. One respondent, a leading cardiovascular surgeon, points out the difficulties in developing optimal regulation:

> The Indian Medical Regulatory Authority (IMDRA) proposed by a government committee would have been optimal. Thanks to turf wars in the government, it has been substituted by a committee under the Drug Controller General of India. It is too highly centralised and too bureaucratic to promote R&D and industrial activity in relation to medical devices and instrumentation. Neither has become an Act yet.

There is some interest in erecting a framework similar to that of the UK's MHRA or the US's FDA. While this would bring the Indian regime closer to the international standard, India might be cautious about copying these frameworks too closely. Both bodies are trying to move toward a regime whereby devices are regulated in a manner similar to drugs despite drugs being much more heavily regulated.[8] Success in doing so could lead to a stifling of innovation similar to that which is being witnessed in the pharmaceuticals setting.

[8] The FDA is seeking comments regarding the possible introduction of more rigorous pre- and post-market requirements than that embodied by the current 510(K) process. In the past, the 510(K) process kept innovation process flowing in moderate risk devices with limited device failures. New pathways *may* stifle incremental user-led innovation process by introducing new barriers and/or regulatory requirements.

d) Summation

The Indian government is working toward establishing a regulatory regime for medicine, but it is struggling to set up a governance structure that can distinguish between medical devices and pharmaceuticals. Until it does, it is likely that the legitimate (and quality) domestic medical devices industry will continue to struggle despite competing against expensive import devices and potentially dangerous counterfeit devices. The result of this is that India's poorer populations continue to suffer from a shortage of accessible diagnostic and treatment devices.

III. CONCLUSIONS

The Argentine evidence suggests that regulation can be an important source of justification in the face of vocal and influential organisations suspicious of the particular scientific pursuit, particularly where participative opportunities are few, thereby creating a more positive science environment more conducive to innovation. The Indian evidence suggests that, while regulation can create more equitable playing fields, which can be vital for harnessing domestic innovation, not just any regulation will do; currently, Indian medical device producers must compete with cheap counterfeit products and more reputable foreign imports but the regulatory framework adopted to facilitate their efforts have not borne fruit. The prevailing situation has led to inquiries as to whether the US and European model for medical devices regulation is more appropriate.

Combined, these case-studies suggest that simply leaving science actors to their own devices is not the answer, particularly where individual and public health are implicated. Despite differences in their factual foundation, they support the claim that regulation *may* curb non-virtuous (or fraudulent) behaviour, and *can be* extremely important to, or supportive of, innovation. Jurisdictions in Argentina's and India's position should eschew the 'to regulate or not to regulate' dichotomy, and focus on how to achieve 'smart' regulation. Smart regulation does not mirror that from other settings that has been shaped by very different contexts and experiences; rather, it has its own clear social/regulatory objectives shaped by the specific context in which it is expected to operate.[9]

While this may mean bespoke regulation which erects standards and rules for a specific field, and which provides direction for innovation that encourages long-term investment in the field, we caution against *excessive regulatory construction*. So in addition to not mimicking other jurisdictions' instruments, it is equally important to avoid recreating the regulatory complexity, accumulation, and fragmentation that characterises other jurisdictions (like the UK and the USA). Smart regulation will identify optimal quality, safety, and efficacy parameters compliant with (local) patient expectations, and will be 'joined up', in at least two ways. First, it will be crafted with partner or associated fields (and their regulatory demands and burdens) in mind so as to avoid conflicting standards or duties and reduce the regulatory cost of operating in the field (through, for example, duplication of regulatorily-imposed actions). Second, it will be crafted so as to dovetail with international standards and/or systems; it must strive for some level of international harmonisation of terms, rules, and responsibilities, thereby paralleling the international nature of the science and its markets with which the stakeholders are aiming to

[9] See Milne and Tait (2009) and Chataway, Tait and Wield (2006) for more on how regulatory systems motivate particular behaviour patterns among those regulated, which would be an important component of 'smartness'.

engage. Again, the aim is harmonisation, not necessarily standardisation.

In short, scientific innovation will be best encouraged through regulatory innovation, and here emerging economies are in a strong position to 'leapfrog' developed jurisdictions. Their development of 'smart regulation' which does not slavishly copy existing models represents the means to do so. Examples of existing regulatory innovation which has led to innovation include California's efforts around the environment, the US's around orphan drugs, and India's around drugs (and the licensing of patented medicines).

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