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## Big-pharmaceuticalisation: Clinical trials and Contract Research Organisations in India

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### ABSTRACT

The World Trade Organisation's Trade Related Intellectual Property Rights [TRIPS] agreement aimed to harmonise intellectual property rights and patent protection globally. In India, the signing of this agreement resulted in a sharp increase in clinical trials since 2005. The Indian government, along with larger Indian pharmaceutical companies, believed that they could change existing commercial research cultures through the promotion of basic research as well as attracting international clinical trials, and thus create an international level, innovation-based drug industry. The effects of the growth of these outsourced and off-shored clinical trials on local commercial knowledge production in India are still unclear. What has been the impact of the increasing scale and commercialisation of clinical research on corporate science in India?

In this paper we describe *Big-pharmaceuticalisation* in India, whereby the local pharmaceutical industry is moving from generic manufacturing to innovative research. Using conceptual frameworks of pharmaceuticalisation and innovation, this paper analyses data from research conducted in 2010–2012 and describes how Contract Research Organisations (CROs) enable outsourcing of randomised control trials to India. Focussing on twenty-five semi-structured interviews CRO staff, we chart the changes in Indian pharmaceutical industry, and implications for local research cultures.

We use *Big-pharmaceuticalisation* to extend the notion of pharmaceuticalisation to describe the spread of pharmaceutical research globally and illustrate how TRIPS has encouraged a concentration of capital in India, with large companies gaining increasing market share and using their market power to rewrite regulations and introduce new regulatory practices in their own interest. Contract Research Organisations, with relevant, new, epistemic skills and capacities, are both manifestations of the changes in commercial research cultures, as well as the vehicles to achieve them. These changes have reinvigorated public concerns that stress not only access to new medicines but also the 'price' of innovation on research participants.

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### 1. Introduction

India signed the World Trade Organisation's [WTO] Trade Related Intellectual Property Rights [TRIPS] agreement in 1995. This

agreement aimed at harmonising intellectual property rights and patent protection globally. India's decision to sign was controversial: civil society activists were convinced that this would reduce Indian people's access to cheap drugs, and many representatives of India's generics drug companies feared the loss of their right to reverse-engineer products that were patent-protected elsewhere in the world through a process that involves the separation, identification and precise estimation of quantities of ingredients in a formulation, for characterization of a competitor's product and the development of a generic alternative (Ramanna, 2003). While a few large-scale companies and most small-scale generics companies

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remained opposed, most Indian large-scale producers welcomed the opportunity to access high-income markets, and the prospect of becoming innovator companies themselves (Smith, 2000). Signing the TRIPS agreement required changes to the 1970s Patent Act that provided Indian companies the same protection for their innovations as companies elsewhere, encouraging them to shift their focus from production of generic drugs to innovation of New Chemical Entities (Schüren, 2013). During the 1995–2005 grace period, for example, the Indian pharmaceutical companies Dr Reddy's and Ranbaxy were able to secure patents on novel compounds and venture out to international markets with them (Chaturvedi and Chataway, 2006).

Extending patent protection to drugs produced in India is, however, but one side of the story of pharmaceuticalisation. One important result of this process has been an increase in the quest for new markets and drug products that has led to an expansion of research organisations, and created new social actors. Legislative changes to implement TRIPS in India made possible not only increased access by innovator companies to the Indian market, but also the introduction of internationally-funded clinical trials. A change in Schedule Y of the Indian Drugs and Cosmetics Act in 2005 removed a phase-lag on clinical trials: pharmaceutical companies could now 'conduct trials of new drugs in India at the same time that trials of the same phase are being conducted in other countries' (Nundy and Gulhati, 2005: p.1633). Data on clinical trials published in the *Indian Journal for Medical Ethics* show an increase from 64 new trials in 2006 to 245 in 2010 (Ravindran et al., 2010) and up to 787 in 2012 (Ravindran and Vaid, 2013), suggesting a 1100% increase in 6 years. However, on global scale India held only 1% clinical trials in 2007 (Thiers et al., 2008). Indian companies also increased their own clinical trials, testing new chemical entities of their own and entering into contracts with international companies. The growth in clinical trials activity allowed innovator companies to sponsor trials both directly and through Contract Research Organisations [CROs] (Drabu et al., 2010; Yee, 2012). The impacts of TRIPS agreement on patent laws and on the encouragement of clinical trials seemingly pull in different directions, but that they are in fact enmeshed processes. This very particular trajectory of pharmaceuticalisation deserves to be unpicked in detail: how have these transformations in the terms of market competition changed research cultures? The significant role played by CROs in enabling this process is the central focus of this paper.

The pharmaceuticalisation thesis has evolved out of the work of Abraham (2010, 2011; also see Davis and Abraham, 2013), and Williams et al. (2011) who suggest that, at the most basic level of the definition, drugs are increasingly seen as pre-eminent solutions to health problems. Abraham argues that drivers of pharmaceuticalisation include 'the redefinition of health problems' and 'changing forms of governance' and note that 'pharmaceutical industry marketing, consumerism, and the ideology of the "expert patient"' are important factors in the process (Abraham, 2010). Williams et al., (2011, p.719) stress in addition that 'pharmaceutical futures are shaping how we think about innovation, policy and the very meaning of health and illness, therapy and enhancement', largely referring to pharmacogenomics and its potentials. This debate has, firstly, been carried out largely as a discussion of changes within 'Western' societies: India appears merely as a source of cheap pharmaceuticals. Secondly, it has failed to take seriously the globalisation of particular kinds of pharmaceuticalisation as part of an emergent neo-liberal market form and associated discourses and practices. Here, we argue that India (perhaps more clearly than elsewhere) is experiencing 'Big-pharmaceuticalisation'. By this we mean the following:

- a. TRIPS has encouraged a concentration of capital, with large companies gaining increasing market share and using their market power to rewrite regulations and regulatory practices in their own interest;
- b. New social forms associated with these changes have been introduced into India – international multi-sited clinical trials and Contract Research Organisations, and have developed new epistemic skills and capacities, as well as regulatory frameworks and practices;
- c. Public contests have been reinvigorated over the well-being of local populations, be they concerning access to pharmaceuticals or the health of trial participants. Concerns stress not only access to new patented medicines but also the 'price' of innovation on research participants, and the regulatory structures that should govern clinical trials and research participation.

Pharmaceuticalisation describes how drug production and manufacturing, along with their sales, branch out to ever more widening global regions (Abraham, 2010, 2011; Bell and Figert, 2012; Williams et al., 2011, 2012). A substantial literature analyses the introduction of clinical trials into developing countries and emerging economies (Kamat, 2014; Petryna, 2009; Sariola and Simpson, 2011; Sunder Rajan, 2005). We extend the definition of pharmaceuticalisation to include the globalisation of pharmaceutical knowledge production by means of clinical trials. Petryna (2009) describes how when CROs 'go global', they work across national and cultural boundaries, spread the methodologies, skills and ideas of the pharmaceutical sector, and facilitate the increase in clinical trial activity in countries like India, China and Brazil. We agree with other analysts of commercial research and pharmaceuticals that such clinical trials ought not be considered 'science' but rather a mechanistic, pre-defined test (Bachelard, 1953, quoted in Gaudilliere and Löwy, 1998, p.10; Cooper, 2012).

Changes within these new locations, and how existing practices are morphed into new settings, need further analysis. When international pharmaceutical companies outsource trials in search of new markets and treatment-naïve patients, they transform the existing pharmaceutical sector, harmonising it to resemble more closely international or 'Big Pharma'. Big-pharmaceuticalisation involves the introduction of CROs, who implement research for international and national pharmaceutical companies, into India. Working with sponsors, doctors on trial sites where patients are recruited, and at times biotechnology companies doing basic research, CROs are actors in their own right. They reinforce how Randomised Control Trials (RCTs) become central to a particular form of knowledge production, and begin to displace pre-existing generic drug production regimes. Thus, Big-pharmaceuticalisation stands for both the arrival of CROs, trials, and the new social forms – regulatory and human capital – that come with them, as well as the process through which India is becoming more like the international sector. CROs are both vehicles and manifestations of this change.

The TRIPS agreement subverted the past reverse-engineering policy, as innovative products can now be patented in India and international companies can include India in multi-sited trials. Arguments concerning these changes are polarised. Innovation-management literature sees them as economic opportunities for the industry (Chataway et al., 2007; Chaturvedi and Chataway, 2006; Chittoor et al., 2009; Gehl Sampath, 2007; Kale, 2009, 2010; Kale and Little, 2007; Kale and Wield, 2008). Others argue that therapeutic access, patients' rights, and the state's responsibilities in health care provision for its citizens are all threatened. India's new Patents Act has clauses that include public health concerns as reasons to deny a patent. They are designed to check 'ever-greening', whereby drug companies exploit legal

loopholes to extend patent protection, for example by patenting new drugs that have small adjustments to the chemical composition of the original ones – combining formulae or making timed-release versions, for example – thus making it harder for generic producers to market their competitor drugs once the initial patent has expired. The Patent act also provides justifications for 'compulsory licensing', whereby generics companies can apply to produce a generic version of a patented pharmaceutical if it is being marketed at prices beyond the reach of Indian consumers, or in only small quantities. These clauses are constantly under pressure from international pharmaceutical companies and the US and other governments, with Novartis and Bayer challenging these clauses in Indian courts. Drawing on the Novartis case, Sunder Rajan (2011, p.983) argues that in such bioconstitutional moments 'rights are reframed in the context of emergent co-productions between law and the life sciences'. Quantifications of effect and monetary value take primacy. According to these readings, the TRIPS agreement has had a detrimental impact on patients in India and internationally by progressively limiting the access of poor people to affordable pharmaceuticals.

Increasing trial activity has realigned concerns over the ethics and politics of pharmaceuticals. The safety of experimental subjects, and how this can be best regulated, are high-profile concerns. New regulations as well as new institutions, namely private and public Research Ethics Committees (Simpson et al., 2014; this special issue), have been established, but critics see the increase in clinical trials as coercive and beneficial neither for the individuals nor the communities involved (Petryna, 2009; Sunder Rajan, 2005). Kamat (2014) and Prasad (2009) question bioethical and legal approaches that have limited their analyses to patient autonomy and recruitment of trial participants, and call for broader discussions of social justice. Tighter regulatory changes were put in place in 2013 and a number of international sponsors pulled out from India (Brennan 16 Oct 2013; The Economic Times 27 Jan 2014; Vijay 1 Feb 2014). The central argument of supporters of clinical trials – that a more permissive atmosphere regarding drug research and development (R&D) could build the capacities of Indian researchers and industries to enable them to become originators of new molecules – was reiterated by industry spokespeople. But the means by which change is promoted cannot be separated from the outcomes (Strathern, 2011). How far do the activities of CROs provide evidence of changes in the direction claimed when India signed up to the WTO? What happens in these relationships and how do the CROs operate? Here, we pay attention to industry-industry relations as clinical trials spread across national boundaries, and outline how CRO staff in India see their role in the local pharmaceutical sector. We address an empirical gap in the literature by providing insights into the kinds of collaborations that CROs establish nationally, how they make connections with those that they work with – research sites and pharmaceutical companies – what their roles and concerns in the process are, and how they respond to the regulatory changes around them. We ask how far and why Indian industry has transformed as a result of the 2005 regulatory changes.

## 2. Methodology

This paper is part of a larger project, that mapped the increase of experimental clinical and public health research in South Asia entitled Biomedical and Health Experimentation in South Asia. To document how the arrival of clinical trials and CROs takes place, we interviewed people in various positions in CROs in India. Interviewees were gathered by snowball sampling: we contacted CRO staff via existing networks, and followed up contacts they provided us with. We conducted 25 semi-structured interviews in

11 different CROs or CRO-related consultancies based in Bangalore, Mumbai, and Delhi. These interviewees were from both Indian and international CROs and their studies were sponsored by both international and Indian pharmaceutical and biotech companies. The CROs conducted multi-sited RCTs as well as comparisons of generics and biosimilars. Three CROs were originally Indian organisations that had merged with international partners, and the rest were international CROs with offices in India.

Our interviews covered research and development, research capacity, the challenges of doing research in India, and interviewees' perceptions and ideas about their role in the broader pharmaceutical sector. Interviews were conducted by the first three authors, often in pairs, in 2011. Research participants were provided with information sheets regarding the study, told about its aims, and offered assurances that the project was academic, rather than scandal-seeking.

The junior Clinical Research Assistants acting as monitors we interviewed held Undergraduate and Master's Degrees in Biotechnology, Dentistry and Ayurvedic Medicine. Other CRO staff roles included Project and Operations Managers with overall responsibilities for trials; Business Managers who interacted with Sponsors trying to secure new projects, Protocol Writers who worked together with Sponsors spelling out research designs and planning studies; Quality Assurers who checked all datasets before handing them over to sponsors; Statisticians who made relevant quantitative analyses; and CEOs who acted as intellectual and public relations heads of the companies. These more senior positions included people with Medical Degrees (MBBS and MD), Masters in Pharmacy and Pharmacology as well as PhDs in Pharmacology. Some had international degrees and all the interviewees had previously worked in international pharmaceutical companies in India and other CROs, bringing their learning with them.

We obtained written informed consent from participants. Interviews were held in English, recorded, transcribed, anonymised, and coded using Atlas.ti. Transcripts were coded by the first three authors with regular checks for consistency. Codes relevant to the paper include: 'knowledge production', 'innovation', 'new social forms', 'regulation and governance' and 'collaboration'. The material was analysed and written up by Sariola while the other authors commented and edited the drafts. In this paper we analyse the interviews with respect to how companies positioned themselves in international outsourcing process and innovation.

The study had ethical clearance from Anusandhan Trust in Mumbai where the research was based, and also from University of Edinburgh where the project's Principal Investigator was based. In what follows, we discuss firstly the perceptions of CRO staff with respect to changes after 1995, and particularly since 2005, and different models of collaboration that have emerged between international trial sponsors and Indian CROs. We then consider the tensions that arise between the commercial and national economic interests in maximising the numbers of trials and the income these activities generate, in the context of rising concerns about the ethical issues raised by such trials, before turning to review the new regulatory institutions and practices that have arisen.

## 3. Findings

### 3.1. From self-sufficiency to innovation: Contract Research Organisations in India

Interviewees described the changes in the Indian pharmaceutical sector as a trajectory from self-sufficiency to innovation. During the era of self-sufficiency prior to TRIPS, they argued, cheap drugs were needed *en masse* whilst clinical trials were not required

– drugs were simply manufactured. As the head of operations of a global CRO put it:

*It was like, just show me chemically that whatever you're doing is equivalent to that chemical entity manufactured, [and] go sell it. I don't need you to test on anything. That was the basic requirement.*

By 2005, as the CRO consultant cited below argued, the nation had evolved and the industry was ready to move onto the 'next' level. An experimental capitalist, open-market era was seen as 'progress' but the rhetoric of benefits to masses remained embedded in specific discourses concerning CRO operations and motivations:

*[Prior to TRIPS] So that was a huge plan, rolling out mass health-care ... For that, primary thing was to have affordable medicines. So that's why we said, we will not follow the patent rule which is being followed by the world, but will create something which we could self-suffice. But by 2005, we said okay, now we will go ahead and follow the patent regime which is being followed across the world, because I think to a very large extent we had taken care of the health needs of the population.*

With TRIPS, the number of clinical trials and CROs in India started to increase. As one of our interviewees described it: 'Everybody and anybody has come here.' International as well as local pharmaceutical companies and CROs took the opportunity to make use of the large populations of India, expecting to run standardised operations, as the head of a Human Pharmacology Unit in an Indian CRO said:

If a CRO is involved in a study, it is exactly how it works in the western countries.

The internal operations of CROs as they were described to us resemble those of international CROs described by Fisher (2009) and Petryna (2009). Our interviewees explained that when an international pharmaceutical or biotechnology company wants to run a trial in India, they contact a CRO based there, an Indian CRO or the side-offices of large international CROs like Quintiles. CROs advertise their services online as well as in international conferences. Typical selling points are: 'understanding of local regulatory cultures', 'ability to recruit participants fast' and 'producing high-quality data'. CROs carry out central tasks in the knowledge production chain and yet their names do not appear in the trial databases set up by regulators, nor in outputs such as publications. Until changes introduced in 2013 that required all implementing participants in clinical research to be certified, CROs had not been regulated in India and estimates of their numbers vary widely. The Indian Association of Contract Research Organisations lists 34 CROs as members, some of which are international, while Kamat (2014) provides an unreferenced estimate of 150.

Depending on the collaborative model in place between the sponsor who owns the intellectual property and the CRO, the entire process of drug development can be broken down, compartmentalised, and the standardised work can be outsourced and offshored. While protocol writing is mostly done by sponsors, applications to ethics committees and the Drugs Controller General of India's office, data collection, quality assurance, safety management, monitoring of investigators, medical writing, pharmacovigilance, etc. are all, to some extent, managed from within India. CROs are paid according to the tasks that they conduct and numbers of trial participants recruited. In some cases, CROs have close relationships with a particular international or Indian

discovery biotech, and also take part in the development of experimental compounds. Many CROs have phase 1 facilities and also conduct later phases. However, in all cases, CROs also act as middle-men for experimentation for international pharmaceutical companies. When working for paid-service, CROs have no intellectual property rights in the compound that is being tested: they receive their tasks and duties from their sponsors and hand over all their data to them.

CROs reach out to doctors at private and public hospitals to act as investigators on the trials, using lists that they build through networks, conferences and other science fairs, and from the Clinical Trials Registry of India. One interviewee said that their company has 10,000–15,000 investigators in their database. CROs maintain contacts with Principal Investigators and Clinical Research Coordinators at the 'sites' where research is implemented (see also Fisher, 2009; Petryna, 2009). Managerial staff in CROs describe having good relationships with site staff but complain that their work is regularly interrupted by aspirations for career mobility – retention of CRAs in particular trials and CROs is described as a challenge. CRAs monitor trials by visiting sites regularly and auditing Case Report Forms where data of each participant is recorded. One CRA might be monitoring several trials at the same time, and the sites at which studies are conducted can be scattered around India – CRAs make use of the expanding local aviation, and travel incessantly between major research hubs and hospitals – Bangalore, Chennai, Mumbai, Delhi, Hyderabad, Jaipur, Ahmedabad in particular. CRAs look for protocol deviations (e.g. if the experimental compound has been administered at a wrong time) and malpractices, like incomplete consent forms.

### 3.2. Collaborative models – outsourcing and offshoring

Though the harmonised everyday practices of CROs do not significantly differ from the international ones, our fieldwork suggests that novel types of 'collaborations' exist between sponsors and CROs in India. At times these models blurred the distinctions between biotech companies and fee-for-service clinical trial operations. For example, the head of an Indian CRO with close ties to an Indian pharmaceuticals company described his collaborations as a 'Web of dependencies, and there is a web within the web'. His classification of these webs illuminates clinical trials and the development of pharmaceuticals as intertwined industries. We found examples of all the six models among the CROs whose staff we interviewed.

- 1) *Outsourcing* – Larger pharmaceutical and biotechnology companies, sometimes a university, join up with a CRO. The former, who usually develop the experimental compound, could be national or regional players. Some companies have their own clinical operations, but most of them are 'lean': they just handle parts of the process, such as 'Regulatory', 'Reporting' or 'Data Management', and outsource the rest of the operations. For example, GSK and Merck use this model.
- 2) *Small tie-ups* – Smaller biotech companies (perhaps with 1–2 scientific personnel) outsource the entire product development to CROs. Bigger/medium size (more than 12 people) companies can handle some parts of the development process themselves. They might outsource different parts of the process to different bodies.
- 3) *Preferred partnerships* – Large international pharmaceutical companies like Pfizer and MSD have preferred large international CROs partners such as ICON and Quintiles. Their preferred partner could offer them a full service or they might outsource only part of their services. For example, Merck give all their lab work to Coax wherever they are in the world.

- 4) *Backward integration* – A CRO can invest in a small biotechnology or pharmaceutical company, so that in future they will be contracted to run the clinical trial phases or other parts of the process. Small companies with small budgets are earmarked by CROs for this kind of investment.
- 5) *Sub-contracting model* – Companies might outsource all the work or certain parts of the development process like a particular lab test. This might be a one-off relationship, or involve only irregular contact, with no formal relationship.
- 6) *Alliances and loose arrangements* – Across regions, companies purchase smaller ones through mergers and acquisitions, and harmonise their Standard Operating Procedures (SOPs).

Collaborative models described above illuminate the complexity and versatility of the relationships between pharmaceuticals companies and CROs. These models all reflect a market that is commercial and financially competitive. The models are as much business models as they are clinical trials service arrangements, and they were strategically tied in order to gain leverage in other contracts, deals and developments. Still, interviewees described how they were rarely in a position to choose who they worked with and what the arrangement was. While models 1 and 3 are more common for global pharmaceutical alliances, models 2 and 4 are novel, hybrid forms that Indian companies specifically use to work towards innovation, either through co-development or producing their own New Chemical Entities. We do not have sufficient data to compare the prevalence of these models and how many of each kind there are in India, but within the sample of 11 CROs, only a few were operating on the innovative models and everybody was conducting fee-for-service contract research in addition to their involvement in one or other of these innovative models.

As CROs manoeuvre within the Indian pharmaceutical sector, two distinct moves are explicit. On the one hand, Indian biotech companies try to expand into innovative research and development, seeking access to international markets by tapping into the funds of larger companies, while on the other hand international partners wanting to venture to India require local expertise. Indian companies need volume and capital. Discussing innovation, the Head of a Human Pharmacology Unit that conducted Phase 1 and Bioequivalence studies for an Indian CRO, described the Indian pharmaceutical sector as resource-poor, which hinders innovation:

*The Indian pharma industry is not that big. Who can afford to develop such molecules and spend like a billion dollars on a molecule? They can't afford to spend so much. Not possible.*

*I: Is that the direction that you see Indian pharmaceutical industry going?*

*Yeah. Indian companies now want to be innovative centrally. So everybody has big ambitions and keeps developing new relations with the innovators and either co-development or on their own start working on new molecules. But as expected, there's not so much coming out of that in India.*

The interviewee argued that Indian pharmaceutical companies forge ties with sponsors because they have limited funds, which is the primary motivation to enter into industrial collaborations. International partners, on the other hand, need local expertise to access Indian patients and markets. A president of an Indian CRO explained how and why international sponsors team up with CROs locally:

*Some EU/US companies don't have the bandwidth to enter the market here and the local regulatory insist on indigenous tests.*

Here, the president alludes to indigenous trials that give access to Indian markets. The CROs conducted at least three different types of trials: 1) multi-sited randomised control trials located in India, often – but not always – sponsored by international pharmaceutical companies; 2) phase 3b trials, small trials required by Indian regulators before a drug is given access to Indian markets; this is a special requirement for international pharmaceutical companies; and 3) phase 1, bioequivalence and biosimilars research, implemented especially by Indian companies but also by international sponsors interested in generic drug production. This last model was especially prevalent among Indian CRO-cum-biotechnology companies.

With the increased research activity came responsibilities for patient safety. Using internationally and nationally recognised guidelines of good clinical practice, industry members held a pragmatic stance whereby research and its risks could be rendered controllable. In the next section we move from descriptions of collaborative models and trials into how CROs staff described their work, given the existing regulatory frameworks and research capacity in India.

### 3.3. Tensions in meaning of innovation and its consequences

Since 2005 and the increase of trials in India, some controversial studies have been reported in Indian media, often depicting patients who died or fell ill following participation in a trial. The depiction represents tensions in the field. On the one hand, there are national interests in developing an innovative pharmaceutical industry, and clinical trials are seen as an inevitable part of that. On the other, there are serious concerns about the price of innovation and how it is achieved. A figure often repeated in the media is about 500 deaths per year ([Tribune New Service 22 Feb 2012](#); [The Hindu 4 March 2013](#); [Lloyd-Roberts 1 Nov 2012](#)) but details of the trials, and whether deaths were causally linked with the experimental compounds or something else that coincided during a trial, are rarely available. The numbers have been used in the public debate to criticise clinical trials, multinational corporations and CROs. Implicit in these accounts is often that international companies are behind the damage. Our interviewees never spoke about compensation in case of death or injury, and questions about such cases were evaded.

Aware of the negative public attention, all industry actors argued that they were committed to the safety of the research subjects. They were quick to claim that trials were done to the highest of standards and that they went out of their way to ensure that patient safety was their priority. They referred to the training given to doctors who recruited participants, and to their junior staff, and to following international guidelines meticulously. The CRO staff emphasised that it was in their interest to build up the final product towards a future approval from the US Food and Drug Administration (USFDA) to gain access to the US market. Clearance would be given subject to USFDA being satisfied that ethical and scientifically sound research had been carried out. Dumit argues that inbuilt into the pharmaceutical industry rhetoric is a certain level of self-regulation (2012, p.88) so that they can be sure that their data will be accepted by the USFDA: *The challenge is to have the most efficient development plan, within regulatory and ethical constraints, that will provide the largest market and best return on investment*' (2012, p.149). Similarly, our interviewees claimed that not doing trials to scientific and ethical standards would prevent the experimental 'product' from accessing the market. It is not surprising that the industry has been heavily involved in shaping clinical trials regulation both in India and internationally. A CRO president claimed to have drafted the rules under Schedule Y before the guidelines were sent out to public review and eventually

subjected to a parliamentary hearing. Another interviewee who headed an international CRO had helped train the Forum for Ethics Review Committees of Asia–Pacific (FERCAP), the pan-Asian non-governmental organisation that aims to harmonise ethical review in the region. FERCAP received funds and support initially from Roche (Roche 2006, p.73). The best-known regulatory guideline, the international ICH GCP, was drafted by an agglomeration of global pharmaceutical companies and regulatory bodies (Abraham, 2002). We have no evidence of the involvement of the pharmaceutical industry in the regulations that were put in place in India in 2013; rather, it seems that the industry does not see the tightening regulations favourably (Sachan 12 Nov 2013; *The Economic Times* 27 Jan 2014; *The Hindu* 10 Jan 2014).

A manager of operations in one of the largest CROs in the world, based in India, exemplified the concerns over the safety of participants as follows:

*Please remember, any failure which happens here, since we contribute to 20–30 percent of global trials, will adversely affect the result when the file or the data is reviewed by the USFDA, which would lead to a commercial failure. So it's as critical as that. It's not like we're the periphery and it's okay, you know, 'we can live with those mistakes'. No. It is critical that we do it in the right way, and the whole clinical research industry. The safety of the patient is paramount. I'm not bothered about your product. I'm not bothered about what it does. Does it give a benefit? Even if it doesn't, I'm okay, but please don't harm the patient when you're conducting a study. In a single sentence, that's where all of us are going. If your patient is not safe, forget about it. Ultimately the way I look at it is that you have subjects on one side, and the others on the other side. All of us have equal, utmost responsibility to ensure that nothing goes wrong with the subject.*

The interviewee was aware of the realities of human experimentation – people's lives were at stake, while there were also commercial and scientific interests involved. Patients were at risk because human experimentation is risky. Across the respondents, there was no naïveté or ignorance about the fact that monetary and human interests overlapped. Claims of exploitation emerged from this overlap when and if one was seen to overtake the other.

Cases of corruption and deaths were described as having been done by 'fly-by-night' CROs who were solely motivated by monetary interests and not 'serious industry'. Malpractice was always depicted as done by 'others'. Those who positioned themselves as ethical and scientific described these activities in terms of negligence but also disparaged such CROs as 'doing lousy business' and 'shooting themselves in the leg'. This rhetoric was vulnerable; for example, at least one of the CROs that we interviewed was implicated in a clinical trials controversy in Bhopal (Chattopadhyay, 2012; Lakhani, 2011). In Bhopal, the CROs that were embroiled were both international as well as Indian (Lakhani, 2011).

On a rhetorical level, then, the industry representatives concerned themselves with the well-being of the human subject of research. They rarely raised questions about, for example, whether the trialled compound was a 'me-too' drug – one that is very similar to an existing product, where the company is merely trying to get a share of the market, without offering any real therapeutic advantage over the existing, patented, drug – or 'ever-greened', or if there were likely to be tangible post-trial benefits to the participants in the trial. The industry representatives implied that there was no need for further deliberation of the moral economy of the pharmaceutical industry and their operations in developing countries and emerging economies if trials were done correctly and according to GCP guidelines and capacity built to that effect.

#### 3.4. New social forms: capacity and new regulations

We discussed the capacity of investigators, junior staff and regulatory agencies in all the interviews. Doctors on site were often described as good clinical practitioners but lacking in a research mind-set and skills; investigators and junior staff were provided with training on GCP guidelines, soft skills like how to appropriately relate to clinicians and other members of the industry, as well as general knowledge about how the pharmaceutical industry operates. An international CRO president described these changes as follows:

*A lot of countries now recognise that clinical trials are not only a growth business that generates a lot of foreign income with very little investment in capital. Trials also bring you skills; it transfers skills into the country. So for me to do a clinical trial in various Asian countries and South Africa as well, I don't need to hire or train my own people. I will train up the site; I will train the leader authorities and so forth. You really need to build capacity in every area in terms of doing clinical trials and it is not just across the institutions, it is not just the investigators but all the supporting staff including the laboratories.*

Building new skill and capacities were needed to do trials 'right'. This is an example of Big-pharmaceuticalisation: these skills deal with conducting trials according to the standards of the international pharmaceutical industry – meticulous documentation of the data collection, following the GCP guidelines appropriately, etc. The above interviewee also suggested that changes took place across multiple domains; capacity building was a part of perfecting the overall knowledge production process, but was not nationally harmonised or regulated.

Through the introduction of new regulations, skills and practices, the industry changed. Guidelines on subject protection, documentation and audit practices increased. Our interviewees described these changes as welcome, aiding the industry towards innovative research. The skills utilised in the past mode of knowledge production of reverse-engineered generics evolved into new skills, which those working in such collaborations, described as 'stepping stones' towards innovation. For example, a CRO consultant argued:

*This knowledge which has been gained is what will make us better. I think we're good at looking at something and imitating it, and moving or increasing that process. Call it the generic mentality of ours. So if you're doing something, I know what it is all about, I can break it down, I can create a much better, more efficient process. Innovation is not something which we did. That's why I said, please understand the policies where we were. We needed to create something which we could sustain and afford. So that's how our education is like that, we're brought up like that, the industry works like that. Now we're coming out into the innovation mode. Maybe in the next two generations, or maybe we won't be able to get into a different this thing ... But we're extremely good at absorbing what is there, and creating better things, better processes, better way of doing things.*

With the new epistemic skills, the Indian industry was said to be headed towards biosimilars, which are biological compounds more complicated than generics. Still, they tend to reproduce something like-with-like (but in more refined forms) rather than completely New Chemical Entities. While the old generics industry did not need clinical trials for their marketing approvals, these biologics do. According to the head of Operations of a Global CRO, this 'hybrid' space is very attractive to Indian companies:

*Indian Pharma, interestingly in the past, have been serving for generic markets, they have been a generic player. In the recent past what we have seen is that they are trying to go for exclusivity period. But as per my personal observation, many of them are getting into what we called as biosimilar space which is a hybrid between generic and new drug development.*

New epistemic skills for researchers, be they in the industry or working on sites, alone was not seen to be enough to push for innovative research cultures, however. Interviewees suggested that for new products to emerge out of the Indian industry, regulatory changes were required. The revision of Schedule Y led to what many interviewees described as bottlenecks. A CEO described these as follows:

*See, security and freedom do not come together. Either we create a secure environment or a free environment. What happens in security, they put a lot of bounds and boundaries so that people cannot counter anything and you be safe, but the cost is going to higher and higher and there are huge lapses. Now, what is going to happen when the environment is very free? People can experiment, people can do many things, they falter, they learn, but in best interest of their funders.*

Despite having been written to align with international pharmaceutical industry and harmonising practices, Schedule Y differs in small particulars from the ICH GCP guidelines. These differences – such as the phase 1 restriction and introduction of the 3b phase – were not criticised in the interviews as such. However, the government was heavily criticised for its inability to provide appropriate support, regulation and protection from unwarranted media attacks as the number of trials increased. While the research environment was deemed freer since 2005, and increasing capital and resources allowed research to be done, approvals were often delayed at the Drug Controller General's office. The head of Operations of a Global CRO also felt that the regulatory changes in 2013 were reactions to scandals and did not give the industry a chance to mature:

*While the number of trials has increased, I don't think the regulatory office has really ramped up their infrastructure to address the needs of what is requested. There is rather a sense of vigilance. It is bordered to the fact that vigilance has turned into the bottlenecks. So now it's like the approving authority is a little reluctant to give any approvals because they feel they don't want be in the eye of storm. We are not saying that everything has been black and white in clinical trials in India. There have been grey areas and we acknowledge the facts that because we are just 12–13 years into this industry, there are going to be areas of improvement.*

This quote reflects on the negative public atmosphere for clinical trials and the capacity of the regulatory office to handle the increased number of clinical trials. The potential of clinical trials for innovation was seen to be difficult to implement when regulations and skills were only partially in place. Overall, the quotes show how interviewees experienced the slow pace of changes in the institutional environment – in human resource availability, legislation and regulatory practices – compared to the rapid pace of change in the industry.

#### 4. Conclusion

*Clinical research is an important dimension of nation building (President of an international CRO in India).*

Despite the promises and hype justifying the new patent regime, the impact of TRIPS agreement on Indian companies' ability to bring new chemical entities to the market has been modest, whereas the increase in clinical trial activity has – until the recent downturn caused by more stringent interpretation of regulatory conditions – been phenomenal. In this paper we have extended the concept of pharmaceuticalisation (Abraham, 2010, 2011; Davis and Abraham, 2013; Williams et al., 2011) whereby drugs are increasingly seen as solutions to health concerns and create new subjectivities and structures of governance for their production, to suggest how research on pharmaceuticals and the associated tools of knowledge production travel to new contexts. The globalisation of pharmaceutical knowledge production in India has taken shape with the backdrop of India's large generics industry and *Big-pharmaceuticalisation* has brought about a rapid concentration of capital, new social forms, and public contests about clinical trial participants' well-being. Following Strathern (2011), we suggest that looking at how change is created illuminates how methods shape outcomes.

The enormous expansion of trial activity in India has required the active involvement of local corporations and researchers. Within pharmaceutical research organisations, we identified a 'web within a web' of collaborations between international and Indian partners. Indian CROs serviced both international and Indian pharmaceutical companies while international CROs are more likely to have tie-ups with international pharma. While international CROs might work with Indian pharmaceutical companies, we found no evidence of this. Other outsourced auxiliary services include lab tests, accounting, etc. which we have not focused on. By 2010–2012, when our research was conducted, there was an overlap between companies aiming to do innovative drug discovery – the objective of signing the TRIPS agreement – and companies that were collaborating with international pharmaceutical companies offering outsourced services, suggesting that Indian pharmaceutical industry has become hybridised. Through skills building, networking and merging, some companies were using the CROs and pharmaceutical companies to gain international prominence. The regulatory changes in 2005 – introduction of innovative patent regimes and lenience on clinical trials – have created connections on the ground through CROs. Thus, in this paper we have broadened existing literature on CROs (Fisher, 2009; Petryna, 2009) by showing how CROs in India not only implement the research but change existing research industries.

Part of the *Big-pharmaceuticalisation* process is changes in ethical and political concerns regarding pharmaceuticals and their regulation. Between 2005 and 2013, changes in the TRIPS agreement and Schedule Y of the Indian Drugs and Cosmetics Act had not taken place hand in hand with regulatory capacity to govern clinical trials. With the controversies that have taken place, new concerns have arisen in the ethical debates concerning pharmaceuticals. While access to drugs remains part of the discourse of drug development, a motivator for commercial researchers, and a concern over the public health benefits after trials are over for the civil society, the primary concern of the commercial researchers was the safety of research participants. Failure to control risks on human subjects and maintain high ethical standards was always externalised to 'other' CROs and their operations. But Indian CROs, and possibly Indian companies, have been included in the controversial trials that have taken place. This adds complexity to the common perception that those who were to blame for malpractices were always international players.

Still, the precedent for the form of innovation and kind of research is characterised by *Big-pharmaceuticalisation* and the era of clinical trials. While Indian biotech and pharmaceutical



companies were conducting both generic studies and research on New Chemical Entities (especially Phase 1 trials), bioequivalence and biosimilars studies with CROs, international pharmaceutical companies outsourcing their research to India were still the largest players in the field. While India's pharmaceutical sector is being influenced by Big Pharma into changing their operational practices in-line with international ones and is starting to look more like the international pharmaceutical sector, most of the trials that we studied were conducted by international sponsors in conjunction with international or Indian CROs. In those cases the role of CROs had little to do with innovative knowledge production within India as such. Using clinical trials to move Indian research cultures towards innovation still has to demonstrate that it can lead to sustainable innovations. While outsourcing and offshoring has brought about a "hybridization" of innovation and operations, it is not clear that engaging in these down-stream activities will enable moves upstream in the knowledge-producing hierarchy. As of today, *Big-pharmaceuticalisation* and clinical trials by CROs in India serve primarily as vehicles for generating universal data for the international pharmaceutical industry and facilitating access to large Indian markets rather than meeting the objective of local knowledge production.

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