With the help of a foreign ally: biopharmaceutical innovation in India after TRIPS

Federica Angeli*

Department of Health Services Research, School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, The Netherlands

*Corresponding author. Department of Health Services Research, Maastricht University, Duboisdomein 30, Postbox 6200 MD, Maastricht, The Netherlands. E-mail: federica.angeli@maastrichtuniversity.nl

Accepted 28 February 2013

This article investigates the implications of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which reached full-fledged implementation in 2005, for the patenting activity of Indian biopharmaceutical companies. The Indian biopharmaceutical industry is well-known for its generic producers, whose business models capitalize on the opportunity to reverse-engineer patented compounds and produce them at low costs through process innovation. By strengthening intellectual property rights, TRIPS determined a major regulative change, which presents the characteristics of an institutional shock. The examination of the patenting and alliance activity of 123 Indian biopharmaceutical firms between 1999 and 2009 reveals two important insights. First, the innovation outcome of Indian biopharmaceuticals has sharply increased during the transition to TRIPS-compliant regulation, suggesting that Indian companies have been capable and willing to transit from an imitation-based to an innovation-based business model. Second, those biopharmaceutical firms holding cross-border alliances to foreign partners have proved significantly more successful at enhancing their innovative capability. This research delivers a multifold contribution to the policy debate surrounding the enforcement of TRIPS in emerging economies. First, it suggests that such regulatory change may have encouraged biopharmaceutical innovation in India, despite the sceptical voices who did not foresee any benefits because of inherent inertia of the industry. Second, by arguing and testing the advantages of foreign partnerships, this research highlights that the much feared return of pharmaceutical foreign companies to India could instead favour adaptation to institutional change. Implications for Indian public health are particularly critical. The impact of TRIPS on drug pricing and on the capability—and willingness—of Indian biopharmaceuticals to invest in local health conditions are two crucial points of discussion.

Keywords Indian biopharmaceutical industry, TRIPS, institutional change, patents, cross-border alliance networks
KEY MESSAGES

- The introduction of TRIPS-compliant regulation has determined a deep institutional change in the Indian biopharmaceutical industry, by legitimating innovator companies and by outlawing imitators.
- Indian biopharmaceutical companies found in cross-border alliances an essential leverage for adapting to the institutional transition, and for successfully shifting from R&D-led to reverse engineering-based business models.
- The return of multinational corporations to the Indian market may entail unexpected benefits, because it multiplies opportunities for cross-border partnerships and thus can trigger Indian biopharmaceutical innovation.
- TRIPS’ implications for drug prices may not be as dramatic as expected. However, the newly acquired R&D capability may still fail to provide new treatments for Indian health needs.

Introduction

The strengthening of the intellectual property regime (IPR) through the full implementation of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) has touched many low- and middle-income countries, such as Brazil and Latin America, India, Central America, China, Northern and Sub-Saharan Africa, Mexico, Thailand, Pakistan, etc.1 The compliance to TRIPS entails regulatory changes at country level that have raised controversial views by policymakers and academics alike, particularly around the Indian case. The Indian pharmaceutical context has traditionally been characterized by reverse engineering of patented compounds, which led generic drug producers to thrive and has kept drug prices low. For this reason, the reintroduction of a strict IPR in India has the potential to deeply stir (and harm) competitive dynamics, modify the focus of R&D investments and change drug pricing policies, with far-reaching consequences for Indian public health (e.g. Ramani and Maria 2005).

The year 2005 marked the final stage of the 10-year-long process that led to the full-fledged implementation of TRIPS-compliant intellectual property regulation in India. This regulatory framework increases the incentives for firms to innovate by ensuring that they are the sole beneficiaries of financial returns of the innovation for 20 years. However, the conversion from a reverse engineering-based business model of generic producers to an R&D-led model requires radical rethinking and substantial investment (Mahajan 2011). A sizable body of studies expressed sceptical views about the possibility of Indian companies to undergo such difficult conversion (Ramani and Maria 2005). Moreover, strong concerns were associated with the massive return of foreign companies to the now more appealing Indian market (KPMG 2010; Chauduri 2011). In contrast, more recent scholarly work has instead evidenced that the compliance to TRIPS has spurred innovation activities of indigenous companies, in the form of increased patenting activity and R&D expenditures (Chadha 2009; Mahajan 2011). This evidence underlines a possibly overlooked capability of Indian biopharmaceutical companies to react to the regulatory change and smoothly sail through the required technological conversion. However, how and why Indian companies radically revisited their business models instead of adopting other available positioning strategies is still an unexplored side of TRIPS implications. Moreover, the effects of these sizable policy and organizational changes on the Indian public health system are still poorly understood.

Two crucial points about the introductions of TRIPS, therefore, need investigation: (i) how Indian companies seemingly succeeded to take on the non-trivial challenge to move from being imitators to becoming innovators and (ii) what the consequences of this transition are for Indian public health. This article aims to tackle the first gap by investigating the role of ‘cross-border alliances’—namely inter-organizational agreements between Indian biopharmaceutical companies and foreign firms or subsidiaries in India of multinational corporations (MNCs)—in leading the technological transition. In this light, this study elaborates on TRIPS-compliant regulation as an example of institutional change, it relates it to the evolution of cross-border alliance behaviour of Indian biopharmaceutical firms and it investigates its final implications on biopharmaceutical innovation.

To tackle the second gap, this research links the highlighted organizational dynamics to two main factors influencing Indian public health and strictly related to biopharmaceutical action: (i) drug pricing and (ii) the focus of biopharmaceutical R&D investments. By establishing monopoly on new compounds and by favouring the return of foreign companies and MNCs to India, the introduction of patent protection may raise the price of drugs and reduce their availability to poor patients. At the same time, the new international partnerships and the newly acquired R&D capability of local producers may divert their production focus away from the treatment of local diseases. The two dynamics can entail disruptive effects for Indian health care, traditionally dominated by low-cost drugs and in desperate needs for new pharmacological discoveries able to cure specific conditions.

This article proceeds as follows: the next section will introduce the theoretical framework of the study. First, the introduction of TRIPS will be described, along with its main characteristics and implications. Second, TRIPS will be analysed as an example of regulatory discontinuity generating institutional change. The third step of the theoretical reasoning will consider the crucial role of cross-border alliances. Since TRIPS-compliant regulation is argued to deeply affect the institutional environment of Indian biopharmaceutical firms, cross-border alliances are expected to influence the companies’ adaptation to the institutional change. The methodological section outlines data collection and data analysis techniques, followed by a commentary on the results. A discussion and conclusion section highlights the main contribution of the work to the current debate about TRIPS consequences for emerging economies. The
implications of the findings for Indian public health are explored, and suggestions are made for future research.

Theoretical framework

The introduction of TRIPS

The biopharmaceutical industry encompasses the set of pharmaceutical firms that have incorporated biotechnology in their drug discovery and development, as well as fully dedicated biotechnology firms (Rothaermel and Deeds 2004; Ramani and Maria 2005). This definition follows an increasingly prominent tradition of studies that underline the profound impact of biotechnology on pharmaceutical industry. The intense networking activity and knowledge transfer between the two sectors have increasingly blurred industrial boundaries, and determined a convergence of biotechnology and pharmaceutical domains (Kulkarni 2008).

The Indian biopharmaceutical industry is a vibrant, dynamic context. Its turnover has grown from $330 million in 1980 to $22.2 billion in 2009–2010 (Indian Department of Pharmaceuticals 2011), registering a two-digit growth against a 7% of the world market overall (KPMG 2010). The Indian pharmaceutical production represents today 10% of the global industry by volume, ranking 3rd in the world, while it is the 14th largest by value. The difference accounts for the fact that drugs in India are priced from 5 to 50% less than in developed countries (Indian Department of Pharmaceuticals 2011). The industry is also characterized by a long history. The first pharmaceutical companies, Bengal Chemicals and Pharmaceutical Works, appeared in Kolkata in 1930. Until the early 1970s, most of the drugs in India were imported by MNCs, either in fully formulated or bulk form, with local manufacturers occupying a very marginal role in the market.

A radical change in the competitive scenario was triggered by the Patents Act in 1970, a regulatory framework that enabled the indigenous industry to thrive to the current levels (Indian Drug Manufacturer Association 2011). By removing composition patents on food and drugs, and by shortening process patents to a period of 5 years after granting, the Patent Act made the Indian market unappealing to foreign companies, whose presence fell from 75% in 1971 to 35% in 2003 (Joshi 2003). While foreign players streamed out, Indian companies took the opportunity for a swift growth (Indian Drug Manufacturer Association 2011). By developing a unique expertise in reverse engineering new processes for manufacturing drugs at low cost, local manufacturers succeeded in carving a niche in both the Indian and in the global market, while providing much needed affordable drugs to the large low-income Indian population strata. In 2002, more than 20,000 registered drug manufacturers in India sold USD 9 billion worth of finished formulations and bulk drugs. About 85% in value of these finished formulations were sold in India, while more than 60% of the bulk drugs (or active principle ingredients) were exported, mostly to the USA and Russia (Joshi 2003). In 1999, the Indian biopharmaceutical industry produced 70% of the bulk drug and 80% of the finished formulations sold in the country, making the Indian biopharmaceutical market one of the few examples in the world to achieve self-sufficiency (Grace 2004).

In 1995, a second major regulatory change intervened to modify again the Indian biopharmaceutical scenario. As a signatory of General Agreement on Tariffs and Trade and founding member of World Trade Organization, India became automatically subject to TRIPS, a set of measures aimed at homogenizing intellectual property rights among the 132 member countries, which were allowed a 10-year transition period to align their IPR laws with the international agreement. After three amendments to the Patent Act in March 1999, June 2002 and March 2005, fully TRIPS-compliant regulation came into force in April 2005, and reintroduced 20-year patent protection on new pharmaceutical compounds. Apart from exceptional cases identified by the Doha Declaration on Public Health of 2001, which takes into account the supremacy and precedence of public health requirements over private patent rights, formally since January 2005 Indian patent laws fully abide by the new regulations and forbid the manufacturing and marketing of patented drugs, unless a legal license is held by the manufacturer.

The main rationale behind TRIPS argues the necessity of full patent coverage to support the research and development and regulatory approval of new compound entities (NCEs), which may take up to 15 years and may cost up to 500 million USD (Fernandez et al. 2007). Therefore, TRIPS strengthens the incentives to innovate for the market innovators, companies that heavily invest in product R&D. At the same time, TRIPS strongly limits the competitive room of second innovators, or imitators, whose business models capitalize on the opportunity to reverse-engineer patented compounds and produce them at low cost through process innovation (Ramani and Maria 2005). While the technological trajectory of Indian companies mainly follows the imitator model, biopharmaceutical firms in the regulated markets of USA and Europe are mainly innovators, and focus more on R&D investments and NCEs discovery. It is therefore not surprising that the introduction of TRIPS in emerging economies and specifically in India had been strongly endorsed by USA and European member states, arguably to protect the interests of their home country biopharmaceutical industry by expanding market opportunities in less regulated markets (cf. Ramani and Maria 2005).

TRIPS as a trigger of institutional change

The implementation of TRIPS forced the Indian biopharmaceutical industry to transition from an imitator (or second innovator) to an innovator (or first innovator) business model. Pure examples of the two types of business models are rare in practice, in that each biopharmaceutical company displays characteristics of both, albeit in different proportions. However, the focus on either aspect—whether reverse engineering or R&D directed to the discovery of new compounds—is typically prominent, which makes the distinction useful and widely used in scholarly work and industrial analyses (e.g. Joshi 2003; Grace 2004; Ramani and Maria 2005). The imitator model is at odds with the innovator paradigm, in terms of capabilities requested (manufacturing and reverse engineering in the case of imitators, R&D and product innovation in the case of innovators), market outlook (domestic, low-cost focus for Indian companies, who adapted to the low-cost needs of the Indian population as opposed to internationally active Western
biopharmaceutical MNCs) and patenting orientation (process patents for imitators vs product patent orientation for innovators).

There are several reasons for looking at TRIPS-induced regulation as a full-fledged institutional change. Institutional theory emphasizes how institutions shape social and organizational life (Scott 1995). The institutional environment comprises the ‘set of fundamental political, social and legal ground rules that establishes the basis for production, exchange and distribution’ (Davis and North 1971, pp. 6–7). Institutions create a taken-for-granted (i.e. institutionalized) social and cultural context (Meyer and Rowan 1977; Scott 1983; Zucker 1987; Powell 1988), which creates pressures for conformity (Meyer and Rowan 1977; Guler et al. 2002). To survive, organizations and individuals are expected to establish and maintain legitimacy by signalling conformity to the established order, whether it is of cognitive, normative or regulative nature (Scott 1995). Regulative aspects ‘stress super-imposed rules, monitoring and sanctioning; normative aspects consider the prescriptive, evaluative and obligatory dimension that is self-constructed by social groups and that orders their social life’ (Scott 2003, p. 880). Each institutional order offers a different rationale for claiming legitimacy, whether by virtue of being sanctioned, morally authorized or culturally supported (Scott 2008).

TRIPS triggered institutional discontinuity because TRIPS-compliant regulation fundamentally altered the institutional domain underpinning Indian biopharmaceutical industry (also Kamiike and Sato 2011). Literature defines institutional change as ‘the abandonment of institutionalized practices, structures and goals and/or the adoption of institutionally contradictory practices, structures and goals by an individual organization or field of organizations’ (Kraatz and Moore 2002, p. 120). The shift from an imitation-based to an innovation-based technological paradigm induced by TRIPS-compliant regulation determined the need for deep modification in business practices and goals and radically redefined the basis for social legitimacy. Although at a cognitive level the imitator paradigm may still elicit consensus because of its suitability to Indian needs for low-cost medicine, it is no longer sustainable at a normative and regulative level, because after the advent of TRIPS-compliant regulation it became susceptible to sanctions and moral blame by the international community. In view of the institutional change entailed by the implementation of TRIPS, immediate organizational actions are needed to signal conformity to the new paradigm, through mechanisms known as mimetic isomorphism (DiMaggio and Powell 1983). This article argues that cross-border alliances have constituted one primary mechanism through which Indian biopharmaceutical companies have pursued isomorphic objectives during the TRIPS transition.

The role of cross-border alliances during the TRIPS transition

Cross-border alliances can be defined as short- or long-term agreements between organizations headquartered in different countries, concerning one or more areas of activity, such as market entry, skill acquisition or technological exchange (cf. Dacin et al. 2007). Cross-border alliances can be a valuable option for firms in emerging economies, who seek for rapid access to technology and managerial capabilities to compete in global markets (Svetlicic and Rojec 1994; Zahra et al. 2000). Hitt et al. (2004) demonstrate this point by observing the evolution of alliance activity of firms in Russia and China. The transition from command to market-driven economies created a lack of necessary managerial competencies, which could be effectively sourced via external partnerships.

Similarly, the transition from an imitator-based business paradigm to innovation-driven competition enforced by TRIPS has entailed a ‘competency-destroying change’ (Mahajan 2011). Since 1970 Indian biopharmaceutical companies have built their competitive advantage on strong manufacturing capabilities and reverse engineering. It is often reported that India has the highest number of FDA-approved manufacturing plants outside USA (Langer 2007; Corporate Catalyst India 2008). Hence, during the implementation of TRIPS, the dearth of in-country R&D capabilities was critical. For example, on average, Indian firms appear to hold strong skills in the chemistry field but are relatively weak in biology and clinical research, which are crucial in the processes of discovery and development (Grace 2004). Beyond R&D knowledge, Indian companies lack expertise in patent writing. Experts suggest that patents written by Indian professionals could be easily circumvented and may thus not ensure protection in international settings (Grace 2004). Furthermore, it is often argued that Indian companies lack the financial resources to pursue international patenting (Raman and Maria 2005). Against this backdrop, reaching out to cross-border partners may provide a cost-effective and quick option to access those complementary assets—namely financial resources, managerial and procedural expertise and scientific knowledge—not available within the national borders. Cross-border alliances may constitute an important strategic resource for quick adaptation to the new IP-oriented regulation.

A second important rationale for expecting Indian companies to leverage cross-border alliances during the TRIPS transition is the search for legitimacy. Alliances may constitute an organizational vehicle to raise consensus of those constituents on whom the organization depends for accessing crucial resources (Dacin et al. 2007). Strategic and economic activity is embedded in a social, normative and regulative context that creates pressures for actors to conform to institutional rules, norms and expectations (Scott 1995; Dacin et al. 2002). In this view, strategic alliances to visible and well-reputed partners who conform to the expected norms can increase the focal firm’s legitimacy by signalling its adherence to the established institutional order (Dacin et al. 2007). The presence of these relationships directly benefits the focal firm’s support and reputation, thereby easing its procurement of critical resources and enhancing its survival chances (Podolny 1994; Pollock et al. 2002; Dacin et al. 2007). Hitt et al. (2004) highlight how legitimacy provided by a firm with a strong global reputation enhances the Chinese partner’s ability to compete in global markets, thereby allowing it to earn needed hard currency and achieve growth (Peng and Heath 1996; Ahlstrom and Bruton 2001).

On a similar vein, Indian biopharmaceutical companies experiencing the regulative transition induced by TRIPS need to re-establish their basis of consensus by signalling their
conformity with the new paradigm. With respect to other strategies available to upgrade Indian firms’ innovative capabilities, such as increasing R&D expenditure, or massive hiring of researchers and scientists, partnering with R&D-driven biopharmaceutical firms has the advantage to display acceptance of the new paradigm and document efforts for tuning organizational practices and structures with the new rules, according to a process of mimetic isomorphism (DiMaggio and Powell 1983). The display of similarity and compliance to the new order may allay the foreign partners’ concerns related to moral hazard and to potential opportunist behavior of Indian companies, and may thus open up new opportunities to procure relevant knowledge and resources. At the same time, the regulative change triggered by the implementation of TRIPS has arguably increased the appeal of the Indian biopharmaceutical market for those foreign, R&D-based firms who were driven away by the abolition of product patents in 1970 (Joshi 2003). Cross-border alliances with Indian biopharmaceutical firms may offer these companies a fast way to regain foothold in the Indian market.

Given the arguments earlier, this study hypothesizes that the number of cross-border alliances held by a biopharmaceutical company will positively influence its innovation outcome during the TRIPS transition.

Methods
Sample and data

The original panel database at the basis of the empirical analysis has drawn on multiple data sources. The sample of firms and the financial data (sales, operating margin, age and R&D expenditures) have been sourced from Datastream. A database offered by Thompson Reuters, Datastream provides comprehensive time series of financial data for listed companies database offered by Thompson Reuters, Datastream provides comprehensive time series of financial data for listed companies operating in the pharmaceutical and biotechnology sector as classified by Datastream (primary three-digit Standard Industrial Classification code 2834 and 2836). This criterion isolated 123 companies, with complete financial data time series.

The alliance network structures of the sample companies have been built through publicly reported alliance data sourced from Thomson Reuters SDC Platinum Joint Ventures and Alliances. The Thomson SDC Platinum Database provides information about a number of inter-organizational deals worldwide and across industries and has been used in several empirical studies examining strategic alliances and networks (e.g. Schilling and Phelps 2007; Somaya et al. 2011). Each selected alliance has been announced between 1985 and 1999, the alliance data for the biopharmaceutical sector are very sparse, 1999 has been considered as the first year of interest. Alliances typically last for more than one year but alliance termination dates are rarely reported. This requires making assumptions regarding the alliance duration. Following recent empirical work, I used a conservative approach and assumed an average alliance duration of 3 years (Rosenkopf and Schilling 2007; Schilling and Phelps 2007). Assumptions of alliance duration ranging from 3 to 5 years have been made to investigate alliance networks in high-technology sectors (Robinson and Stuart 2007), and specifically, in chemicals (Ahuja 2000), semiconductors (Podolny et al. 1996) and telecommunications industries (Baie and Gargiulo 2004). I then created alliance networks based on a 3-year moving window (Robinson and Stuart 2007): the network at the focal time t represents the overlap of all alliances announced between t − 3 and t. This approach returned 11 cross-border yearly networks and 11 domestic yearly networks, one for each year between 1999 and 2009. To avoid left-censoring bias on the network in 1999, I complemented by adding alliances announced between 1996 and 1998, which are assumed as still active in 1999. Each network snapshot has been constructed as an undirected binary adjacency matrix (Wasserman and Faust 1994). Multiple alliances between the same pair of firms were treated as one link. UCINET 6 was used to obtain network structural measures.

Indian patent data have been sourced from the Indian Patent Office (IPO) online database and Indian Patent Information Retrieval System. The online interface offers information for all patent applications from 2000 till the present date. To capture the international orientation of patenting activity, I also gathered information about patents granted by the US Patent and Trademark Office (USPTO). The online search interface provides details about patents issued from 1975 onwards. The yearly count of granted patents for the 123 focal Indian companies in the 11 years of observation has been derived by relying on the date of filing of the patent application to assign a granted patent to the respective year. This approach returned a number of USPTO-granted patents and a number of IPO-granted patents per firm per year. Notably, the gap between patent application and patent grant may engender right-censoring issues. The latest check on granted patents on both USPTO and IPO database has been performed on 1 November 2012. Since the average patent pendency duration is estimated around 3 years, this approach provides reasonable mitigation to the right-censoring concern. Finally, I complemented and cross-checked information about firm age, firm size and R&D expenditures reported by Datastream through companies’ financial reports and websites.

Measures and analysis

The dependent variable is operationalized as the yearly number of granted patents by year of application (e.g. Ahuja 2000; Schilling and Phelps 2007; Whittington et al. 2009). To ensure robustness of the measure, and also to adequately capture the international orientation of the innovation activity, two yearly counts have been produced for each firm in each year: one derived from patents issued by IPO and one by USPTO. Patents
provide a measure of invention that is externally validated through the patent examination process (Griliches 1990), particularly salient in the biopharmaceutical context (Whittington et al. 2009). Moreover, patent counts are reported to correlate well with new product introductions and invention counts (Basberg 1987). For these reasons, patent counts are accepted as valid and robust indicators of knowledge creation by a substantial tradition of studies (Trajtenberg 1987), including well-known contributions in the network literature (Ahuja 2000; Schilling and Phelps 2007; Whittington et al. 2009). A 2-year lag between the point of measurement of the independent variable and the point of measurement of the dependent variables has been introduced, as the network effect on innovative output reportedly reaches its peak after between 2 and 3 years (Schilling and Phelps 2007). The independent variable is measured as the ‘size of cross-border network’, namely the number of cross-border alliances a firm holds in the year of observation. The performed network analysis provides this information in the form of the degree of the cross-border network related to firm \( \text{i} \) at time \( t - 2 \).

The model includes a variety of firm-level controls. First, the ‘size of domestic network’, namely the number of domestic alliances held by a firm at time \( t \), has been taken into account. This term controls for whether a general network effect is responsible for the innovation outcome rather than a specific cross-border effect. Following prior studies, a control variable measuring the ‘previous patenting activity’ of the firm has been introduced, to account for experience with patenting process and propensity to engage into commercial behaviour (Whittington et al. 2009). Previous patenting activity has been operationalized as the number of patents at time \( t - 1 \), when the dependent variable is measured at \( t \), and the independent variables are measured at time \( t - 2 \) (e.g. Whittington et al. 2009). Moreover, I took into account continuous variables controlling for ‘firm age’, ‘firm size’ and ‘R&D expenditures’. Age has been measured by subtracting the foundation year from time \( t \), firm size has been operationalized through total sales at time \( t \), while ‘R&D expenditures’ report the total yearly expenditure on R&D activities as reported in the companies’ balance sheet. A yearly dummy variable for every year except one has also been included, to control for period effects and unobserved heterogeneity across time (Ahuja 2000; Whittington et al. 2009).

Data analysis has relied on descriptive statistics and negative binomial regressions, following a well-established approach in modelling longitudinal patent count data (Ahuja 2000; Whittington et al. 2009). I used generalized estimating equations procedure within the Statistical Package for Social Sciences (SPSS) 19.

Results

Table 1 reports the descriptive statistics and correlation matrix of the variables included in the model. No multi-collinearity issues appear to undermine the regression results. The high-correlation value between firm size and R&D expenditure was expected, as firm size is measured through total sales. Nevertheless, both R&D expenditure and firm size are kept in the model, because of the relevant influence they may both bear towards patenting activity.

Before discussing the results of the regression analyses, it is worth considering the longitudinal trend of the dependent, independent and control variables. Figure 1 highlights the trend of cross-border alliances vs domestic alliances, computed as the yearly sum of the size (degree) of the sample firms’ cross-border and domestic networks. As such, the figure reports not the number of alliances announced per year, but yearly number of active alliances. In 2002, the cumulative size of cross-border networks reaches a peak, with 115 cross-border alliances out of 132 alliances in total. The trend keeps almost stable in 2003, with 114 cross-border alliances out of 135 total alliances, while it displays a sharp decrease in 2004, with 60 cross-border alliances out of 81 alliances in total. It appears that the number of alliances with foreign partners is decreasing right before the full implementation of TRIPS in 2005, though it displays a rising trend afterwards: in 2008, the number of active cross-border alliances is 114 out of 127 total alliances. In 2009, maybe due to financial crisis, a sharp drop again reduces the number of foreign alliances back to 69 out of 80 total alliances. It is interesting to notice how the size of domestic alliance network remains stable over time.

Details about the geographical and industrial composition of foreign partners reveal two main insights into the nature of cross-border alliances. First, 85% of cross-border partner firms fall in the standard industrial classification (SIC) category related to drugs, namely 2834 (pharmaceutical formulations) with 64%, 2836 (biological products) with 13%, 2835 (in vitro and in vivo diagnostic substances) with 4% and 2833 (medicinal chemicals and botanical products) with 4%. Second, the geographical distribution of the partners highlights that USA (42%), Germany (10%), Japan (6%), UK (6%), Canada (5%) and Switzerland (4%) account for 83% of the deals with India. Over the period of observation, Indian biopharmaceutical companies have thus allied mostly with other biopharmaceutical companies in developed economies and in highly regulated markets.

Finally, cross-border alliances can be investigated according to their R&D orientation, as provided by Thomson SDC database. Notably, biopharmaceutical firms may establish alliances to discover new compounds by sharing R&D efforts with the partner, or to license-out or license-in compounds for further manufacturing/marketing activities. Figure 2 presents the trend of R&D vs non-R&D deals and reveals that the numerical gap between R&D deals and manufacturing/marketing oriented agreements is narrowing over time, the first becoming increasingly prominent just around 2004–05. Interestingly, R&D expenditures also, as a share of sales, display a steady increase over time (Figure 3).

The characterization of partners as biopharmaceutical companies in a developed, highly regulated market, the increase in R&D expenditures and the increasingly prominent R&D orientation of cross-border deals together suggest that Indian biopharmaceutical firms are attempting to move up the value chain, and thus to shift from a manufacturing-oriented to an R&D-oriented business model.

Figure 4 displays the yearly trend of the number of USPTO and IPO granted patents by year of application. The highest
cumulative number of granted patents has been filed in 2002, 2003 and 2004, with 227, 281 and 267 patents, respectively. While the patent activity with USPTO registers a peak in 2003 with 83 patents but remains quite stable over time, the trend with IPO is much more skewed towards a maximum in 2004 with 214 patents, which rapidly decreases to 61 in 2006 and 11 in 2008. The peak in the number of patent applications that have subsequently led to granted patents is thus registered in 2003–04, the year immediately preceding the full enforcement of TRIPS-compliant regulation.

The fixed-effects negative binomial regressions reported in Table 2 test the causal relationship between cross-border alliances and innovation performance, measured both at international and national level through USPTO- and
IPO-granted patents. Model 1 has IPO patent count as dependent variable, and Model 2 has USPTO patent count as dependent variable.

The baseline Model 1 represents the regression with control variables only, whereas Model 1 includes also the size of cross-border alliance network as explanatory variable. Previous patenting activity and firm size are positive and significant in both models, indicating that the larger a firm the higher its propensity to patent, and the more the granted patents in the past the higher the firm’s likelihood to file successful patents in the future. In addition, Model 1 shows the effect of the size of cross-border alliance network. The variable displays a positive and highly significant coefficient, thus proving the relevance of cross-border alliances in explaining national patenting activity.

Baseline Model 2 tests the effect of the control variables against the number of USPTO-granted patents, whereas Model 2 adds the explanatory variable, cross-border network size. Like in Models 1, firm size and previous patenting activity report strong and significant effects in both models. Model 2 shows that the size of cross-border alliance network bears a very significant influence on the number of USPTO-granted patents. Hence, cross-border network fosters innovative performance also at international level.

Interestingly, R&D expenditures are significant in both Model 1 and Model 2, with a negative sign. This result seems to suggest that, in the presence of cross-border alliances, the effect of firms’ R&D investments may be detrimental rather than beneficial to innovation. In addition, noteworthy is the behaviour of the domestic network variable. Clearly, the benefits of alliances are not universal, but instead contingent on whether the alliances are cross-border or domestic. In fact, while the size of cross-border network is highly significant, the size of domestic network is not.

Taken together, these findings corroborate the central hypothesis of this study: cross-border alliances play a strong and significant role in explaining innovative performance of biopharmaceutical firms during and after the introduction of TRIPS, both nationally (IPO-granted patents) and internationally (USPTO-granted patents).

### Discussion and conclusions

Notably, the strengthening of IPR in India following TRIPS-derived regulation has received mixed acceptance, around two main issues. On the one side, views diverge on whether the regulatory change can provide an actual incentive to Indian companies to invest more on innovation. On the other side, scholars and policymakers have been debating around the effect of TRIPS on drug prices and on the focus of the new R&D investments, thus considering the implications for the larger public health system. This section will consider the contribution of this work to the two lines of speculation.

A tradition of early scholarly works argue that TRIPS will provide a positive trigger for the mature Indian biopharmaceutical sector to develop innovation-based business models (Ganguli 1999; Lanjouw and Cockburn 2001; Lalitha 2002; Lall 2003). This line of reasoning represents the main rationale for the homogenization of IPR across countries, and seems to be corroborated by more recent studies (Chadha 2009; Kamiike and Sato 2011; Kamiike et al. 2011; Mahajan 2011). In contrast to this standpoint, Ramani and Maria (2005) predict a negligible effect of TRIPS on innovation capabilities of Indian firms, for a set of reasons. In view of the impressive wave of biogenerics, vaccines and diagnostics coming off-patent in mid-2000, the authors predicted that the focus of Indian biopharmaceutical companies in the post-TRIPS era would fall on the massive production of these compounds, rather than on researching new drugs under the influence of the new regulation. Second, Indian firms in most instances lack the financial resources to undertake the costly patenting process. The few indigenous companies that possess the wealth to patent a drug blockbuster are more likely to pursue an EU or US patent, which may guarantee more visibility and act as a technological signal. However, TRIPS has no impact on Indian firms patenting outside India, so the regulatory change is not likely to either boost or depress the patenting activity of wealthy Indian companies. Third, Ramani and Maria (2005) did not foresee any increase in the number of collaborations between Indian companies and multinational pharmaceuticals, as they perceive north–south co-operation issues not as primarily related to intellectual property legislation but rather...
to infrastructure, commitment and information factors. Following the arguments earlier, the authors view the future of Indian biopharmaceuticals not as innovators but as part of a global division of labour of the innovation creation process by western firms. Similar conclusions have been reached by Chaudhuri (2008).

This article advances the debate in two main directions. First, it provides evidence of an increase of biopharmaceutical innovation in India during the TRIPS transition. At least in the Indian case, the new intellectual property regulation following TRIPS seems to have triggered organizational action towards the pursuit of more R&D-oriented business models, which manifest through: (i) higher number of R&D-oriented alliances towards innovative biopharmaceutical partners in regulated markets and (ii) increased patent filings and R&D investments. It is important to note that the number of patents filed and granted has increased not only domestically but also, most importantly, internationally. This research proves that Indian biopharmaceutical firms have been able to pursue international patenting activity, in contrast to earlier expectations (Ramani and Maria 2005) and highlights that cross-border alliances may have been crucial in providing the necessary financial resources, scientific knowledge and managerial and procedural expertise to do so. These findings add to previous studies showing that export and productivity of Indian pharmaceutical firms during and after the introduction TRIPS-compliant regulation have increased (Kamiike et al. 2011), along with the effort devoted to the development of generic products for regulated markets (Kamiike and Sato 2011).

Against this backdrop, this article evidences that cross-border alliances are one previously unexplored resource underpinning the successful and swift shift of Indian biopharmaceutical companies from being mainly imitators to being mainly innovators. Cross-border alliances during the TRIPS-induced regulatory transition have increased and have experienced a decrease only slightly before the full-fledged implementation of the new legislation abiding to TRIPS. Particularly, the R&D-oriented deals towards companies in highly developed, regulated markets have gained prominence. This finding contrasts with the expectations advanced by Ramani and Maria (2005) and proves that cross-border alliances may thrive and be extremely beneficial, despite the inherent difficulties of international agreements and of north–south collaboration in particular. Partnerships with foreign firms provide indispensable access to R&D capabilities, financial resources, managerial expertise and international legitimacy, and appear to be a strong asset for those companies willing to enhance their innovation capability and thus shift to an R&D-based business model. Interestingly, their decrease in number shortly before 2005 suggests that cross-border alliances may provide a transitory leverage for achieving a business model transition and for acquiring the necessary jump-start resources. As such, cross-border deals do not necessarily constitute a long-term strategy, but may offer a stepping stone for more permanent strategic choices.

This study thus provides new nuances to the potential impact of foreign companies returning to the Indian market as envisioned by Chaudhuri (2011). On the one side, cross-border alliances can provide Indian biopharmaceuticals with important strategic assets to promote a fast and effective development of an innovation-driven business formula. On the other side, TRIPS-compliant regulation has increased the interest of foreign players to establish alliances with Indian companies, as a means to achieve fast market penetration under the condition of stronger intellectual property rights (cf. Joshi 2003; Kamiike and Sato 2011). The interests of local and international players during and after the TRIPS transition may thus be aligned in the opportunity to establish cross-border deals and to promote a win–win situation. It follows that policy measures favouring collaboration between local and foreign firms may be crucial for fostering biopharmaceutical innovation in India.

With regard to the impact of TRIPS-compliant regulation on drug prices and medicine access, the scholarly community is yet to reach a consensus. Several voices have argued that, since newly introduced product patents establish 20-year-long monopolies on drugs, the reintroduction of patent protection on new compounds would induce dramatic raises in the drug prices in the whole developing world (Chaudhuri 2011; Hafner and Popp 2011). However, simplistic predictions may be misleading, since a complex interplay of factors concurs to determine drug prices. The influence of drug price policy control and the dynamics of price determination in different segments should be taken into account, to fully understand how stronger intellectual property rights are likely to influence drug affordability.

Drug price control policies are aimed to cap drug prices in the interest of public health. In the case of India, between 1970 and 1995, the drug price control order (DPCO) and weak patent protection have both contributed to maintain drug prices among the lowest in the world, although the latter factor is considered the most influential (Chaudhuri 2005). To favour liberalization, DPCO has progressively shrunk its control from 347 in 1987 to 74 bulk drugs in 1995, on which ~1577 formulations are based (National Pharmaceutical Pricing Policy 2012), ~20% of the market (Kamiike and Sato 2011). The drug price directives following the full-fledged implementation of TRIPS-compliant regulation envisage that all patented drugs introduced in India after 1 January 2005 would be subject to price negotiations before market approval. However, it is argued that foreign companies can easily manipulate government price control, as the government has limited ability to check for overpricing against the claim of the manufacturers, when the internal production costs are unknown and when benchmarks are unavailable. And in fact, drug prices in India have risen sharply in the post-TRIPS period (Kamiike and Sato 2011).

Recent reforms of drug control policy measures, in the form of National Pharmaceutical Pricing Policy (2012), aim to strengthen policy control over drug prices by adopting the concept of ceiling prices and market-based pricing on final formulations, and by emphasizing essentiality of drugs (National Pharmaceutical Pricing Policy 2012). These new criteria led to 348 bulk drugs under control, corresponding to 654 finished formulations.8 A 20% price reduction on 30% essential drugs is expected.

When considering the influence of IPR on drug prices, it is important to take scale into account. TRIPS-induced regulation has an influence on patented medicines only. After 2005, generic copies of products already off-patent in regulated
markets and generic versions of compounds patented before 1995 are still allowed. Grace (2004) pinpoints that the two categories together account for more than 90% of the drugs on the Indian market, which bounds the potential price rise due to TRIPS-compliant regulation to the remaining 10% of the market only. Price rise in the generic, off-patent segment may still occur as a consequence of market consolidation, but would not be directly associated to the implementation of TRIPS, and would arguably be far from the 200% price rise hypothesized by some analysts (Ford 2004). Also within the on-patent segment, an estimated 10% of the total market, Grace (2004) highlights that other factors may cap the drug price rise in India, such as therapeutic competition, the limited domestic purchasing power, the lack of an insurance market, parallel importing and compulsory licensing. The two latter elements in particular are flexibilities of TRIPS, which respectively allow for accessing less expensive medicines in the first case and force the innovators to license the product to domestic producers in the second case, to ensure that essential drugs are available at prices that support public health (Grace 2004).

Finally, it is also interesting to note that other mechanisms may be at play in defining the retail drug price in developing countries. For example, Russo and McPake (2010) highlight that much of the drug prices in private pharmacies in Mozambique is made by local mark-ups, which contribute to up of two-thirds of the price (also Waning et al. 2010). Even when present, statutory profits and cost ceilings are applied unevenly because of lack of control and suppliers’ collusion. In addition, the authors highlight that uncertainty around the quality of generics may induce consumers to purchase less affordable drugs (also Patel et al. 2010). Local market conditions and idiosyncratic consumer behaviour may thus play a relevant role in the determination of drug prices in Mozambique, which could suggest a similar pattern in other unregulated markets. This leads to the conclusion that drug prices are also highly sensitive to macro- and micro-mechanisms other than intellectual property protection. It follows that the impact of TRIPS-compliant regulation on drug affordability and availability in India may be much less straightforward than expected by previous work (e.g. Ramani and Maria 2005; Chauduri 2011).

However, an important point remains open. A crucial side of the rationale driving the enforcement of TRIPS in emerging economies claims that new R&D investments in developing countries like India will foster the generation of drugs able to cure specific diseases that fall out of the interest of US and EU corporations. Yet, Ramani and Maria (2005) do not envision any sensible increase in the pharmaceutical R&D addressing developing countries’ conditions, such as malaria, because of lack of financial incentives. And, in fact, if TRIPS is able to trigger Indian biopharmaceuticals’ innovation, will this innovation translate into better treatments of local conditions? Unfortunately, this work falls short in providing evidence on this point. This limitation can, however, pave the way for future research. Revealing insights can be drawn, for example, from the examination of the technological content of the new patents issued to Indian biopharmaceutical companies after 2005, following a research agenda already set by Lanjouw and Cockburn (2001). And, in fact, on the one side, Indian companies may opt for researching and producing compounds for the sizable, yet low-margin Indian population, thus maintaining their traditional focus on the local needs. However, TRIPS, the competitive pressures from international players, and new global opportunities accessed through international alliances may also drive Indian biopharmaceuticals’ investments to the global arena and to higher-margin markets. In the latter case, the resulting R&D efforts will produce new compounds able to easily sell worldwide, ensuring maybe higher profit and a better competitive position, but reducing the availability of new medicines tackling local needs.

Two additional limitations of this work need to be highlighted and both relate to the use of patent data in measuring innovation. First, patent data do not capture the commercial success of the product nor the financial returns from the patent. Patents are filed at an early stage of new drug development and are to be considered a measure of invention rather than innovation. Nevertheless, the use of patents can be suitable to study innovation for Indian biopharmaceutical companies, which often lack the financial resources to pursue pre-clinical and clinical trials and opt instead for licensing out their discoveries (Kamile and Sato 2011). Second, this study does not discern the nature of granted patents, whether they covered new processes or products, whether they addressed new dosage forms or new chemical entities and which therapeutic area they targeted. Future scholarly work could overcome these limits by investigating regulatory approvals filing, and by developing a refined analysis of the type of patents granted. Deeper insights into the nature of patents could help understand which organizational and systemic factors underpin the propensity of a biopharmaceutical firm to direct R&D efforts towards clinical conditions typical of developing countries. Such evidence could inform academics and policymakers alike, and build the opportunity to structure regulations and incentives able to channel the renewed innovative capability of Indian companies towards local neglected health needs. Moreover, future research may shed further light on how intellectual property regulation can affect biopharmaceutical innovation in emerging economies at large, by developing comparative analyses across different emerging contexts. The complex nexus between regulation, organizational action and repercussions for public health in developing countries is crucial and yet far from being fully understood. Research in this direction is critical for developing timely and effective policy actions.

Endnotes

1 http://www.wto.org/english/tratop_e/trips_e/trips_e.htm
2 http://thomsonreuters.com/products_services/financial/financial_products/a-z/datastream/
3 http://thomsonreuters.com/products_services/financial/financial_products/a-z/sdc/
4 http://164.100.176.38/patentssearch/search/index.aspx
5 http://patft.uspto.gov/netahtml/PTO/search-bool.html
6 http://uspatentstatistics.com/averagependenciestechcenter.html
7 http://economictimes.indiatimes.com/
8 http://www.aalatimes.com/2012/10/24/drug-price-control-in-india/
References


