Cross-Border Spillovers from Pharmaceutical Policy in the United States: Evidence from Large Molecule Drugs in India

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In 2010, United States Congress passed the Biologics Price Competition and Innovation Act (BPCIA) to inject generic competition into biologic product markets in order to bring down prices. The provisions in BPCIA created incentives for Indian pharmaceutical industry - leading generic manufacturer of the world - to produce generic variants of original biologic drugs. Exploiting this as a quasi-natural experiment, we utilize the event-study design set-up to analyze the cross-border effects of the new drug regulation on the market structure of Indian industry dealing in biologic drugs. We find that the U.S. regulation increased competition which led to reduction in prices of the biologic drugs compared to control drugs in India, where these results were mainly driven by the entry of new firms, and expansion of product variety. Our results indicate that firms made their initial entry decisions based on the patent duration, and technological complexity underlying different product markets. Our findings imply welfare effects of policies with strong incentives in eliciting a desirable response in the context of healthcare.

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I. Introduction

Our study aims to measure the cross-border effects of pharmaceutical regulation that took place in the United States. It is important to understand the cross-border effects of drug regulations for various reasons. First, spatial spillovers of a regulation may spur (positive spillovers) or reduce (negative spillovers) the competitiveness of foreign markets by creating supply side incentives to invest or divest in certain technologies. Second, the drug regulation might act as a vehicle for diffusion of new technologies in the form of complex drugs from technologically advanced nations to other nations lying behind on the curve, especially when developed countries like USA are mainly responsible for innovating and bringing vast majority of new drugs to the market. While there is plethora of evidence on the cross-border effects of a regulation in domains such as banking (Hills et al. (2018), Franch et al. (2021), Fidrmuc and Hainz (2013)), environment (Dechezleprêtre et al. (2015), Ambec et al. (2013), Dechezleprêtre et al. (2013)), trade (Artuç et al. (2010), David et al. (2013)), however cross-border spillovers of drug regulation policy has been paid scarce attention with the exception of some studies (Kedron and Bagchi-Sen (2011), Guth and Zhang (2021), Srihari et al. (2009), Horwitz and Polsky (2015)).

Can a law aimed at regulating an expensive drug market influence the decisions concerning firm entry, investment and subsequent choice of a product portfolio for bio-pharmaceutical companies abroad? Many studies have estimated the cross-border effects of environment regulations. In particular, (Jaffe and Palmer (1997), Chakraborty and Chatterjee (2017)) show that environmental regulations induce innovation which ultimately leads to reorientation of production technologies and product portfolios at the firm level (Verdolini and Galeotti (2010), Popp (2002), Gray and Shadbegian (1998), Aghion et al. (2016)). Understanding technological change and how it gets affected by the economic incentives presented by a government regulation is instrumental in designing an appropriate policy, especially more so in the context of drug policy which possess the potential to affect the lives of millions of patients across the globe. If that regulation is carried out by an innovator country, then it may have global repercussions as incentives presented by the regulation might induce response of developing countries who follow innovator countries for new technologies and products. However, to the best of our knowledge no study has attempted to capture the cross-border market response to a new drug regulation introduced in the country leading in drug innovation. Furthermore, there is a prominent gap in documenting and understanding the shifting market structure and associated welfare implications ensuing from the strategic response of a foreign country to the innovator country's policy.

In this study, we focus on the inward cross border spillovers, namely on the reaction of pharmaceutical companies located in the domestic economy to changes of drug regulation abroad. In particular, we analyze the cross-border effects of the passage of Biologics Price Competition and Innovation Act (BPCIA) of 2009 in the United States (US) which created an abbreviated pathway for biosimilar products to promote price competition in the market for biologic drugs. That law created an incentive channel for bio-pharmaceutical companies to grab a share of the lucrative and heretofore highly pro-

tected biologic drug market of US, by investing their resources in order to come up with biosimilar alternatives to biologic drugs. As an unintended consequence, it ended up shifting the market structure of biologic drugs in India. Hailed as the 'pharmacy of the world', Indian pharmaceutical market comprises numerous firms experienced in manufacturing and distributing generic drugs across the globe. That experience and position of Indian pharmaceutical companies coupled with the incentive channel (of regulatory approval from FDA) presented by BPCIA set off a motion in process that lead to domestic companies entering the domestic market with newer and cheaper biosimilar variants of biologic drugs, and as a byproduct it resulted in increased competition in the market of biologic drugs in India.

Biologic drugs are large complex molecules typically produced in genetically modified organisms such as bacteria, and are composed of therapeutic proteins and monoclonal antibodies. They can be extremely effective in curing a variety of diseases ranging from cancer to autoimmune illnesses, however the exorbitant price they command- often exceeding $100,000 per patient per year- can restrict its widespread adoption by many lacking substantial financial resources (Ingrasciotta et al. (2018)). The excessive price that biologic drugs command stems from their unique market environment characterized by the regulations governing competition and market entry, intellectual property claims made by manufacturers, and the insulation from the price competition that biologic drug market enjoys. For instance: each of the top 10 biologics have had a cumulative sales in excess of $40 billion and they had exclusive sellers for an average of 17 years (Frank et al. (2021)). However, US government in the past one decade has been directing efforts to increase the competition in biologic drugs market by promoting more affordable alternatives in the form of biosimilar drugs, and BPCI act could be seen as a culmination of that effort. A biosimilar drug should not possess any meaningful clinical differences from its innovator biologic that serves as a reference product. In fact, a drug is designated to be a biosimilar only when it is deemed to be 'highly similar' to its reference product.

The BPCI act mirrored the Hatch-Waxman Act of 1984 which facilitated the introduction of generic drugs to compete with the small-molecule drugs in order to bring down prices and stimulate competition. That legislation was widely hailed as a success towards attaining the objective of affordable healthcare through reduced spending on prescription drugs. Nason et al. (2020) estimates that brand name drugs which faced competition following the loss of their exclusivity period saw their 75% to 90% of the sale volumes shifted to generic drug producers within first year post loss of exclusivity. While it is somewhat early to infer if BPCIA succeeded in attaining its objectives, however many studies have shown the subdued response in generating a similar price competition in the biologics market of US that followed after the introduction of Hatch-Waxmann Act-1984 (Frank et al. (2021), Matters and Weil (2019), Falit et al. (2015), Blackstone and Joseph (2013)).

By utilizing the aggregate demand data of drugs that comes from All India Organization of Chemists and Druggists (AIOCD), an organization responsible for maintaining database Pharmatrac^{TM}, we test the impact of this plausibly exogenous drug regulation on the shift in the market structure of biologic drugs in India. That allows us to trace out

the spillover effects of a cross-border regulation in terms of how Indian pharmaceutical companies responded by varying their entry/exit decisions, pricing strategy and product portfolio choices related to biologic drugs after the passage of BPCIA law in US.

The central role of Indian pharmaceutical firms in fulfilling the global generic drug demand is crucial to our analysis. Even in US, India acts as a major supplier of generic drugs. A major chunk of the generic drug demand in US has had been met by the Indian pharmaceutical companies- according to some estimates they supply over 40% of the generic drug demand in the US. The experience and capacity formation of Indian pharmaceutical companies that follows from their unique position of global generic drug producer coupled with the incentive channel presented by BPCIA in the form of abbreviated pathway to US and global biologic drugs market might have appealed Indian manufacturers to grab a share of the lucrative drugs market by introducing their own biosimilar variants of highly sought out biologic drugs. With a desire to capture the market share with their own variants of biosimilar products, local companies perhaps invested their resources in developing those drugs, and their subsequent introduction to local market may have lead to a shift in the market structure of biologic drugs in India. Hence, our empirical approach requires an examination of the effect of the market expansion (or diminution) stemming from the regulatory changes (which essentially presented an incentive to Indian manufacturers to enter the biologics market by shortening the regulatory approval pathway) on the prices, sales and variety of products for biologic drugs in India relative to other closely related drugs whose prices, sales, and variety of products should have been invariant to that specific regulatory change.

We start by showing some descriptive evidence linking the cross-border regulatory change and the relative change in prices, sales, and variety of biologic drugs vis-a-vis closely related drugs that form our control group in our sample of Indian pharmaceutical market for the period of 2009-2020. Figure-A1 shows the average monthly sale trends for advanced biologic drugs[1] (which are primarily affected by regulation, therefore our treatment group) and other closely related drugs (our control group). The figure shows that while sale trends did not vary widely before the introduction of BPCI act, the average sale trends for biologic drugs seem to have increased after FDA released detailed guidelines on establishing an abbreviated pathway for biosimilars to gain approval in the US. Clearly, there is a lagged effect of the passage of law and the release of guidelines on the average sale trends. Intuitively, it makes sense because developing a biosimilar drug on average takes 2-5 years. Perhaps, Indian manufacturers initiated their plans to enter the market of biologic drugs and made associated product portfolio choices right after the release of guidelines by FDA, however, the lengthy gestation period to bring a biosimilar variant of a biologic drug to the market lead to a lagged response that we observe through our market sales data of India.

Figure-A2 show average monthly trends for the price of biologic vis-a-vis other drugs in our control group. Even though no clear pattern is emerging from the graph, however, we observe a relative increase in fluctuations in the average price of biologic drugs.

[1] In particular, all the molecules in our sample with the suffix 'MAB' belong to our treatment group because those molecules fall under advanced category of biologic drugs. We discuss it in detail in a later section.

Through a more rigorous analysis, we will later on show that there was a decrease in the average price post the introduction of BPCI act. Figure-A3 and A4 does the same, but for number of firms producing the drugs, and no. of distinct 'stock keeping units' (SKUs) that corresponds to variety of products within a specific molecule market for both biologic and control drugs. Both these figures indicate that new firms entered the market of biologic drugs with new variants of biosimilar drugs. While the lagged response that we observe in new variety of drugs closely follows the explanation cited earlier, the lagged entry of new firms is also explicable from the fact that the AIOCD market sales data captures a new firm only when it starts selling a particular drug, which again would require 2-5 years for a new entrant to develop a biosimilar drug and launch that product in the market- hence, new firms show up in our data with some lag. Lastly, figure-A5 shows that average Herfindahl Hirschman Index (HHI) of the molecules in our treatment category sharply declines in the aftermath of the BPCI act, which coincides with the entry of new firms and products. No similar pattern is visible for the molecules in our control group. That in itself indicates that biologic drug market became more competitive after the introduction of BPCI act, albeit the effect is visible only after a certain lag.

The crucial point in exploiting this particular event for causal inference is that the introduction of BPCI act in US provides a plausible exogenous change in market level dynamics in India, in our case for biologics drug market (representing our treatment group) relative to the drugs belonging to the same group[2] as biologic drugs[3] (representing control group). Using an event-study design framework based on difference-in-difference estimator, we find intriguing results which are remarkably persistent across different specifications. In particular, our main finding is that the BPCI act led to a market shift for biologic drugs in India-which is evident through several economic indicators. The direction of those effects also aligns with the economic intuition. We document increase in sales at the both national and sub-national level (even after accounting for regional fixed effects). We also record that these effects are driven by new firms entering the market of biologic drugs. Even though incumbent firms and new entrants try to differentiate their products by introducing new varieties of SKUs which we document in our results, nevertheless the presence of more firms introducing new variety of products induce more competition as indicated by a decrease in HHI and an overall reduction in price of biologic drugs. The coefficient estimates are robust to different specifications, various controls, and alternating estimation techniques.

We further examine the mechanisms that led to the observed increase in the presence of firms in biologic drug market as well as market expansion effects visible through increase in sales and product varieties. We find that the above effects were prominently

[2]AIOCD data comes with five different set of classification of drugs. The coarsest classification is **Therapy** which is based on the target of therapeutic action of the drug. **Supergroup** is the next category which classifies drugs based on the broader categorization of targets. **Class** forms the next category which includes drugs similar in terms of their mode of action on target. **Group** is next to the last classification which includes drugs that share same mechanism of action based on route of administration. The most narrow classification is **Subgroup** which is based on the Molecules/Active Ingridients/ Compositions.

[3]Note that the BPCI act affected molecules which are specified at the **Subgroup** level, and we are selecting our control group-one level up from the **Group** category. In particular, we select all the residual molecules from all those groups where atleast one drug with suffix 'MAB' or 'ZUMAB' was found.

driven by those biologic molecules whose patent expiration was around the corner. In other words, Indian pharmaceutical companies when faced with the prospect of investing their scarce resources to produce biosimilar variants of complex biologic drugs in the light of BPCI act, chose, first to invest in those drugs whose patent protection was set to expire in the decade leading up to 2020. Intuitively, it makes sense as firms who are seeking to enter a market with highly similar version of the original product would form higher ex-ante profit expectations for those product markets which are set to loose its patent protection. The reason mainly stems from the low entry barriers coupled with the prospect of quick market penetration after the protected drug market is liberalized. In addition, firms possessing biosimilar versions of such biologic drugs can move fast (and therefore gain the first mover advantage in the race of biosimilars) to file for a regulatory approval in US through the BPCI act channel, therefore paving their way to US and subsequently global market-given that US regulatory approval is considered as gold standard throughout world. Therefore, if the market shift happened through the channel of BPCI act, then we should expect to see (at least in the short run) firms producing biosimilar variants of those biologic drugs that were set to loose patent protection, and indeed our results indicate that market expansion in terms of sales, and product variety was driven by the same set of molecules, inducing a price competition and ultimately resulting in reduction of prices and HHI.

In addition, we also find that product markets based on complex technologies are less preferred by new firms for their initial entry. We capture the variation in technology complexity through the heterogeneity among the group of MABs that we have in our sample. Similar to the previous case, we conjecture that provisions in BPCIA would have incentivized firms to first enter in product-markets which employ relatively simpler technology because they require less technical know-how and resources which mean, firms could come up with biosimilar alternatives more quickly and with less uncertainty compared to starting off with more sophisticated products. Again, our results show that indeed the reduction in prices, and increase in firm effects were driven by the least sophisticated molecule-markets in our treatment group, at-least in the short run after the passage of the BPCIA.

We conclude the paper by summarizing the main findings and discussing the implications that our results entail on the role of cross-border regulations in inducing a technical change in a foreign country (Acemoglu (2002), Acemoglu et al. (2012), Acemoglu et al. (2015)). In particular, we find a dramatic shift in the market structure of biologic drugs in India triggered by the strategic response of pharmaceutical companies to the incentive channel presented by the BPCI regulation in US. Therefore, our findings suggest that firms respond to strong incentives, especially in a globalized context when such incentives entail opportunities for a firm to venture into global markets. A regulation encompassing proper incentives may prove to be an effective means for directing the efforts of companies towards attaining the objective of consumer welfare. That is our primary contribution.

This paper is related to different branches of literature. Our main mechanism works through documenting the market shift that resulted from the reaction of firms to a pol-

icy shift in a foreign country. There is a huge literature that examines the role that spatial regulatory differences play in inducing cross-border innovation and technology diffusion: (1) innovation in clean automobile technologies (Hascic et al. (2008), Dechezleprêtre et al. (2015), Beise and Rennings (2005)), (2) relationship between regulatory leaders and laggards (Porter and Van der Linde (1995), Taylor (2004), Eskeland and Harrison (2003), Jänicke and Jacob (2004)), (3) role of knowledge, technological, and regulatory spillovers from frontier country in driving diffusion of technologies in the catching-up countries (Rubashkina et al. (2015), Verdolini and Galeotti (2011), Voigt et al. (2014), Popp et al. (2011)), (4) exploiting regulatory differences for cross-border prescription shopping (Casner and Guerra (1992), McDonald and Carlson (2014), Cepeda et al. (2014), Guth and Zhang (2021)), and (5) technological diffusion induced by policy change abroad further leading to a policy shift and directed technological change in the home country (Acemoglu et al. (2012), Haščič et al. (2010), Vogel and Wagner (2010)), (5) how policy-pioneer country's change in regulation lead to cross border effects (Costantini and Crespi (2008), Costantini and Mazzanti (2012), Costantini et al. (2017), Rexhäuser and Rammer (2014), Herman and Xiang (2020)).

Most of these studies focus on environmental regulation and its effects on the technology innovation and its subsequent diffusion. Our study deviates from this literature and looks at the effect that a foreign drug regulation plays on the product and pricing strategy across a set of firms in the home country and how that leads to a shift in the market structure. To the best of our knowledge this is the first study that focuses on a cross-border drug regulation (which is plausibly exogenous in nature) and investigate the market response in terms of attracting new suppliers who introduce new product varieties. Our paper complements the studies documenting the market response of pharmaceutical industry to domestic regulation (Zweifel and Crivelli (1996), Pavcnik (2002), Arora et al. (2008), Duggan et al. (2016)) and contributes to this literature by adding a new dimension-namely documenting the response of pharmaceutical sector to an incentive channel presented by a regulatory change in a foreign country.

We also add to the debate concerning welfare implications of increased competition resulting from the policy shift favoring entry of generic competition in the market of branded drugs (Caves et al. (1991), Saha et al. (2006), Reiffen and Ward (2005)). The same literature also discusses the role played by favourable policy shift in influencing the entry and exit decisions of generic manufacturers (Hurwitz and Caves (1988), Grabowski and Vernon (1992), Grabowski and Vernon (1995), Frank and Salkever (1997), Berndt et al. (2003), Hudson (2000)), prices (Danzon and Chao (2000a), Danzon and Chao (2000b)), entry costs (Djankov et al. (2002)), and price controls (Danzon et al. (2005), Lanjouw (2005), Kyle (2007)).

Our study contributes to this strand of literature by examining the same relationships for complex biologic molecule markets as they were also recently subjected to the regulatory change that favored the entry of biosimilar producers in order to promote price competition and to increase access to these costly drugs. Even though, our study analyzes the effect of US policy change on the Indian pharmaceutical market and that restricts us to infer the impact of the BPCI act in attaining its objective (that is to analyze how compet-

itive US biologic market became post BPCI act), nevertheless, our study which records the heightened competition in India that resulted from the entry of biosimilar producers, could be seen as a first effort in documenting the estimates of the impact of this policy towards generating competition in a market setting, and to evaluate the incentive channel underlying this act. However, we caution our readers to take our results with a grain of salt-as the nature of institutions and regulatory framework underlying each country can substantially alter its market response, and therefore we refrain from drawing any generalized conclusions from our analysis.

The layout of the paper is as follows. In section two, we briefly discuss the institutional background of the regulation. The details on the data-set that we use is provided in section three along with some first-cut evidence supporting our main findings. In section four, we discuss in detail our empirical strategy and how we deal with the identification problem. Section five presents our baseline findings and we also describe the main mechanism driving our results. Lastly, we conclude by summarizing our findings and end with a brief discussion on the policy implications.

II. Institutional Background

Biologics as per the definition provided by FDA corresponds to drugs derived from biological processes and are used as therapeutic cures to certain diseases like rheumatoid arthritis, neutropenia, multiple sclerosis, diabetes and various types of cancer. The process of creating a biologic drug through biotechnological means has presented enormous opportunities to produce blockbuster drugs customized uniquely to provide treatments for hitherto ignored diseases. In due course perhaps, the underlying technology of biologic drugs can also be used to modify a drug for a specific individual. Therefore, the nature and scope of biologics differ from the conventional pharmacological drugs which targets common conditions, whereas the model for biologics allow for customization and adaptability. For the same reason, they are extremely structurally complex which hinders their mass production and poses many replication challenges. The complex manufacturing processes coupled with the demanding requirements for FDA approval, translates to a very expensive creation process for any biologic drug.

Some studies put the cost estimates for building manufacturing facilities (excluding materials) for a new biologic drug between $200-$400 million (Woollett et al. (2003)). Adding to that, ten to fifteen years that it takes to launch a new biologic drug in the market takes the overall costs to to $1-2 billion (Blackstone and Fuhr Jr (2012), Grabowski et al. (2011)). Among all US industries, bio-pharmaceutical companies are the largest spenders on research and development (R & D)- roughly they spend on average about 30% of their overall revenue (Blackstone and Fuhr Jr (2012)). And the same study estimates that around 75% of the R&D expenditure does not even bear any fruit, as only 5-10% of the drugs entering clinical trials eventually gets approved.

The extremely risky process of coming up with successful biologic drugs disproportionately affect small bio-pharmaceutical companies compared to the multi-billion dollar corporations like Merck, Pfizer, etc. who possess deep pockets to fund their R&D

projects (Martines et al. (2011)).[4] Small biotechnology firms, however, play a vital role in the bio-pharmaceutical industry. Martines et al. (2011) estimates that from 2006 to 2008, small firms were responsible for discovering 50% of all new biologic drugs. In addition, they also developed 56% of the 'orphan drugs'- discovered for the purpose of treating rare diseases. Lacking well-funded coffers coupled with the little appetite for error, turns the process of drug-discovery a lot more riskier for small companies than the established players. Therefore, risk-mitigation prompts business mergers among small bio-pharmaceutical companies, which results in reduced competition by limiting the availability of new variety of a drugs to the consumer (Martines et al. (2011)). To some extent, these factors are responsible for the extremely high prices that biologic drugs command. According to some estimates, tens of thousands of dollars are spent annually on these drugs by patients (Engelberg et al. (2009)).

Modern biotechnology drugs have gained more prominence in US, especially after FDA approved the use of human insulin in 1982 (Johnson (2009)). In future, biologics are expected to grab even a larger share of the US drug market. In 2009, approximately 20% of all the drugs on the market were biologic drugs (Schacht and Thomas (2007)). In 2013, biologic drugs comprised four of the top ten commonly sold drugs in US.[5] However, the exorbitant costs of these drugs prohibit their widespread usage. Take the case of commonly used drug in the US- Humira which is used to treat Crohn's disease-costs on average $51,000 annually per patient (Johnson (2009)). That seems to be a conservative estimate against price reaching six figures for other biologic drugs. Even though, prescription costs are covered (at least to some extent) by insurance, insurers had over time deployed many strategies to pass on the costs of biologics to consumers, which disproportionately affects poor people who upon failing to pay the high prices, loose access to drugs essential for their treatment (Johnson (2009)). This situation prompted US government to find a remedy to the exorbitant prices of biologic drugs.

In 2010, US Congress passed the 'Patient Protection and Affordable Care Act' often referred to as 'Obamacare'. While it contained many provisions to make healthcare more affordable, one of the most important provisions was present in section seven- the Biologic Price Competition and Innovation Act (BPCIA) (Johnson (2009)). The act aimed at overhauling the market of pharmaceutical industry by establishing a pathway for the creation of generic variants of drugs produced through biotechnological means. In addition to specifying the twelve year exclusivity period for the original reference product, it also provides a 12-48 months of exclusivity period for the first interchangeable-biosimilar drug approved. That provision created an incentive channel for bio-pharmaceutical companies to accelerate their efforts to come up with their own variants of biosimilar drugs to leverage the exclusivity period for market penetration. The legislation acted as a means to promote more competition with the end goal of reducing consumer prices for costly biologic drugs.

India is the major producer of generic drugs and currently the largest exporter of

[4]Biotechnology, *Biotechnology Standard & Poor's Industry Surveys*, available at: `http://www.scribd.com/doc/49646708/bio-0211`

[5]See U.S. Pharmaceutical Sales: Q4 2013, DRUGS.COM, `http://www.drugs.com/stats/top100/sales`

generic drugs to countries across the globe.[6] Forty percent of the generic demand in US is fulfilled by Indian pharmaceutical companies[7] Even among biologic drugs, India was the first country to approve a biosimilar in 2000 for hepatitis B, although it happened without any specific guidelines on how to develop and market the biosimilars in India (Rushvi et al. (2016))[8]. A recent report by McKinsey & Company (2020) estimates that India's biotechnology sector is among one of the fastest growing segment with a turnover of $7 bn during the year 2015, and since then it has been growing at a rate of 16.3% annually.

Indian bio-pharmaceutical sector was the leading candidate to benefit from the BPCI act passed in US. There are two main reasons for that: (a) the knowledge accumulation and capacity formation of Indian bio-pharmaceutical industry in domains such as production facilities and human capital formation that accrued from its role as the leading exporters of generic drugs over several decades would have helped Indian companies to adapt to the challenges involved in producing and marketing the biosimilar variants of the biologic drugs. (b) In the post TRIPs regime, the regulatory changes requiring domestic firms to comply with the intellectual property claims made by multinationals for their new drugs, might have pushed domestic companies to realign their research and business strategies. Besides, the experience of Indian manufacturers coupled with the international collaborations are creating ample opportunities for Indian firms to move up the drug discovery chain by participating in drug discovery research. And unlike small chemical molecules, producing a biosimilar variant requires some (although substantially less than what is required for discovering a new biologic) R&D investment and clinical trials, and that sequential learning could help companies tomorrow to usher into their own new innovative programs for drug discovery. Therefore, our hypothesis that BPCI act would have incentivized Indian bio-pharmaceutical firms to leverage their production capabilities and huge experience of producing generic drugs to develop biosimilar drugs, intuitively seems plausible and that forms our motivation to investigate that claim empirically.

Unlike generic drugs, biosimilar alternatives are not identical copies of the biologic drugs and in majority cases FDA does not grant a biosimilar drug the 'interchangeable' status- a measure designated by the Food and Drug Administration (FDA) to indicate the extent of substituability of the drug. In addition, the slight variation in the chemical composition of biosimilar drugs from their reference products leads to hesitancy among physicians to freely substitute them with the biologic drugs (Cohen et al. (2016), Jacobs et al. (2016), Brennan (2018), Zhai et al. (2019), Diependaele et al. (2018)). These frictions coupled with the high entry barriers that bio-pharmaceutical companies face from innovator companies[9] while entering the market of biosimilars has had subdued

[6]See:`https://ispe.org/pharmaceutical-engineering/march-april-2017/growing-influence-pics-asia-pacific`

[7]See: `https://thewire.in/economy/pharmaceutical-drugs-exports-india`

[8]In Europe and US, the first biosimilar was approved in the year 2006 and 2016 respectively.

[9]These entry barriers can come in various forms. The innovator companies try to extend the period of their exclusivity by accumulating patent thickets around their biologic drugs. In addition, they also take aid of courts and tribunals to elongate or block the entry of other bio-similar alternatives. (See: Cottler et al. (2017), Zhai et al. (2019), Franco and

the diffusion of biosimilar drugs and inhibited the BPCIA to imitate the success story enjoyed by the Hatch-Waxman Act, which forms the motivation behind BPCIA. One mechanism driving this result could be that the lower expected returns stemming from the above frictions render the market unattractive for companies seeking to introduce their biosimilar variants to compete with the original biologic drugs (Vokinger et al. (2017), Van de Wiele et al. (2021), Van de Wiele et al. (2021), Matters and Weil (2019), Hwang (2017)). And that lower competition only results in mild reduction in prices of biologic drugs as some studies have documented (Blackstone and Joseph (2013)).

III. Data and Descriptive Analysis

A. Data Description

For this study our main data comes from the database of retails sales concerning pharmaceutical drugs which we obtain from the All India Origin of Chemists and Druggists (henceforth referred as AIOCD data) Pharmatrac^{TM}. This data is collected through a joint effort between The National Pharmacist Trade Union, AIOCD, and a private pharmaceutical research company. It includes drug sales data from more than half a million retailers and/or stockists associated with AIOCD, representing upto 60% of drug sales in India. The data is specified at the stock-keeping unit (SKU)-region-month level and contains information on the manufacturers and their domicile status, quantities sold, price offered to retailers, maximum retail price in addition to the product characteristics information like dosage form (tablets/capsules), their respective strength, etc. The same data has been used in prior academic studies trying to analyze Indian pharmaceutical market in various contexts (Dutta (2011), Bhaskarabhatla and Chatterjee (2017), Adbi et al. (2020), Aggarwal et al. (2020a), Aggarwal et al. (2020b), Bansal et al. (2021)). For our current analysis, our baseline data ranges from April 2009 to June 2020 with monthly data consisting of 107 molecules sold by 302 companies all over India.

Biologic drugs can be broadly divided into three categories- monoclonal antibody (MABs) products, non-MAB products, and vaccines. For our baseline results, our treatment group consists of advanced biologic drugs- i.e. all molecules with the suffix 'MABs'. 'MAB' was introduced as a stem for monoclonal antibodies, and these drugs are made by collecting antibodies from some source which are then distilled down until there are multiple copies of the same antibody. The source is typically mouse, human, or some combination of both. For instance: If the source is completely mouse (human), then the letter 'o' ('u') precedes 'MAB' in the drug name (example-Blinatumomab (Adalimumab)). Similarly, if the source is predominantly human and part non-human, then 'MAB' is preceded by the letters 'zu' (example-Trastuzumab, Bevacizumab, etc.). Since 'MABs' are foreign proteins (even when the source is humans) entering the body, there is a high risk of infusion reactions during administration; however the degree of risk is lowest when the source is fully human (i.e. case of 'umab'), relatively lower when source is predominantly human ('zumab'), and highest when the source is mouse ('omab').

Banacu (2021), Loftus and Roland (2018), Humira (2019), Vokinger et al. (2017))

For our analysis, we work with the entire class of 'MABs' in our sample as our treatment group, and we identify 20 such molecules in our database. In our database, drugs are classified at five different levels based on the European Pharmaceutical Market Research Association (EphMRA) system. EphMRA along with Pharmaceutical Business Intelligence and Research Group (PBIRG), has had developed and maintained anatomical classification of drugs since 1971.[10]. **Subgroup** classification (which is the formulation level) is the narrowest one containing molecule names while coarsest classification-**Therapy** is based on the target of therapeutic action of the drug. For our analysis, we focus on **Group** classification, which lies one step above to **Subgroup** in the classification ladder. A particular group comprises molecules/drugs that share same mechanism of action based on route of administration. Therefore, our control group consists of all the residual molecules from all those groups where at least one drug with suffix 'MAB' was found. Thus, our control group consists of 87 such molecules.

B. Indian biologics market before and after FDA released guidelines

We start our analysis by comparing raw averages of several economic indicators like sales, revenue, price, etc., to understand how BPCIA shaped the biologic segment of Indian pharmaceutical market. Even though, BPCI act was passed in February-2010, bio-pharmaceutical companies did not have a clear idea on what exactly the legislation entailed as the law only defined broader objectives that it aimed to achieve. By transferring powers to FDA, the US Congress passed the responsibility for setting detailed rules and regulations governing biosimilar drugs. Therefore it wasn't until February-2012-when FDA released guidelines on establishing an abbreviated pathway for the approval of biosimilars in US, that market players got to know about the provisions underlying that law which would also include incentive channels if present any.

In panel-a of table-1, we show how the market of biologic drugs performed vis-a-vis drugs in our control group. The numbers in column-1 & 2 corresponds to values averaged over months before and after the FDA guidelines were released- for biologic drugs in our sample, and we run a standard t-test to see if the change in mean values are statistically significant. The numbers indicate that the market of biologics expanded in terms of sales, number of firms operating in the market as well as variety of products, however the monthly average revenue numbers decline. These simple average comparisons also indicate the rise in average prices of biologics drugs in the post BPCIA era. We also witness a significant decline in the average HHI for the market of biologic drugs. Columns (3) & (4) provide analogous numbers for the drugs in our control group.

Next, we show the variation within treatment group to understand the factors driving the effect. For that we construct two subgroups from our treatment group, and the division is performed on the basis of the patent expiry date of molecules. If the drugs' patent protection is set to expire in the decade of 2011-2020, then we classify it as a low patent drug, and if the patent is set to expire in any of the year beyond 2020 then we put it in

[10]EphMRA Anatomical Classification Guidelines,2014.See: `ephmra.org/media/4973/atc-guidelines-2021-final.pdf`

Table 1—: Summary Statistics: Pre and Post 'Release of guidelines by FDA in Feb-2012

	Pre-BPCIA Guidelines	Post-BPCIA Guidelines	Pre-BPCIA Guidelines	Post-BPCI Guidelines
	(1)	(2)	(3)	(4)
Panel A: Across Treatment Variation	Biologic Drugs		Control Drugs	
Revenue (in millions)	0.25	0.19**	0.06	0.077***
Sales in mg (in 000)	0.64	0.83***	2232.3	2297.84
Price (per mg)	994.8	2366.4***	89.2	69.15***
No. of Firms	5.3	12.4***	61.14	93.8***
Variety of products	8.8	27.3***	330.2	446.3***
HHI	0.926	0.863***	0.669	0.672
Panel B: Within Treatment Variation	Low Patent Protection		High Patent Protection	
Revenue (in millions)	0.25	0.21	0	0.086***
Sales in mg (in 000)	0.66	1.0***	0	0.24***
Price (per mg)	994.8	2470.86***	NA	531.3
No. of Firms	5.31	10.86***	0	6.25***
Variety of products	8.77	21.39***	0	9.81***
HHI	0.926	0.833***	NA	0.924

Note: The numbers correspond to values averaged over months for different category of drugs. 'Pre-BPCIA' guidelines period correspond to the April-2009 to Feb-2012 period, and Post BPCI guidelines period correspond to March-2012 to June 2020 period. The sales and revenue variable refers to the average of the same across all regions and companies for a given month. Sales variable, has been transformed to daily dosage format specified in terms of mg, and similarly price of a drug is constructed at the per mg level. 'Low patent' refers to all those drugs in our treatment group whose patent ended in any of the years leading up-till 2020, and conversely 'High Patent' corresponds to drugs whose patent protection would end in any of the years beyond 2020. Notably, we see no firms dealing in high patent biologic drugs in India prior to FDA releasing guidelines, which explains the NAs in the price and HHI row. ***, ** denotes statistical significance at 1%, and 5%, respectively.
Source: AIOCD Pharmatrac (2009-19)

the high-patent protection category. The purpose is to understand whether ex-ante profit expectations of a pharmaceutical company would play any role in shifting the market

structure of a particular segment of the biologic drugs more than the other segment. In panel-b of table-1, we observe that there was almost zero market presence of firms in molecules with high patent protection before 2012, but after that companies seem to be entering the market dealing in those molecules. The table also provides the evidence of the market expansion in both the segments of the drug markets, however the number of firms, and product variety numbers indicate that the firms were more interested in expanding their market presence in molecules with low patent protection.

Two important implications can be drawn from the above findings. First, the BPCIA seemed to have a significant impact on the competitiveness as well as size of the market for biologic drugs but not much of an effect is visible for other closely related drugs in our control group. Second, the mechanism to understand precisely how the effect manifested itself could be found by analyzing the change in market structure of biologic drugs with high vis-a-vis low patent protection. Since the company's ex-ante profit expectations for a product market is closely linked with the entry barriers that it could potentially face, and profit expectations play a big role in the company's entry decisions to a new market. Therefore, the extent to which a particular product is protected (entry barriers) may have a bearing on the entry decisions of potential entrants. Apparently, these inferences are only based on plain averages (without controlling for many observable and unobservable factors), and so, we cannot interpret our results in a causal manner. Therefore, we test our results along with the potential mechanisms using an explicitly causal framework in the next section.

IV. Causal Evidence & Empirical Identification Strategy

In this section, we describe our empirical strategy to capture the effect of the drug regulation-namely BPCIA from US on the Indian pharmaceutical market using a reduced form equation.

A. Empirical Strategy

As described earlier, the passage of BPCIA act in US Congress, and the subsequent release of detailed guidelines by FDA on the approval process concerning biosimilar drugs, incentivized the entry of new firms into biologics drug market. We measure the impact of this regulation using an event-study design around the time window of passage of the law by utilizing the market level monthly sales data from April 2009 to June 2020. Our baseline specifications examines whether timing of the regulation is orthogonal to unobserved factors affecting our outcome variable of interest- by investigating how these outcomes evolved in the months leading to the one in which the guidelines of BPCIA were released by FDA[11]. The impact on various outcome variables at the regional and national level is estimated using the below specifications:

[11] The passage of BPCI act in Feb-2010 was only symbolic, as all the detailed rules and regulation governing biosimilar entry were provided by FDA in March-2012. Therefore, we should expect to see any effects only after March-2012.

(1)

$$y_{mgt} = \alpha_0 + \alpha_m + \alpha_g + \alpha_t + \alpha_g \cdot \alpha_t + \alpha_m \cdot \alpha_g + \sum_{k=-10}^{123} \beta_k \cdot \mathbf{I}\{\text{k months since BPCIA}\}_{mgt} + \varepsilon_{mgt}$$

(2)

$$y_{mt} = \alpha_0 + \alpha_m + \alpha_t + \sum_{k=-10}^{123} \beta_k \cdot \mathbf{I}\{\text{k months since BPCIA}\}_{mt} + \varepsilon_{mt}$$

where y_{mt} corresponds to outcome c $\in$ {Log Sales (log of milligrams sold), Log Price (per mg), HHI, Number of Firms, Variety} for a particular molecule m present in geography g in month t, where subscript mgt corresponds to a sub-national sample, and mt refers to a national sample. $\mathbf{I}\{\text{k months since BPCIA}\}$ is an indicator variable for the number of months before and after the law is passed. The result from this specification indicates whether there are differential trends in the months leading upto the introduction of BPCIA and how any post BPCIA effects evolve over time. Since, our outcome variable c $\in$ { Number of Firms, Variety} belongs to the category of count data, we employ Poisson regressions for these two variables, and for rest of the variables we rely on ordinary least square regressions. Our leading coefficients of interest is β_k which represents the relative change in the growth rate of our treatment group's average outcome variable vis-a-vis control group's average outcome- for example average sales (specified in mg)/ or average price (in mg) in k months before or after the BPCIA was passed.[12] For equation (1) & (2), we cluster our standard errors at the molecule-geography, and molecule level respectively.

We account for molecule (α_m) and time specific heterogeneity (α_t) in the above specification. To account for unobserved heterogeneity stemming from regional-level, we control for geography-level fixed effects (α_g). Different regions in India may strike distinct equilibrium in the same product market, primarily because of historical path dependency, differential economic well-being, variation in healthcare infrastructure changing with region-time, disease prevalence changing with region-time, and other such unobserved reasons. For that, we also employ geography and time paired fixed effects ($\alpha_g \cdot \alpha_t$), and geography and molecule (but time-invariant) fixed effects ($\alpha_m \cdot \alpha_g$)[13].

V. Results

A. *Baseline Findings*

We provide our estimates from Equation-1 & 2 in Figure-1 for both log-sales and log-average price (per mg). In particular, the figure display the evolution of growth rate in

[12] Analogously, the coefficient could also be interpreted as the percentage change in average sales/price of treatment group. For that, we need to exponentiate our coefficients to get precise results. In particular (exp(β)-1)*100 gives us the percentage change in the dependent variable.

[13] Due to the non-linear nature of Poisson regressions, we exclude $\alpha_g \cdot \alpha_t$ and $\alpha_m \cdot \alpha_g$ from the econometric specification due to the amount of time that it takes for the results to converge. However, our results are almost similar even if we include or exclude those effects.

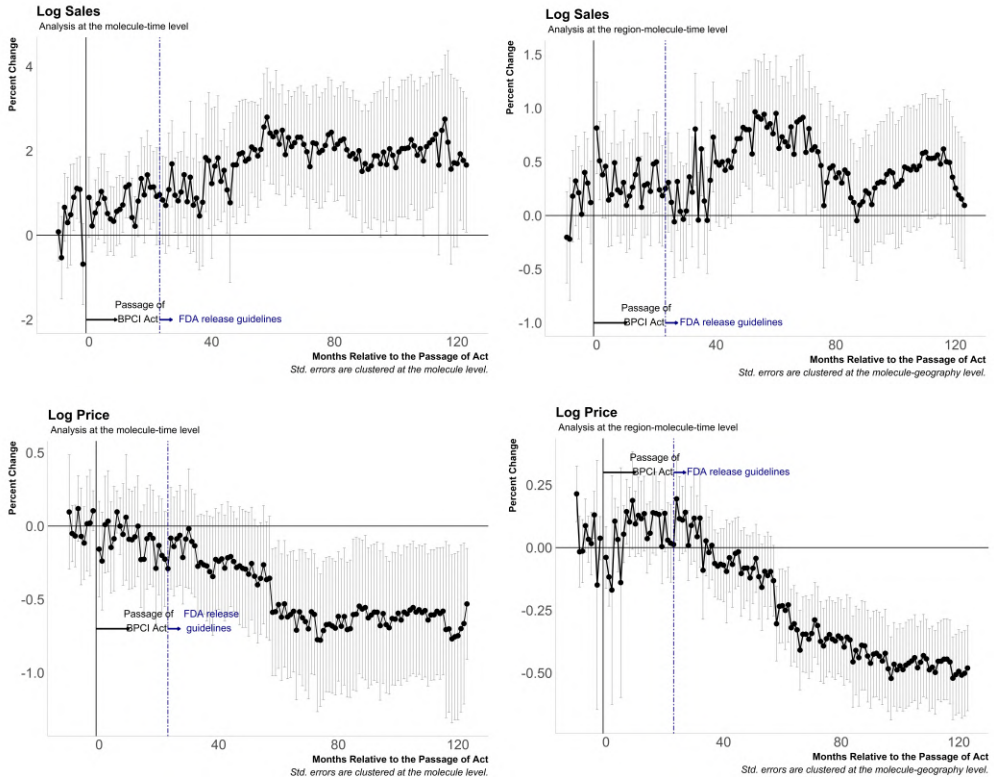
sales and price of monoclonal antibody drugs (relative to control group) before and after the act is passed from an event study version of our baseline specifications at the national and sub-national level. Prior to the introduction of the BPCI act guidelines by FDA (in March-2012), we do not observe any significant departure in the growth rate of sales and average price for treatment and control drugs. And post the passage of the act, we see a lagged response both in terms of sale and price of monoclonal antibodies. As explained earlier, this lagged response could be rationalized by the time FDA took in rolling out detailed guidelines governing the entry of biosimilar products in the US, which forms the basis of the BPCI act. In addition, the process of creating a biosimilar takes on average 2-5 years, and that explains the further lag it took for the sales and price effect to manifest in the aftermath of February-2012 when guidelines were released. We see a significant reduction in average price of biologic drugs after accounting for unobserved heterogeneity stemming from regional variation. In addition, the results from upper panel also indicates that the market of biologics expanded-as measured through increasing sales, albeit the evidence on that front is slightly weak especially after accounting for unobserved regional heterogeneity.

Overall, our national level estimates suggest that on average the sale of a typical molecule in biologic drugs increased by 261% compared to a typical molecule belonging to control drugs in Indian market, after the passage of BPCI act in US. We also record a price reduction of 33% for an average biologic vis-a-vis control drug at the national level. At the sub-national level, the results indicate an additional 20% reduction in average prices for biologic drugs compared to control drugs, and the results are statistically insignificant for the sales after we account for unobserved regional heterogeneity.

Next, we test for the channel through which market of biologic drugs expanded. In other words, we want to understand the factors driving the trend of increasing sales and declining prices. We plot the coefficients β_k with number of firms and variety of products in a particular molecule market as our dependent variable in Figure-2, upper and lower panel respectively. We find a persistent increase in new firms entering the biologic drugs market compared to the drug markets in our control group. The entry of new firms coincides with the expansion of product variety of biologic drugs vis-a-vis control drugs. Both of these empirical facts are clearly visible from the upper and lower panel of Figure-2, and are robust to the inclusion of unobserved regional heterogeneity. In particular, as per our national estimates, the number of new firms that entered in any average monoclonal antibody molecule was 63 percent greater than those that entered in any typical molecule in our control drugs. This estimate becomes more conservative once we include geography fixed effects as in our sub-national specification, the estimate shows a 25 percent increase in number of firms in biologic drug market compared to control drugs. We find a similar effect in terms of product variety. After the passage of BPCIA the number of unique SKUs that got sold in an average monoclonal antibody molecule was 83.6% and 21.3% greater than those that got sold in an average molecule in control drugs, at the national and sub-national level specification respectively.

The above estimates show that the sales and price effect was manifesting itself through an expansion in the market of biologic drugs. Perhaps, the passage of BPCIA attracted

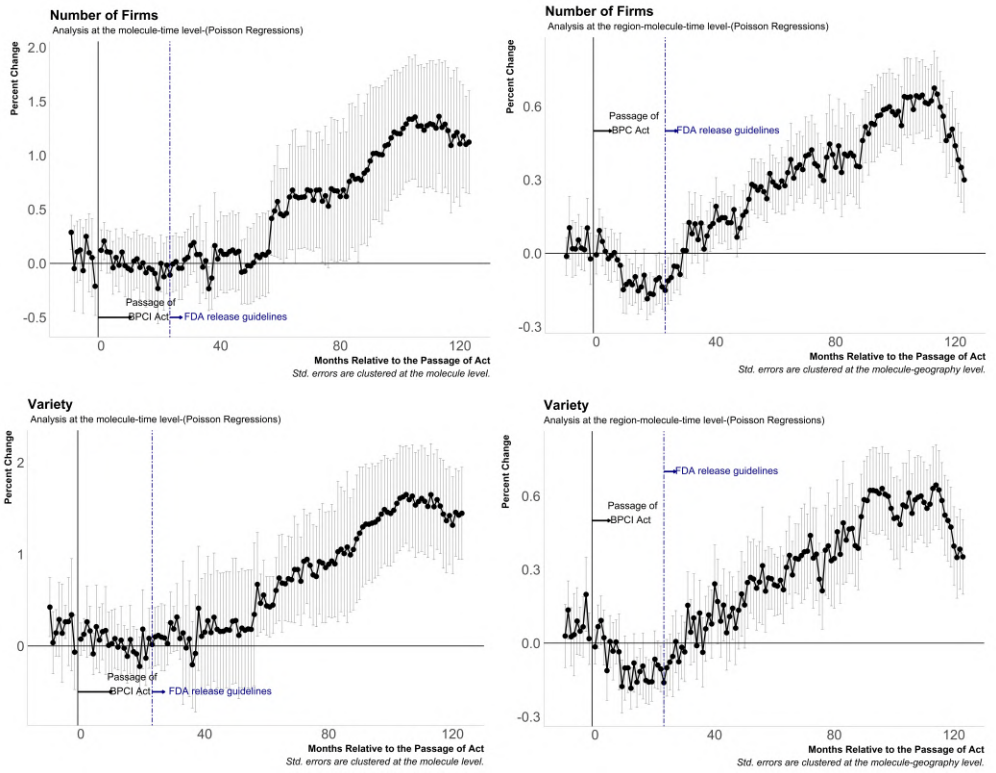
Figure 1. : Event-study (E.S.) estimates at the national and sub-national level for the log of sales and log of average price (per mg) before and after the BPCIA in March 2010



Note: The black line represents the estimated coefficients for the indicator variable corresponding to the number of months before and after the BPCI act was passed in March, 2010. The upper and lower panel corresponds to the log-sales (in mg dosage), and log average price (per mg) as our outcome variables respectively. The results in the left (right) panel are derived from the econometric specification at national (sub-national) level as specified in equation-2 (equation-1).Sample comprises 107 molecules & 2200 SKUs. Out of 107 molecules, 20 of them constitute our treatment group, and rest form our control group. The error bar represent the 95 percent confidence intervals with standard errors clustered at the molecule and molecule-geography level for results at national and sub-national levels respectively. Time period of sample used in this figure goes from April-2009 to June-2020.
Source: AIOCD Pharmatrac

new firms in the biologic drug market, and those firms introduced multiple variants of biosimilar substitutes of original biologic drugs which ultimately lead to price competition among firms. That perhaps, led to the gradual reduction in prices that we observe in the lower panel of Figure-1. We further document the welfare implications associated with the changing market conditions following the BPCI act. In Figure-3, we plot the coefficients from our specification with HHI as our outcome variable. The upper panel shows a gradual decline in HHI both at the national and sub-national level which resembles that market of biologic drugs became more competitive compared to the market of

Figure 2. : Event-study (E.S.) estimates at the national and sub-national level for the number of firms and variety of products before and after the BPCIA in March 2010

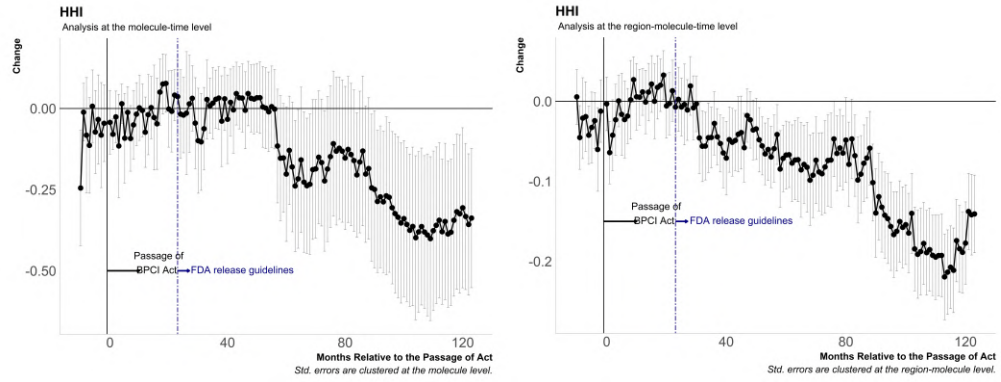


Note: The black line represents the estimated coefficients for the indicator variable corresponding to the number of months before and after the BPCI act was passed in March, 2010. The upper and lower panel corresponds to the number of firms and variety of SKUs as our outcome variables respectively. The results in the left (right) panel are derived from poisson regressions using the econometric specification at national (sub-national) level as specified in equation-2 (equation-1). Sample comprises 107 molecules, 302 companies & 2200 SKUs. Out of 107 molecules, 20 of them constitute our treatment group, and rest form our control group. The error bar represent the 95 percent confidence intervals with standard errors clustered at the molecule and molecule-geography level for results at national and sub-national levels respectively. Time period of sample used in this figure goes from April-2009 to June-2020.
Source: AIOCD Pharmatrac

control drugs.

The above estimates document that the structure of the Indian biologic drug market shifted in the period after the passage of the BPCI act. However, several other factors could have been responsible for driving this market shift. In order to be certain that the incentives present in the BPCI act were responsible (at least to a certain degree) for the changes that we observe, we need to address exactly how the market of biologic drugs shifted in Indian context. And then inquire if those changes would have transpired in exactly the same way in the absence of BPCI act. We address these questions in the

Figure 3. : Event-study (E.S.) estimates at the national and sub-national level for the number of firms and variety of products before and after the BPCIA in March 2010



Note: The black line represents the estimated coefficients for the indicator variable corresponding to the number of months before and after the BPCI act was passed in March, 2010.Here the results correspond to the HHI as our outcome variables. The results in the left (right) panel are derived from poisson regressions using the econometric specification at national (sub-national) level as specified in equation-2 (equation-1). Sample comprises 107 molecules, 302 companies & 2200 SKUs. Out of 107 molecules, 20 of them constitute our treatment group, and rest form our control group. The error bar represent the 95 percent confidence intervals with standard errors clustered at the molecule and molecule-geography level for results at national and sub-national levels respectively. Time period of sample used in this figure goes from April-2009 to June-2020.
Source: AIOCD Pharmatrac

following section.

B. Tracing out the mechanism: Biosimilar diffusion through product market attributes

We now explore mechanisms that could explain how BPCIA led to a shift in the market structure of Indian biologic drug market as documented in the previous section. By examining how problems are formulated at the firm level and analyzing what factors they take into consideration while preparing their strategic response to any new policy, could shed light on our understanding of the process of technological change and/or product diffusion at a more disaggregate level- in our case at the market level. We start by looking at the factors affecting entry decision of firms to any new product market.

B.1. Entry barriers in the form of patent protection

The crucial point that forms the basis of our argument is that firms take into account the entry barriers they face while deciding their entry into a new product market. Product features as well as its market structure can determine the kind of entry barriers that new entrants face. In the context of this paper, we want to test if entry barriers influenced the firm's entry decision. In addition, we also examine if firms took those factors into account while deciding which particular segment of the biologic drug market they should enter. We exploit the time horizon of the patent expiration date of the monoclonal antibodies

in our sample to investigate the effect of BPCIA in Indian market. Our conjecture is that the incentive channel presented by BPCIA would have incentivized the entry of bio-pharmaceutical companies into the entire market of biologic drugs, however some sub-markets would have been more appealing to firms in the light of new regulation. In particular, pharmaceutical companies would have preferred to divert limited resources at their disposal to produce biosimilar versions of those drugs whose patent protection was set to expire sooner rather than later. The BPCIA approves biosimilar versions of only those biologic drugs whose patent protection has ended. Furthermore, provisions in BPCIA also provides an exclusive period (of 12-48 months) for the first biosimilar version of an off-patent biologic drug. That exclusive period help firms to penetrate the market hitherto controlled by a monopolist. Therefore, any new entrant's utility over the set of biologic molecules would be decreasing in the duration of patent protection that a molecule still holds. And if our conjecture holds, then the majority of the effects presented in the previous section should be driven by the low-patent duration molecule among biologic drugs.

To test our mechanism, we divide the set of our monoclonal antibody drugs (MABs) in the following manner. All those MABs whose patent protection is due to expire in the time period 2010-2020, goes into the 'Low-Patent' category, and for MABs whose patent protection expires after 2020, goes into the 'High-Patent' category[14]. That classification allows us to evaluate if the main source of market shift in biologic drugs market could be traced through the channel of entry barriers of molecule markets, when BPCIA came into effect. To do that, we split our overall sample into 'High-Patent-MABs', and 'Low-Patent -MABs' and their respective control group, and then conduct a similar econometric analysis using equation-1 & 2 at the sub-national and national level respectively.

B.2. Biosimilar adoption by product technology complexity

Even in the absence of any substantial entry barriers, there can be other factors that bio-pharmaceutical firms take into account while deciding their entry strategy into a particular molecule market. As explained earlier, innovating an original biologic molecule require huge sums of investment and time. Not only that, even coming up with a viable version of biosimilar alternative to a biologic drug require tremendous resources and huge investment compared to what is required for producing a generic variant of small molecule drug (refer to section-2 for a more detailed discussion). If the manufacturing process of a particular MAB is exceedingly complex, then perhaps new entrants might not have sufficient resources or technical know-how to reverse-engineer and produce biosimilar alternatives of such drugs. Therefore, firms may have a preference ordering over different biologic drugs based on their underlying technology. And as we discuss

[14]Please refer to column-(1) & column-(2) of Table-1 for the classification of the MABs into these two categories. Notably, all the molecules falling under the 'High-Patent' category had no market presence in Indian drug market before the passage of BPCIA. They all came into existence after 2012. We also provide the year when all of those molecules started selling in Indian market column-(3). Also, for the purpose of our analysis, we take the minimum of the patent expiry date in US and European markets as our threshold to classify the molecules into low and high patent categories.

below, there is substantial amount of heterogeneity within the broader class of MABs in terms of complexity of the manufacturing process required to produce different drugs.

While the hybridoma technology that generated hybrid cells secreting rodent-derived monoclonal antibodies, revolutionized the use of antibodies in therapeutic illnesses-like chronic diseases in need of long-term treatments, however, one limitation of such approach was the murine nature of MABs, which induced adverse reactions and the immunogenecity response- known as human anti-mouse antibodies (HAMA) (Hwang and Foote (2005)). Subsequently, MABs technology evolved with an aim to enhance their safety and efficacy, reduce their immunologic potential, so that this antibody technology could be used for long-run therapeutic cures. In order to do that, techniques were developed to modify the rodent antibodies to closely resemble the structures of human antibodies without giving up on their binding properties to the target. The gradual accumulation of knowledge, and technological advancements in the field of molecular biology led to the emergence of recombinant DNA technology which allowed for the use of antibody engineering technologies to produce recombinant antibodies (Almagro and Fransson (2008)). That in turn led to the advent of several technological breakthroughs- each of them inching closer to producing a fully humanized MAB.

First of this humanization approach led to the generation of chimeric antibodies based on the principle of combining the sequences of murine variable domains with human constant domain region (Morrison et al. (1984)). This technology reduced the immunogenicity while retaining the powerful properties of MABs, however, human anti-chimeric antibody (HACA) was found among 40% of the patients using this class of drugs- a side effect closely related to HAMA found among the patients using the first generation MABs (Hwang and Foote (2005)). The next big innovation was the production of humanized antibodies by complimentary-determining regions (CDR) grafting technique, and it proved to be a major breakthrough as it increased the approval of therapeutic MABs (Jones et al. (1986)). It led to a significant reduction in immunogenicity responses- as only 9% of the patients who used these drugs were detected with the presence of human anti-humanized antibodies (HAHA). While both chimeric and humanized MABs are composed of part human and part non-human antibodies, the former carried a larger stretch of non-human proteins compared to former, and that was the main reason behind the success of humanized MABs, since larger stretch of non-human proteins considerably increases the risk of immunogenicity. Despite the fact that humanized MABs were more complicated than their predecessor-in terms of structural complexity involved in manufacturing processes, nevertheless, they became the gold-standard for therapeutic MABs, and therefore are considered an upgrade to the chimeric MABs. Following the success-story of the humanized MABs, scientific community began their pursuit of new technologies to obtain fully human MABs, in order to eliminate any stretch of antibodies of foreign species present in the MAB, which would eliminate the danger of immunogenicity, and make MABs extremely safe and effective option for therapeutic cures, especially for chronic diseases that requires long treatments. And, in the past decade they have succeeded in discovering that technology which sources all of the required antibodies from humans, and are called human MABs. Although, extremely efficient and

safe in terms of immunogenicity risks, the technology underlying such molecules is very complex, which is the main reason for the low number of human MABs in the market.

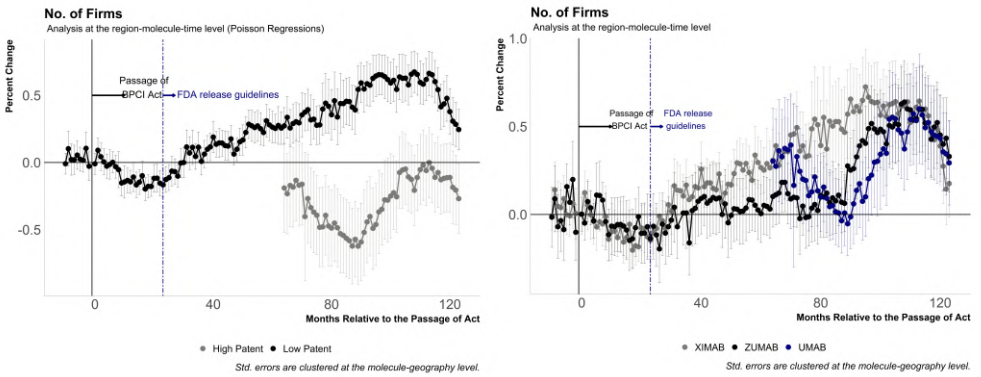
Our conjecture is that the incentive provisions laid in the BPCIA coupled with the heterogeneity in the technological complexity underlying different type of MABs would have induced bio-pharmaceutical firms to first produce biosimilar versions of those MABs which demand less resources and technical know-how. Even after devoting substantial resources and time, the uncertainty behind replicating a complicated technology in the first-go might have made the prospect of immediately entering the market of advanced MABs unappealing to many bio-pharmaceutical companies. Besides, in the light of the key provision of BPCIA, which provides an exclusive period to the first biosimilar approved of any biologic drug, the assumption that firms would prefer to enter and produce an identical copy of a drug which is less complicated to replicate, seems plausible.

As described in the data description section, our treatment group could be further divided into sub-classes depending on the letter preceding the suffix 'MAB' in their name. That letter, essentially signifies the source of the antibody present in the molecule. In our data, we do not observe any first generation MABs- molecules whose antibody is sourced entirely from a mouse(for such molecules letter 'o' precedes the suffix 'MAB'). However, our treatment group possess chimeric, humanized and human monoclonal antibody molecules, with letter 'xi', 'zu', and 'u' preceding the suffix MAB in their names respectively. In terms of complexity, the technology underlying chimeric MABs is relatively simpler than humanized MABs, and the latter's technology is relatively simpler than what underlies human MABs. Therefore, to test our mechanism, we divide the molecules in our treatment group based on their underlying technology- as discussed above along with their respective control group, and conduct a similar econometric analysis using equation-1 & 2 at the sub-national and national level respectively.

Now, we present our findings for the mechanisms discussed above. In figure-4, we show how the entry of new firms evolved in biologic drug market before and after BPCIA came into effect, and we split the effects by the patent expiration date, and type of MABs, in left and right panel respectively. Before describing our results, we want to mention one important point. As shown in column-(2) of table-1, the molecules in our treatment group were launched in Indian market over different years. And given that, we want to understand how BPCIA affected different segments of biologic drug market, we divided our treatment group further into sub-classes to estimate the differential impact. Therefore, it is possible that some sub-groups may not have existed in Indian market before BPCIA came into effect, and we may lack the pre-treatment data for the molecules belonging to those sub-groups.

The left panel of figure-4 clearly shows that the entry of new firms were directed towards those molecule markets whose patent protection was going to expire in the period of 2010-20 rather than later. In fact, the molecules belonging to the high-patent category did not have any market presence in India before BPCIA came into effect, and they only started emerging in the later half of the 2010-20 period. If we do a breakdown of the estimates by complexity of the technology underlying MABs, then the right-panel of the same figure indicates that most of the new firms entered the market of chimeric

Figure 4. : Event-study (E.S.) estimates at the sub-national level for the number of firms before and after the BPCIA by the patent status and product complexity of molecules

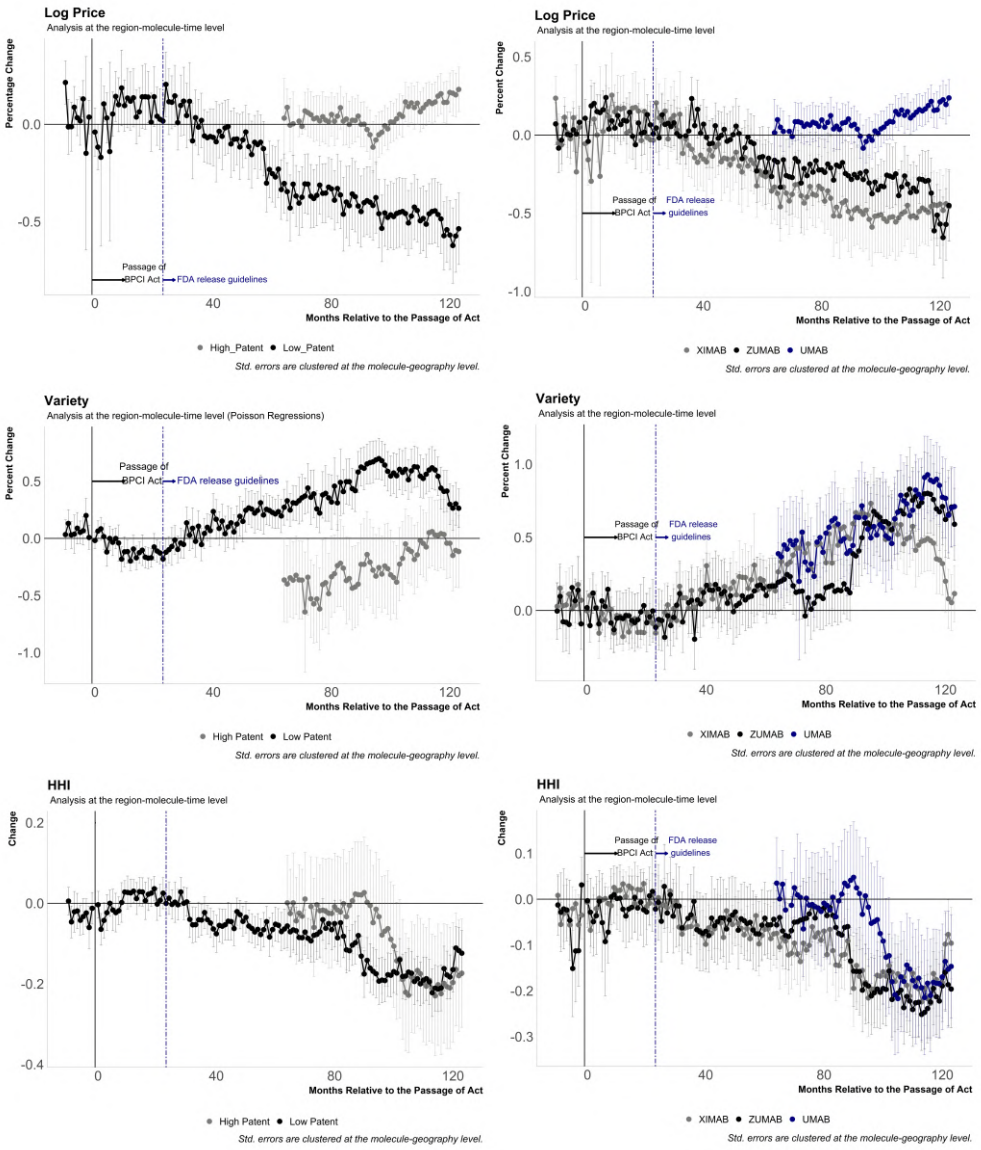


Note: In the left panel, black and gray line represents the estimated coefficients for the indicator variable corresponding to the number of months before and after the BPCI act was passed in March-2010, for number of firms in case of monoclonal antibody molecules with 'low' and 'high' patent protection respectively. In the right panel, black, gray, and blue line represents the similar estimated coefficients for the same outcome variable in case of monoclonal antibody molecules belonging to 'XIMAB', 'ZUMAB' and 'UMAB' category respectively, where we use this categorization as a proxy to the complexity of the molecule's underlying technology, increasing in that particular order. The results in the both left and right panels are derived by running the Poisson regressions using the econometric specification specified in equation-2. The error bar represent the 95 percent confidence intervals with standard errors clustered at the molecule-geography level. Time period of sample used in this figure goes from April-2009 to June-2020.
Source: AIOCD Pharmatrac

MABs-the least sophisticated technology among different type of MABs that we have in our sample. And the figure also shows, that rate of firm entry started to converge among the three type of MABs after approximately eight years of the passage of BPCIA act. To some extent, these results confirms with our initial hypothesis - that with time firms would have gained the required technical know-how to operate in the market of more sophisticated MABs, however their initial reaction to the incentives presented by the BPCIA, would have induced them to enter in the market of least technologically sophisticated molecules. Note that these estimates are provided at the sub-national level after accounting for unobserved heterogeneity stemming from regional variation, and therefore they are the most conservative estimates among our specifications (for the same results at national level- refer to figure-A6 in the appendix).

In the left panel-(a) of figure-5, we show a similar breakdown of the price effects within our treatment group by patent protection. The left panel shows that the price reduction was mostly concentrated among the set of molecules with low patent protection. It presents a consistent picture when we combine this result with our earlier result on the firm entry because, when more number of firms have to compete against each other to gain market share, they normally resort to price competition to attract more customers,

Figure 5. : Event-study (E.S.) estimates at the sub-national level for the number of firms and variety of SKUs before and after the BPCIA in March 2010 by the patent status and competitiveness of molecule market



Note: In the left panel, black and gray line represents the estimated coefficients for the indicator variable corresponding to the number of months before and after the BPCI act was passed in March, 2010 for log average price (per mg) (panel-a), variety of SKUs (panel-b), and HHI (panel-c) in case of monoclonal antibody molecules with low and high patent protection respectively. In the right panel, black, gray, and blue line represents the similar estimated coefficients for same outcome variables in case of monoclonal antibody molecules belonging to 'XIMAB', 'ZUMAB' and 'UMAB' category respectively, where we use this categorization as a proxy to the complexity of the molecule's underlying technology, increasing in that particular order. The results in the both left and right panels are derived by running the simple OLS (in case of Log price and HHI) and Poisson regressions (in case of Variety) using the econometric specification specified in equation-2. The error bar represent the 95 percent confidence intervals with standard errors clustered at the molecule-geography level. Time period of sample used in this figure goes from April-2009 to June-2020.
Source: AIOCD Pharmatrac

especially when their products do not vary too much[15]. We also see that variety (left panel-b) and HHI (left panel-c) effects were also driven by the set of molecules with low patent protection, albeit we observe some reduction in HHI over time for high-patent group of molecules also.

Lastly, we see a similar story unfolding if we decompose our treatment group based on the complexity of the technology underlying each molecule. As shown in the right panel-(a) of figure-5, most of the price effects were driven by the molecules in the chimeric MABs, followed by humanized MABs, and we do not observe any price reduction in the human MABs-molecules powered by the most sophisticated technology among all MAB types. Right panel-(b) and (c) of the same figure presents the results for outcome variables-variety and HHI respectively, with findings more or less consistent with our initial hypothesis.[16]

Summary of results & Conclusion

In this paper, we analyze the cross-border effects of a new pharmaceutical regulation by an innovator country. We evaluate this question by exploiting an exogenous event of the passage of BPCI Act in the United States Congress, in March, 2010, which aimed to contain the soaring prices of biologic drugs by providing various incentives to bio-pharmaceutical companies to produce generic variants (or biosimilar versions) of the original biologic drugs. And in doing so, we document the shifting market structure of biologic drugs in India.

The BPCI act essentially created an abbreviated pathway for bio-pharmaceutical companies to get an approval for their biosimilar versions of biologic drugs in order to market their drugs in US. The main aim of the act was to inject competition in the market of biologic drugs to bring down their prices in US. That act was broadly based on its predecessor, Hatch-Waxman Act of 1984, that created a similar incentive structure to so-called 'small-molecule' products and was widely hailed as success towards its objective of bringing down prices. Some of the main provisions underlying BPCI act to incentivize generic-firm entry into the market of biologic drugs were to reduce the regulatory and pecuniary burden of market entry, a 12-48 months of exclusivity period for the first interchangeable biosimilar approved, etc. The past experience of Indian pharmaceutical industry as a dominant generic exporter to rest of the world made Indian pharmaceutical companies a leading contenders to benefit from the BPCI act. Getting an approval from US's drug regulatory body not only opens up the US market, but also the global market given that FDA's approval is considered a gold standard across globe. And therefore, Indian bio-pharmaceutical firms ventured into the area of biologic drugs, perhaps with an objective to go global through FDAs approval by utilizing the pathway laid out by BPCIA. Although, we do not observe the global sales of biologic drugs of Indian companies, our AIOCD database allows us the capture the market dynamics unfolding in

[15]As we discussed earlier, there is not much room for biosimilars to vary from the original version of biologic drug if they want to get an approval from the drug regulatory body.

[16]All these results are at sub-national level, and our results are consistent at national level also. For analogous results at the national level please refer to figure-A6 in the appendix.

Indian market.

In particular, our baseline models utilize an event study design based on a difference-in-difference estimator to test if the passage of BPCIA , and subsequent release of detailed guidelines by FDA had an impact on the market structure of biologic drugs in India. Our novel data captures time varying information on sales, price, and other market variables at the firm-molecule-geography level in the Indian private retail market for pharmaceuticals. Our treatment group include all the monoclonal antibodies, since they belong to an advance category of biologic drugs. We analyze changes in market sales, price, number of firms, variety of product, and hhi in our treatment group compared to the drugs in our control group, which are closely related to treatment drugs as encoded in our data.

Broadly speaking, we attempt to answer two fundamental questions through our study. First, how does our study contribute to our understanding of the cross-border effects of drug regulation. Second, what are the potential channels through which this market shift happened in Indian context. We contribute to the first question through our baseline empirical evidence. Controlling for various sources of unobserved heterogeneity, we show that that the Indian market of biologic drugs became more competitive, with more number of firms entering the market resulting in variety expansion with a certain lag after FDA released detailed rules and regulation governing biosimilar drugs in March-2012, compared to our control group. We also show that there was a marked increase in sales, and reduction in average prices, mainly resulting from the increased competition in the biologic drug market. These results contribute to the growing literature that examines cross-border effects of regulations in multiple domains like banking, environment, etc. (Hills et al. (2018), Franch et al. (2021), Fidrmuc and Hainz (2013), Dechezleprêtre et al. (2015), Ambec et al. (2013), Dechezleprêtre et al. (2013), Artuç et al. (2010), David et al. (2013)). There are very few studies that examine this particular question in the the context of health regulation and its spatial spillovers (Kedron and Bagchi-Sen (2011), Guth and Zhang (2021), Srihari et al. (2009), Horwitz and Polsky (2015)), however there are very limited studies which specifically investigate that question in case of a drug regulation. To the best of our knowledge, our study is the first attempt to capture the cross-border effects of a drug regulation and examine the market response of pharmaceutical industry located in a foreign country, and therefore could be seen as a first step towards filling this gap in the literature.

Secondly, there is a vast amount of literature that discusses the microeconomic as well as macroeconomic influences on the firms entry and exit decisions (Siegfried and Evans (1994),Ilmakunnas and Topi (1999), Shapiro and Khemani (1987), Mata (1996), Johnson and Parker (1994), Geroski (1995)) including factors influencing the entry and exit decisions of generic manufacturers (Hurwitz and Caves (1988), Grabowski and Vernon (1992), Grabowski and Vernon (1995), Frank and Salkever (1997), Berndt et al. (2003), Hudson (2000)). Our study contributes to this branch of literature by examining the role played by a favorable policy shift on the entry-exit decisions made by bio-pharmaceutical firms based on the (1) entry barriers in the form of patent protection periods (Cockburn and MacGarvie (2011), Von Graevenitz et al. (2013)); (2) the complexity of the technol-

ogy underlying the product (Hall et al. (2021)) . As we showed, firms who responded to the incentives of the new policy, on average went on to enter product markets with low patent protection. Moreover, when they have a choice to enter a product market with an underlying complex and novel technology vis-a-vis a relatively simpler one which is in existence for a long duration, they tend to choose the latter option, perhaps to minimize the element of risk and uncertainty that exist in succeeding with new technologies, which is at odds with other studies who document opposite findings (Hall et al. (2021)).

From the perspective of policy, our study highlights the role that strong incentives play in bringing forth a desirable change, that otherwise could prove very costly if mandated through price controls. The BPCIA regulation was meant to promote competition and bring down prices in the biologic drug market in U.S. Since, our focus of study is Indian market, we cannot comment whether the policy succeeded in creating a competitive environment in U.S.; however as we document through our study that it played some role in increasing competition which subsequently brought down prices of biologic drugs in India. While our study highlights the role that a good policy comprising strong incentives can play in eliciting a desirable response, we acknowledge that our study does not capture the general equilibrium effects of such a policy shift (For instance: whether this policy shifted the focus and resources of firms from some other drug innovation program to producing biosimilar drugs), therefore our study should be at best seen as conducted in a partial equilibrium setup. Clearly, therefore much more remains to be done.

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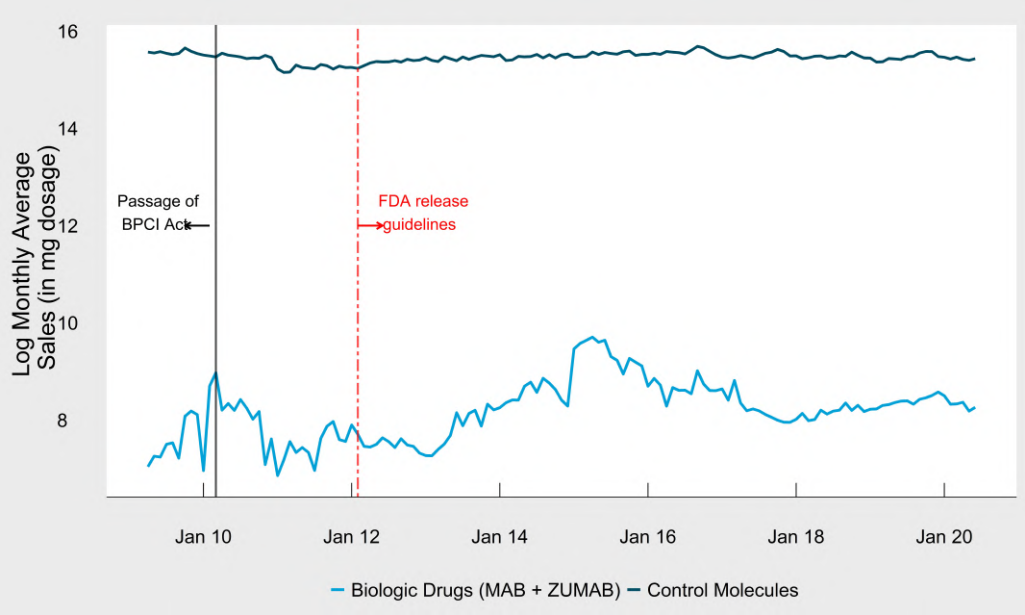
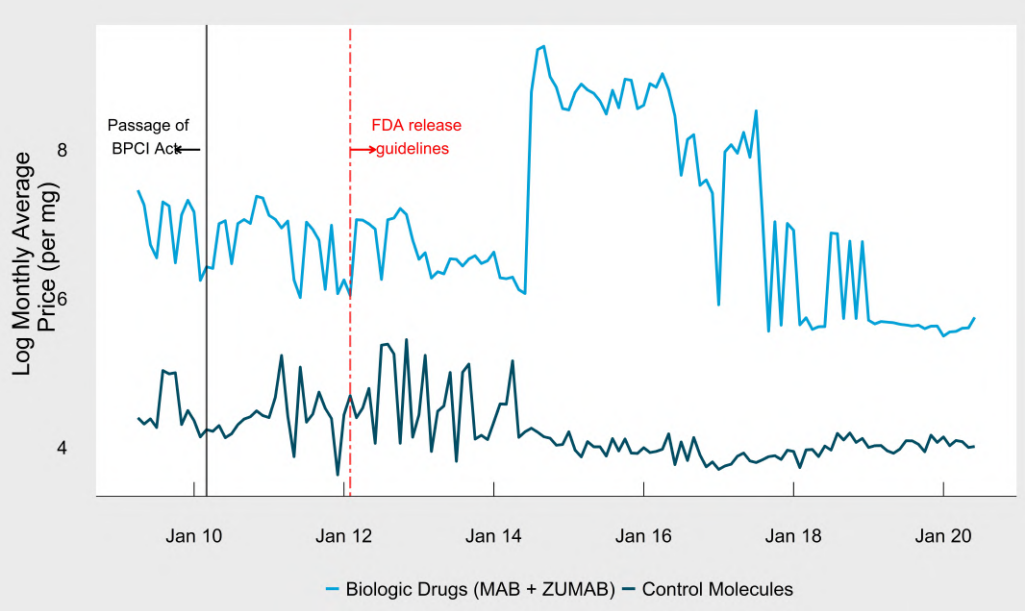
APPENDIX

Figure A1. : Average Sales-Biologic and Other Related Drugs



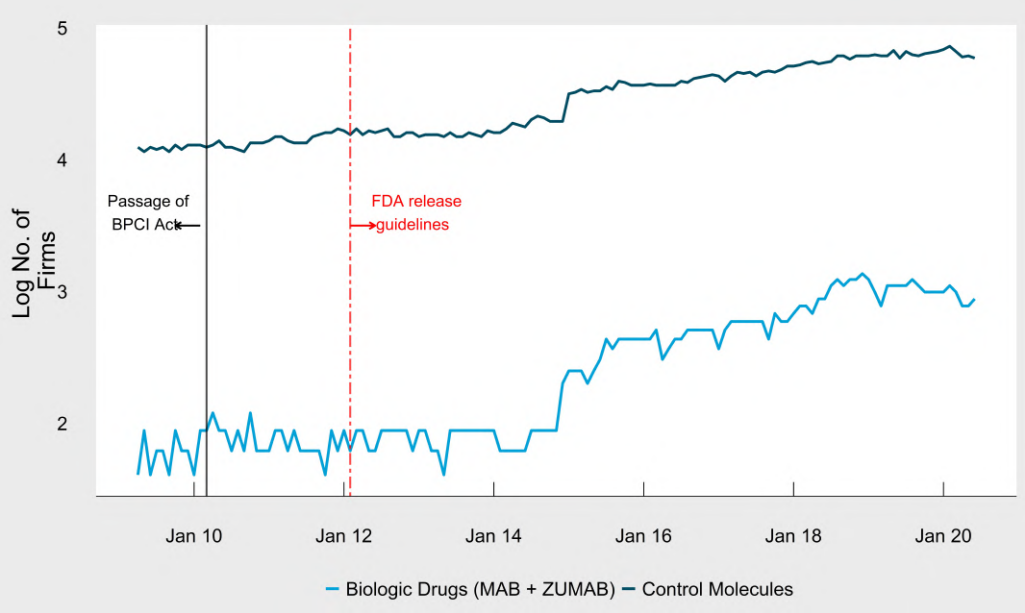
Note: This figure show the monthly national averages of sales for advanced biologic drugs-MABs and ZUMABs which belong to our treatment group vis-a-vis their control drugs for a cumulative time period of April 2009 to June-2020. Sales variable, has been transformed to daily dosage format specified in terms of mg. The two vertical lines refer to regulatory interventions in the US. Black vertical line corresponds to the passage of BPCI Act in the US in March-2012. Red dotted line refers to Feb-2012 when FDA released guidelines on establishing an abbreviated pathway for biosimilars to gain approval in US.
Source: AIOCD Pharmatrac

Figure A2. : Average Price-Biologic and Other Related Drugs



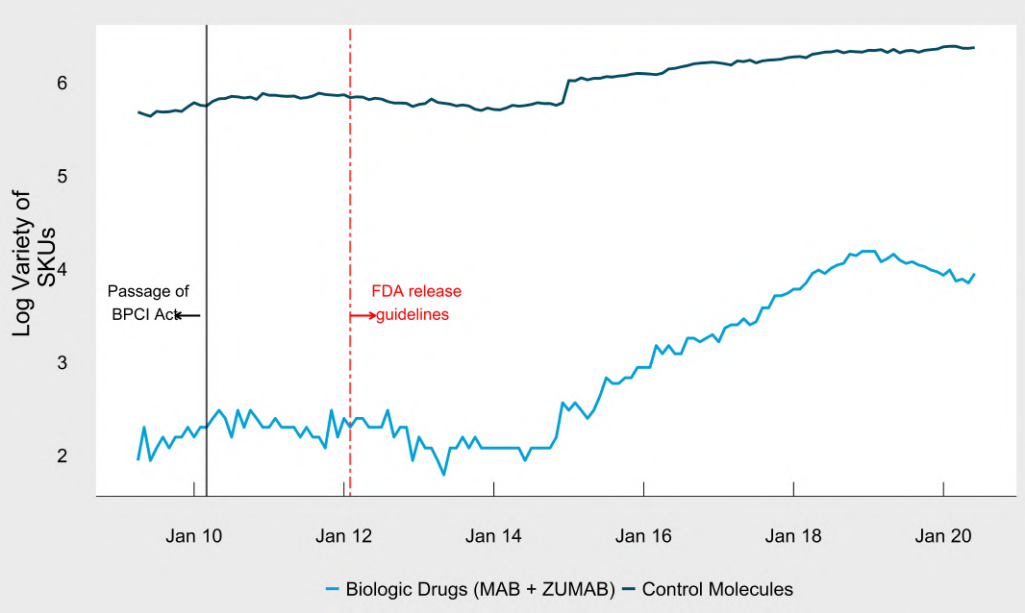
Note: This figure show the monthly national averages of price (per mg) for advanced biologic drugs-MABs and ZUMABs which belong to our treatment group vis-a-vis their control drugs for a cumulative time period of April 2009 to June-2020. Price variable, has been transformed to specify it in terms of per mg dosage format. The two vertical lines refer to regulatory interventions in the US. Black vertical line corresponds to the passage of BPCI Act in the US in March-2012. Red dotted line refers to Feb-2012 when FDA released guidelines on establishing an abbreviated pathway for biosimilars to gain approval in US.
Source: AIOCD Pharmatrac

Figure A3. : Number of Firms-Biologic and Other Related Drugs



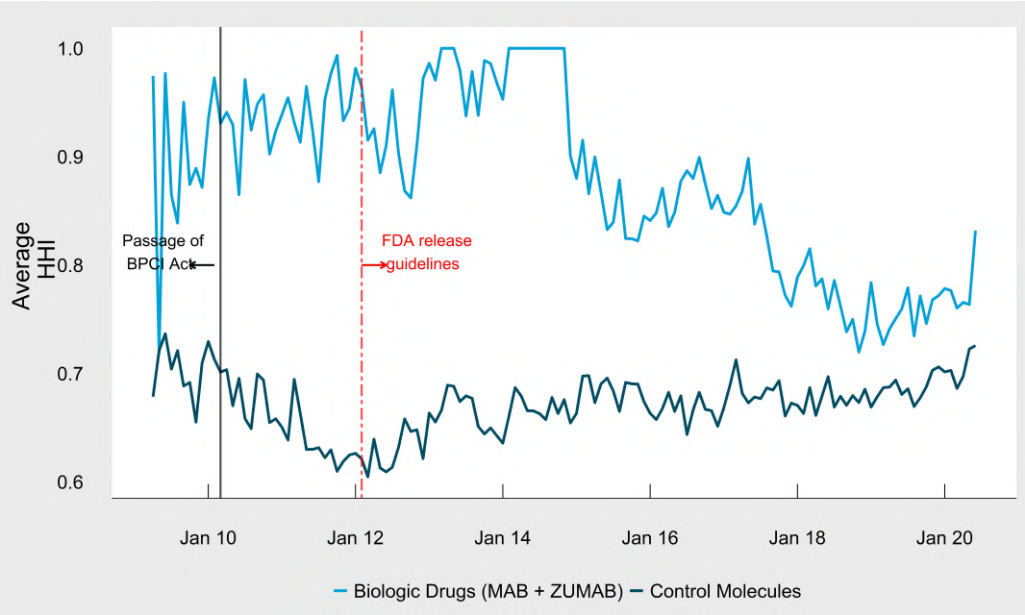
Note: This figure show the number of firms operating in advanced biologic drugs-MABs and ZUMABs which belong to our treatment group vis-a-vis their control drugs for a cumulative time period of April 2009 to June-2020. Number of companies refer to the total companies in a particular month involved in the sales of a certain molecule. The two vertical lines refer to regulatory interventions in the US. Black vertical line corresponds to the passage of BPCI Act in the US in March-2012. Red dotted line refers to Feb-2012 when FDA released guidelines on establishing an abbreviated pathway for biosimilars to gain approval in US.
Source: AIOCD Pharmatrac

Figure A4. : Variety of SKUs-Biologic and Other Related Drugs



Note: This figure show the variety of sku's present in advanced biologic drugs-MABs and ZUMABs which belong to our treatment group vis-a-vis their control drugs for a cumulative time period of April 2009 to June-2020. Variety of SKUs refer to the number of distinct alternatives present within a certain molecule category. The two vertical lines refer to regulatory interventions in the US. Black vertical line corresponds to the passage of BPCI Act in the US in March-2012. Red dotted line refers to Feb-2012 when FDA released guidelines on establishing an abbreviated pathway for biosimilars to gain approval in US.
Source: AIOCD Pharmatrac

Figure A5. : HHI-Biologic and Other Related Drugs



Note: This figure show the monthly averages of HHI for advanced biologic drugs-MABs and ZUMABs which belong to our treatment group vis-a-vis their control drugs for a cumulative time period of April 2009 to June-2020. Average HHI is simply the mean of monthly HHI for all the molecules in our treatment and control group respectively. The two vertical lines refer to regulatory interventions in the US. Black vertical line corresponds to the passage of BPCI Act in the US in March-2012. Red dotted line refers to Feb-2012 when FDA released guidelines on establishing an abbreviated pathway for biosimilars to gain approval in US.
Source: AIOCD Pharmatrac

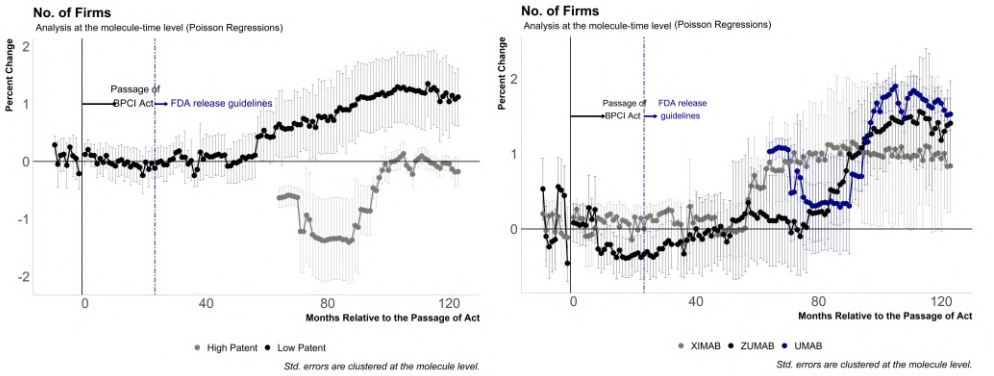
Table A1—: Characteristics of molecules in the treatment group

Name	Launch Date in Indian Market	USA Patent Expiry Date	Europe Patent Expiry Date	Type of MAB
RITUXIMAB	2003	2016	2013	XIMAB
ABCIXIMAB	2007	2015	NA	XIMAB
CETUXIMAB	2006	2014	2016	XIMAB
INFLIXIMAB	2007	2018	2015	XIMAB
BEVACIZUMAB	2001	2019	2022	ZUMAB
TRASTUZUMAB	2010	2019	2015	ZUMAB
ITOLIZUMAB*	2014	NA	NA	ZUMAB
RANIBIZUMAB	2014	2020	2025	ZUMAB
NIMOTUZUMAB*	2010	NA	NA	ZUMAB
PEMBROLIZUMAB	2018	2036	2028	ZUMAB
OMALIZUMAB	2017	2017	2017	ZUMAB
IDARUCIZUMAB	2018	2030	2030	ZUMAB
PERTUZUMAB	2017	2024	2023	ZUMAB
ADALIMUMAB	2014	2034	2018	UMAB
DENOSUMAB	2015	2025	2022	UMAB
GOLIMUMAB	2016	2024	2024	UMAB
DARATUMUMAB	2018	2025	2026	UMAB
DURVALUMAB	2019	2035	NA	UMAB
RAMUCIRUMAB	2018	2023	2025	UMAB
PANITUMUMAB	2019	2020	2018	UMAB

Note: This table provides some baseline characteristics of the molecules that form our treatment group. In the second column, we provide the date on which the molecule was first launched in Indian market. This information was present in our database. Second and third column provides the patent expiry date of molecules in US and European markets, respectively. This information was gathered from multiple sources on the internet. Finally, last column categorizes the molecules into three categories based on the letter preceding MAB in the molecule name. NA means, we were not able to gather information.

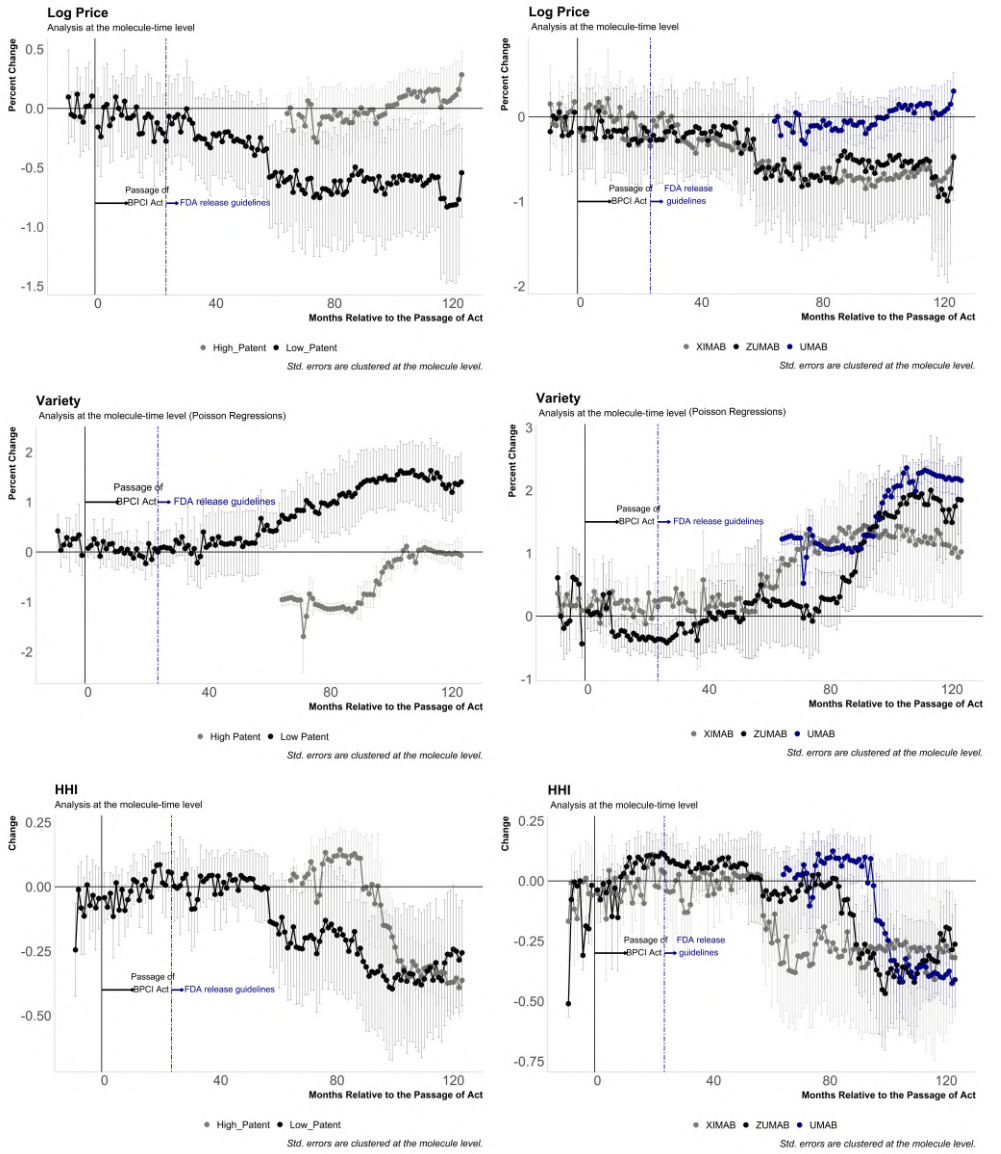
* These molecules are produced by Indian company Biocon, and currently they do not hold any US or European patent.

Figure A6. : Event-study (E.S.) estimates at the national level for the number of firms and variety of SKUs before and after the BPCIA in March 2010 by the patent status and competitiveness of molecule market



Note: In the left panel, black and gray line represents the estimated coefficients for the indicator variable corresponding to the number of months before and after the BPCI act was passed in March, 2010 for log average price (per mg) (panel-a), variety of SKUs (panel-b), and HHI (panel-c) in case of monoclonal antibody molecules with low and high patent protection respectively. In the right panel, black, gray, and blue line represents the similar estimated coefficients for same outcome variables in case of monoclonal antibody molecules belonging to 'XIMAB', 'ZUMAB' and 'UMAB' category respectively, where we use this categorization as a proxy to the complexity of the molecule's underlying technology, increasing in that particular order. The results in the both left and right panels are derived by running the simple OLS (in case of Log price and HHI) and Poisson regressions (in case of Variety) using the econometric specification specified in equation-1.The error bar represent the 95 percent confidence intervals with standard errors clustered at the molecule level. Time period of sample used in this figure goes from April-2009 to June-2020.
Source: AIOCD Pharmatrac

Figure A7. : Event-study (E.S.) estimates at the national level for the log of average price (per mg) and HHI before and after the BPCIA in March 2010 by the patent status and competitiveness of molecule market



Note: In the left panel, black and gray line represents the estimated coefficients for the indicator variable corresponding to the number of months before and after the BPCI act was passed in March, 2010 for log average price (per mg) (panel-a), variety of SKUs (panel-b), and HHI (panel-c) in case of monoclonal antibody molecules with low and high patent protection respectively. In the right panel, black, gray, and blue line represents the similar estimated coefficients for same outcome variables in case of monoclonal antibody molecules belonging to 'XIMAB', 'ZUMAB' and 'UMAB' category respectively, where we use this categorization as a proxy to the complexity of the molecule's underlying technology, increasing in that particular order. The results in the both left and right panels are derived by running the simple OLS (in case of Log price and HHI) and Poisson regressions (in case of Variety) using the econometric specification specified in equation-1. The error bar represent the 95 percent confidence intervals with standard errors clustered at the molecule level. Time period of sample used in this figure goes from April-2009 to June-2020.
Source: AIOCD Pharmatrac