Tempting drug cocktails: the role of pharmaceutical branding in the proliferation of fixed-dose combination medicines in India

An empirical analysis of the effect of brand loyalty on sales performance within formulations of metformin combinations

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ABSTRACT

The proliferation of controversial fixed-dose combination (FDC) medicines has become a major health policy concern in India. In this paper, I examine the previously-neglected role of pharmaceutical branding, which has allowed drug manufacturers throughout the industry to acquire exceptional market shares. Using panel data from 2007 until 2015 on five popular combinations of metformin, a prescription-based oral antidiabetic drug, I identify which type of brands are driving the spread of FDCs. Within-formulation regression analyses indicate increased sales performance for brands which grant a higher retail margin, which are older, and which belong to a company with a high market share in the market for plain metformin. Brand loyalty among physicians and pharmacists is likely to be the propelling mechanism behind these findings. Additionally, I find that brand loyalty becomes a bigger factor in more competitive and mature markets, pointing towards the hindering effect on competitive action. My results suggest public policy makers should take brand loyalty seriously in order to contain the diffusion of FDCs. However, de-branding medicines is at best an incomplete solution to the problem, which requires addressing several systematic failures.

1. Introduction

India has been referred to as the 'diabetes capital of the world' (Times of India, 2016). Over 60 million people have been diagnosed with type 2 diabetes mellitus (Shetty, 2012). It is one of the fast growing markets in the nation's 55 billion dollar industry for pharmaceuticals (McKinsey & Company, 2013). Although metformin is the preferred first choice in medical treatment, the market is dominated by fixed-dose combinations (FDCs[1]).

[1] An overview of all abbreviations used in this paper can be found in Appendix A1.

FDCs are oral drugs for which each pill contains two or more plain molecules, usually metformin and a supplementary agent. Despite several benefits of FDCs for patients such as improved adherence and lower costs, concern has been raised about the hazards for public health. The main risk of FDCs is that patients do not receive the optimal dose of each ingredient, having an adverse effect on the treatment (International Diabetes Federation, 2005). The diffusion of FDCs has been investigated by scholars, mainly by focussing on the roles of regulators and physicians. Evans et al. (2018) document the inadequate performance of regulators, who have approved many irrational FDCs without proper evidence from clinical trials. Kannan et al. (2015) highlight the attitudes of prescribers and patients, who might perceive FDCs as a 'quick fix' to diabetes due to high momentary efficacy. Bhaskarbhatla and Chatterjee (2017) identify which type of physician contributes most to the prescription of irrational FDCs.

Beyond the obvious act of introducing the FDCs, the role of pharmaceutical firms has been largely overlooked. Attention has been given to the marketing techniques employed by firms to influence physicians and pharmacists (Waheed et al., 2011; Narendran and Narendranathan, 2013; Srivastava et al., 2014). These practices probably only reflect part of a bigger problem, considering that the Indian pharmaceutical industry is characterised by substantial market power of manufacturers (Bhaskarabhatla, 2018). The market power of firms can largely be attributed to the prevalence of branded drugs. Most generic drugs in India are sold under brand names. Companies can increase their market share by gaining brand loyalty of physicians and pharmacists. Brand loyalty allows firms to set higher profit margins at the cost of consumers. The approval of 41 anti-diabetic FDCs has given rise to more than 500 new brands (Evans and Pollock, 2015). The aim of this study is to investigate the commercial drivers behind the proliferation of FDCs. More specifically, I ask how brand loyalty among pharmacists and physicians contributes to the excessive use of FDCs. Therefore, my research question is as follows. What is the

role of brand loyalty in the use of FDCs?

I review the economic literature on product bundling to find out why firms sell FDCs. Next, I exploit panel data from a commercial drug sales data base (PharmaTrac) to identify which type of brands are driving the spread of FDCs. Five metformin FDCs are studied from 2007 until 2015: three traditional combinations and two new generation combinations. Together they accounted for 85% of the sales value from metformin FDCs consisting of two components, and they are marketed through 454 brands. Using fixed-effect regressions, I analyse the sales performance of brands within the same formulations by looking at sales volume and wholesale margin. The concept of brand loyalty is approached by focussing on the following determinants: retail margin, brand age and a firm's marker power in the market for plain metformin pills.

Based on the bundling literature, I argue that product differentiation is one of the main commercial drivers for firms to promote FDCs. Firms introduce FDCs under a new brand to increase variety, which in turn increases consumer demand. Consequently, the market share of some brands grows disproportionally as a result of brand loyalty. The results of the empirical analyses indicate that brand loyalty indeed plays a considerable role in the use of FDCs. Higher sales performance is found for brands which grant a higher retail margin, which are older, and which belong to a company with a high market share in the plain metformin market. These respective findings are probably related to pharmacist's loyalty, physician's loyalty and loyalty transfer between brands. In addition, I find that brand loyalty becomes a bigger factor in more competitive and mature markets, suggesting that it undermines the positive forces of competition for consumers.

This study contributes to the existing literature in several ways. First, I emphasize the commercial drivers behind the diffusion of FDCs. Whereas medical considerations may explain the initial choice for FDCs, brand loyalty contributes to repeated use. Second, I confirm the role of pharmacists in pushing the demand for products with a high retail

margin (Srinivasan, 1999; Selvaraj, 2007; Bhaskarbhatla, 2018). The distribution system favours expensive FDC brands over cheaper alternatives or plain pills. Third, this paper underlines the importance of properly educated physicians, as advocated by Bhaskarbhatla and Chatterjee (2017). Inadequately trained physicians are more likely to base their drug choice on brand familiarity than rationality. The main implication for policymakers is that they should pay special attention to the branding strategies of pharmaceutical firms in containing the proliferation of FDCs. Although I only study the case of metformin, the findings may also apply to other medicines, as excessive use of FDCs is a general issue in India (Nigam, 2013).

The remainder of this paper is structured as follows. Section 2 presents a theoretical framework around the sale of FDCs, covering the product, the market and economic drivers of firms. Section 3 hypothesises how brand loyalty affects the sales performance of FDCs. Section 4 introduces the data and variables employed, while Section 5 presents the empirical model employed. The results of the empirical analysis are presented in Section 6 and discussed in Section 7. Section 8 addresses limitations of this study and provides recommendations for future research. Finally, Section 9 concludes.

2. Theoretical framework

The theoretical framework starts with background information on the medical nature of type 2 diabetes. I explain why using FDCs for the treatment of this disease is controversial from a medical point of view. Next, I describe the economic context of the Indian pharmaceutical industry. A combination of market characteristics places drug manufacturers in a position of great power. Loyalty of physicians and pharmacists to the leading brands plays a key role in the choice for drugs in India. Lastly, I review the bundling literature to find out why pharmaceutical firms offer so many FDCs. The most plausible drivers are product differentiation, increasing consumer loyalty and cost savings.

2.1. The medical controversy around metformin FDCs

Type 2 diabetes is a chronical disease characterized by high blood sugar (glucose). Glucose is an important source of fuel for the body. The movement of glucose into the cells is regulated by the insulin hormone. With type 2 diabetes, the body either resists the effects of insulin or it does not produce enough insulin, and the glucose builds up in the blood instead. There is no cure, however there are progressive treatment regimens to manage the disease. The International Diabetes Foundation (2005) guidelines advocate losing weight, a healthy diet and exercise to begin with. If these measures prove insufficient to reach good glucose regulation, metformin is the preferred first choice in medical treatment. Metformin helps the body respond better to the insulin it makes. In case monotherapy does not provide effective glycaemic control, an add-on therapy is required. There are many different antidiabetic agents that can be combined with metformin. They are spread across various drug classes with different mechanisms of action. I will elaborate on the five combinations thar are studied in this paper in Section 4.

Medication for a combination therapy can be taken in separate standard dose formulations (SDFs) or as a FDC. FDCs have the clear advantage of reduced medication burden to the patient. As a result, the relative adherence rates of patients can be improved (Vijayakumar et al., 2017; Arya et al., 2019). In addition, FDCs can improve glycaemic control swifter and to a greater extent than separate SDFs when used correctly. However, FDCs make assessment of efficacy or side effects due to individual drugs more difficult. This is of vital importance, because constant monitoring and rapid adjustments of treatment regimens are required in order to maintain control over glucose regulation (Kannan et al., 2015; Evans et al., 2018). For this reason, only a couple metformin FDCs are allowed in the UK, USA, Canada and Australia. In contrast, 52 FDC formulations have been approved in India. Fortunately, the most irrational formulations (27 of them) have been banned in March 2016. Nevertheless, Evans et al. (2018) have evaluated the

clinical trials of the five top-selling metformin FDCs and find that none of them provide robust evidence of safety and efficacy according to the guidelines of the World Health Organisation.

2.2. Brand loyalty in the Indian pharmaceutical market

The market for medicines consists of three main players. Patients represent the final demand side and pharmaceutical firms provide the supply of drugs. Physicians and pharmacists act as intermediaries. Physicians choose the drug for their patients and write a prescription, while pharmacists fulfil a retailing role in the provision of medicines. A distinctive attribute of pharmaceutical products complicates the transactions between these parties, namely, medicines are a typical example of credence goods (Bhaskarabhatla, 2018). This means that customers find it hard to judge the quality or utility of the product (Wolinsky, 1995). Credence goods are characterised by high search and switching costs. Search costs involve the time and money that go into learning, assessing and selecting the right product. Once that choice has been made the costs of switching from one brand, supplier or product to another are again substantial. This reduces elasticity of demand and hinders competition (Farrell and Shapiro, 1988). Moreover, patients largely rely on the medical advice of their physician. This could lead to supplier-induced demand if the interests of the physician (agent) do not align with those of the patient (principle) (Evans, 1974). As a result of information asymmetry, consumers buy more of a good at a higher price than they would if they were fully informed.

In addition to the economic nature of pharmaceuticals, India's pharmaceutical market possesses three traits that further worsen the position of consumers. First and foremost, generic medicines are often marketed under brand names in India (Bhaskarabhatla, 2018). A pure generic substitute has the exact same chemical composition as the branded product, but is offered at a much lower price. Brands create value above the generic benefit that allows them to become less vulnerable to competitive

action (Panchal et al., 2012; Sanyal et al., 2013). Yet this value is arguably more emotional rather than rational, resulting from feelings of trust (Blackett and Harrison, 2001). De-branding medicines would benefit consumers as it is likely to intensify competition on prices rather than brands (Bhaskarabhatla et al., 2017).

Secondly, pharmacists are able to charge exorbitant resale margins (Srinivasan, 1999; Selvaraj, 2007; Bhaskarbhatla, 2018). A manufacturers sells its products to a pharmacist at the price to retailer (PTR), and sets a maximum price at which the pharmacist can sell the products to consumers, the maximum retail price (MRP). The retail trade organisation, the All India Organisation of Chemists and Druggists, controls the entire distribution of medicines, protects the retail margin and prohibits sales on medicines (Bhaskarabhatla et al., 2015). Hence, pharmacists rarely sell below the MRP and appropriate all of the vertical margin, a practice known as resale price maintenance. Moreover, firms grant a high retail margin to ensure retailer's loyalty (Asker and Bar-Isaac, 2014). By transferring its profits to a pharmacist, an upstream firm incentivises its downstream retailer not sell the products of rivals. As pharmacists want to protect these quasi-rents, their costs of switching to another brand increase. This makes the demand for an individual firm's product more inelastic, resulting in higher equilibrium prices and lower consumer welfare (Gans and King, 2006).

Thirdly, the quality of medical advice from Indian physicians is generally poor. India is one of the developing countries where trained physicians are scarce, as it loses substantial numbers of educated physicians to developed countries (Kaushik et al, 2008). Prior studies have found that prescriptions are often inappropriate (Gopalakrishnan et al., 2013; Banerjee and Bhaduri, 2014) and guidance from medical associations is lacking (Bhaskarabhatla and Chatterjee, 2016). Indian physicians are often unaware of the chemical compositions of the drugs they prescribe (Bhaskarabhatla, 2018). These factors probably increase physicians' loyalty to a particular brand. They might not even regard

the generics as substitutes and/or succumb to the promotional activities of firms (Waheed et al., 2011; Narendran and Narendranathan, 2013).

The result of these market characteristics is that choice and competition in local markets are limited in India. Whereas the number of firms and product substitutes is large at national level, local markets are often dominated by leading brands. (Bhaskarabhatla, 2018). Brands that charge the highest price, often have the largest market share. In many cases, this phenomenon is unrelated to product quality differences and is more likely to be associated with brand loyalty of pharmacists and physicians. Bhaskarabhatla (2018) found that firms selling multiple versions of the same medicine grant different trade margins to pharmacists. The more expensive versions with a higher absolute margin were also the leading in terms of market share. Moreover, multiple studies document the influence of pharmaceutical marketing techniques on the prescription behaviour of physicians and dispensing behaviour of pharmacists (Waheed et al., 2011; Narendran and Narendranathan, 2013; Srivastava et al., 2014). In order to persuade them to choose their brand, firms give samples, send sales representatives, sponsor travel and even award gifts.

2.3. Bundling motives of firms

In this subsection, I ask what the commercial drivers are for firms to sell FDCs. To answer this question, I turn to the bundling literature as FDCs are actually a form of product bundles. Product bundling is defined as the integration and sale of two or more separate products in one package (Stremersch and Tellis, 2002). Other examples of product bundles include a sound system or a microwave-oven combination. The alternative to product bundling is price bundling, which does not involve the integration of the products. This would imply the sale of two separate SDFs as a package at a discount. The bundling literature offers numerous motives for firms to sell FDCs. This subsection addresses the most prominent ones, and discusses their likelihood in the Indian pharmaceutical market.

2.3.1. Product differentiation

Offering products alone and in a bundle is considered to be the optimal strategy in competitive markets (so-called "mixed bundling"; Stremersch and Tellis, 2002). Some consumers wish to mix and match products themselves, while others value integration. The introduction of new bundles increase variety, which in turn increases consumer demand (Matutes and Regibeau, 1988). Indian pharmaceutical firms seem to apply this theory to medication in an effort to escape price pressure. They introduce new combinations of existing molecules under a different brand name with the aim of obtaining a differentiated position in the market. The issue with this practise is that many of these FDCs have no therapeutic justification (Evans et al., 2018), and are merely an attempt to build new brands. The scale of the problem is reflected by the fact that an expert committee has disapproved nearly 6000 FDCs in India.

2.3.2. Increase loyalty

Bundling can also be used by a firm to increase loyalty of physicians and pharmacists. By bundling their products companies reduce the incentives to sample and switch to a competitor's product (Eppen et al., 1991). This is particularly effective for complementary products compared to substitute or unrelated products, since bundling makes the inherent cross-selling/buying a much simpler task (Paun, 1993; Yan and Bandyopadhyay, 2011). Physicians are inclined to spend less effort in gathering information on various SDFs when they can simply prescribe a single FDC. This can make a big difference, since the search costs for pharmaceuticals are very high. For pharmacists, FDCs simplify procurement and take up less shelve space. In a country like India, where there is a general lack of infrastructure to deal with the storage of medicine, this comes in very useful. (Bhaskarabhatla et al., 2016). Gu et al. (2010) support these arguments by showing that the lower frequency of drug administration is an important advantage of FDCs. In sum,

the loyalty resulting from the simplification of prescriptions and distribution is likely to play a considerable role in the proliferation of FDCs.

2.3.3. Cost savings

Metformin FDCs are offered substantially cheaper than the separate SDFs. Buying sulfonylurea-metformin FDCs instead of the two components individually, can save the patient over 20% in monthly costs (Kannan et al., 2015). In a country like India, with many low-income citizens and little health insurance, this considerably helps to reduce the economic burden on diabetes patients. Pharmaceutical firms are able to offer FDCs at a discount due to savings on fixed costs. The fixed costs of packaging and distribution can be reduced considerably when selling multiple products together. Evans and Salinger (2005) find for the combination of cold remedies and pain relievers prices are 30% lower than for the separate products. The costs of the active ingredients represent only a small proportion of the price of these products. Hence, large efficiencies may arise for manufacturers and retailers if they cut on packaging costs and shelf space by selling bundles. This would be a compelling reason why many Indian pharmaceutical companies only sell metformin FDCs without selling the separate components (so-called "pure bundling"). Enough consumers must want only one of the separate SDFs to justify the additional fixed costs (Evans and Salinger, 2005). This is unlikely for the supplement since it is primarily prescribed in combination with metformin.

2.3.4. Price discrimination

Bundling is also a common strategy for price discrimination (Stigler, 1968; Adams and Yellen, 1976; McAfee et al., 1989; Salinger, 1995). This opportunity arises when there is asymmetry in reservation prices, meaning that different consumer segments highly value different products of the bundle. In this case, a firm can capture more surplus from each segment by offering the bundle at a discount. By selling FDCs at a discount, a

pharmaceutical company could sway physicians to prescribe a FDC even though they would not prescribe all the components individually. Whether Indian pharmaceutical firms actively apply this theory is questionable. On one hand, physicians generally do not have the knowledge to form a specific reservation price. On the other hand, many Indian consumers are very price-sensitive and this might transfer to the prescription behaviour of physicians.

2.4.5. Anti-competitive tying

An alternative explanation for Indian pharmaceutical firms to apply pure bundling strategies could be anti-competitive tying. Tying entails that the seller of primary product A refuses to sell A to a consumer unless the consumer also purchases complementary product B (Whinston, 1990; Carlton and Waltman, 2002). The practice of tying is rather controversial, as strategic tying arrangements have been challenged on the basis of antitrust laws in the past. The reason for this is that a monopolist in its primary market can use tying to transfer monopoly power into the complementary market. The monopolist is able to increase its current prices and profits in the complementary market by inducing exit. A real-life case of tying is the integration of Internet Explorer web browser into the Windows operating system. Since Microsoft had made it impossible for Windows users to uninstall Internet Explorer, the US court of justice ruled that Microsoft abused its monopoly power to gain an unfair advantage in the competition for dominance in the market for web browsers (Stremersch and Tellis, 2002).

Along these lines, large manufacturers might use FDCs to transfer their market power from the primary market, i.e. plain metformin, to the complementary market, e.g. some type of sulfonylurea. If the leading firms primarily offer metformin in combination with a complementary drug and it is unlikely that retailers switch to another supplier, then the market for complementary drugs will become less attractive to other firms. As a result, there will be fewer suppliers of complementary drugs. The demand for metformin

FDCs from leading brands increases and so do their prices. However, I doubt that this kind of practise would be possible, let alone profitable, in the market for metformin. The theoretical models on anti-competitive tying assume that there is monopoly power in the primary market. Although monopolies are non-existent in the Indian market for metformin, local offerings are often dominated by leading brands. A monopoly position in the plain market may not be necessary to leverage market power if the retailer's loyalty to a particular supplier is sufficiently high. In most cases though, there is sufficient competition in the plain market for patients to switch to another supplier of metformin SDFs. Hence, offering only FDCs is not a profitable strategy as it would mean losing sales in the market for plain metformin.

3. Hypotheses

In the previous section, I presented a theoretical framework covering the role of brand loyalty in the Indian pharmaceutical market, and the economic motives for firms to sell FDCs. Amongst other reasons, firms introduce FDCs under new brand names to differentiate their products. In this section, I apply the concept of brand loyalty to FDCs in order to identify which brands drive the proliferation of FDCs. By reasoning how brand loyalty affects sales performance, I develop three hypotheses that will be tested with the available data.

Generally, pharmacists are loyal to the brands which offer the highest retail margins. This is reflected by the fact that those brands are being sold the most (Srinivasan, 1999; Selvaraj, 2007; Bhaskarbhatla, 2018). This form of brand loyalty might contribute to excessive use of FDCs. Regardless of the medical need, a firm might market a more expensive FDC as substitute to a plain pill of a rival. Even if the relative trade margins on both products are the same, the higher price of the FDC implies a greater profit for a pharmacist in absolute terms. The profit-maximising retailer puts its efforts

in selling the FDC and the firm's market share increases. In response, other firms might copy this behaviour to maintain their market shares. This leads me to the first hypothesis:

Hypothesis 1: The retail margin of a brand is positively related to its sales performance.

Although a firm might win retailer's loyalty by granting a high retail margin, it is unlikely that physicians switch brands frequently due to high switching costs. This is supported by Janakiraman et al. (2008), who find significant levels of persistence in drug prescriptions. Not surprisingly, long term investments in public relations have shown to be more effective marketing techniques than short term incentives such as sales promotion (Waheed et al., 2011; Narendran and Narendranathan, 2013). Public relations involve a variety of programmes designed to promote a company's image or its individual products. Examples include organising seminars and sponsoring physicians for conferences. Measuring these kind of practices is beyond the scope of this study, yet it can be assumed that it takes time to build physician's loyalty. This gives incumbent firms with established brands a competitive advantage over new entrants. They are likely to benefit from a lower elasticity of demand, allowing them to set higher prices and increase their sales units at the same time (Farrell and Shapiro, 1988; Bhaskarabhatla, 2018). This leads me to the second hypothesis:

Hypothesis 2: The age of a brand is positively related to its sales performance.

The past hypotheses focussed on loyalty to a particular brand in line with Bhaskarabhatla (2018). The reason for this is that pharmaceutical manufacturers market their products through different brands, and loyalty might differ across product groups. However, the effectiveness of public relations programmes suggest that physician's loyalty is more company-wide. This effect might be reinforced by the progression of recommended treatment phases. To recall, every patient should first try metformin monotherapy, and only if that has proven insufficient to reach glycaemic control, the step should be made to

a combination therapy (International Diabetes Federation, 2005). When these guidelines are met, a manufacturer could possibly extend its acquired market power from the plain to the combination market. Physicians develop trust in a medicine based on repetitive product usage and positive experience (Bednarik, 2005). A positive experience with a company's product in first-line therapy, could result in a preference for the same company in selecting a FDC for combination therapy. Since a firm usually sells its metformin SDFs and FDCs under different brand names, this implies a transfer of brand loyalty. This leads me to the third hypothesis:

Hypothesis 3: The market power of a manufacturer in the plain metformin market is positively related to its sales performance in the FDC market.

4. Data

The data section is divided into three parts. Firstly, I address the data source of this study and describe the construction of the final sample. Secondly, I define the variables used to test the hypotheses. Thirdly, descriptive statistics are presented to get an overview of the data and the market.

4.1. Data sources

The data used in this study have been collected by the union of pharmacists in India. The data are regarded as highly accurate, since the union controls the entire flow of medicines and the data have been verified by the Indian pricing authority (National Pharmaceutical Pricing Authority, NPPA). Previous studies on the Indian pharmaceutical market employ the same database, referred to as PharmaTrac data (Bhaskarabhatla et al., 2017; Evans et al., 2018; Benischke and Bhaskarabhatla, 2019). From this source, a SDF and FDC dataset are obtained. The SDF dataset contains monthly MRP and sales units of different metformin brands for the three different dosage strengths of 500mg, 850mg and 1000mg. Furthermore, the delivery type (plain tablet or extended release tablets) and size (number

of tablets) of each package are given. The FDC dataset contains information about metformin combinations consisting of a 500mg metformin dose and one other ingredient. Note that combinations with three ingredients are not included in this study. This does not severely limit the scope, since Evans and Pollock (2015) found that only one out of the five top-selling metformin FDCs is a triple combination (glimepiride-pioglitazone-metformin). In addition to the information included in the SDF dataset, the FDC dataset contains the PTR and the launch date of a brand.

The construction of the final sample is outlined below. The two datasets are merged so that each observation represents a stock keeping unit (SKU), which is the specification of combination - dosage strength - delivery type - pack size - brand. The sample spans the entire country, separated into 23 regional markets for the period of April 2007 until March 2015. The prices and sales units of SKUs variate over months and across regions. I reduce the sample to include only SDFs of 500mg to align with the FDC data. I limit the scope of my research to the five top-selling combinations within the sample: (1) glimepiride-metformin, (2) gliclazide-metformin, (3) glibenclamide-metformin, (4) vildagliptin-metformin, (5) sitagliptin-metformin. These FDCs have a combined market share of 85.3% in terms of sales value, and can be divided into two drug classes: sulfonylureas (FDCs 1 to 3) and dipeptidyl peptidase-4 inhibitors (in short DPP4i; FDCs 4 and 5). More information about the studied FDCs is given in Section 4.3.

4.2. Variable specification

First, I address the dependent variables measuring sales performance. Sales performance is approached from two different perspectives: sales volume and sales margin. Volume is simply the amount of sales units, hence the variable *SalesUnits*. Margin refers to the ability of a firm to price above marginal costs. Since I do not know the marginal costs for all formulations and firms, I take the lowest PTR in the sample for each formulation as a proxy. The minimum PTR at which a firm still sells its products is most likely to resemble

the marginal costs (Bhaskarabhatla, 2018). The variable *WholesaleMargin* measures the sales margin, and is computed as the difference between a brand's PTR and the minimum PTR.

Next, I address the explanatory variables quantifying brand loyalty. The effect of the retail margin of a brand is measured by the variable *RetailMargin*. It is defined as the difference between MRP and PTR. I have chosen the absolute retail margin over the relative margin, since more expensive products with lower relative margins can still yield higher profits for retailers. The effect of brand age is measured by the variable *BrandAge*. It is defined as the yearly difference between the time of observation and the launch date of a brand. The effect of market power in the plain metformin market is measured by the variable *CsharePlain*. It is defined as a firm's market share in the plain metformin market on a month-region basis.

Lastly, the Herfindahl-Hirschman Index (HHI) is used to control for differences in market concentration. The variable *HHI* is calculated using the market shares of firms at combination-month-region level. I have chosen the combination market over the market for a single formulation, because it gives a better indication of the competition companies face. Some specific formulations are sold by only a limited number of firms, but can easily be substituted by other formulations of the same combination.

4.3. Descriptive statistics

The two drug classes exhibit a number of differences, which I will illustrate with the help of descriptive statistics. The differences provide useful variation for the empirical analyses. Moreover, by performing the analyses separately for each drug class, I can see whether brand loyalty is manifested differently under various market conditions.

Summary statistics (mean and standard deviation) of the explanatory variables are shown for each drug class in Table 1. First of all, sulfonylureas have been introduced decades earlier than DPP-4 inhibitors. DPP-4 inhibitors are a relatively new type of anti-

diabetic drug with clinical studies performed during the 2000s (Ahrén, 2019). While sulfonylureas have been in the market for over 50 years, DPP4i is combined with metformin in India only since December 2008. This is reflected by the differences in brand age and HHI. The brands of sulfonylurea-metformin FDCs are on average more than twice as old and the market is more competitive. The high value of HHI for DPP4i-metformin FDCs indicates that there are only a few suppliers on the local market.

Table 1. Summary statistics of explanatory variables

Drug class	Sulfonylurea-metformin		DPP4i-metformin	
Supplements	Glimepiride, gliclazide, glibenclamide		Vildagliptin, sitagliptin	
Variable	**Mean**	Std. Dev.	**Mean**	Std. Dev.
RetailMargin	**1.62**	0.96	**5.94**	1.36
BrandAge	**6.58**	4.13	**3.03**	1.76
CsharePlain	**1.59**	4.47	**2.73**	6.81
HHI	**0.44**	0.23	**0.85**	0.23
No. Of Obs.	430,141		9,763	

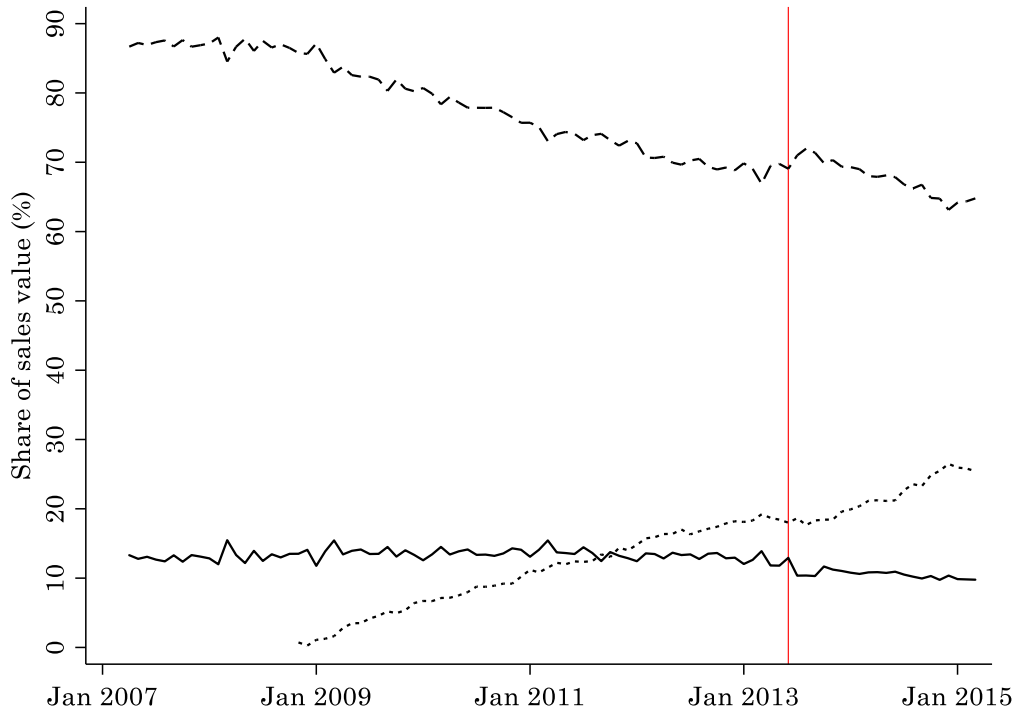
Secondly, sulfonylureas are much cheaper than DPP-4 inhibitors. The daily costs of recommended intake are four to eight times lower (CADTH, 2015). In return, DPP-4 inhibitors achieve the same efficacy with lower risks. In a systematic review of the medical literature, Vijayakumar et al. (2017) find an advantage of DPP-4 inhibitors over sulfonylureas as add-on to metformin in regard to both lower risk of hypoglycaemia and no weight gain. Whether these benefits are worth the increase in costs is beyond the scope of this study. Nonetheless, Table 1 shows that the higher price of DPP-4 inhibitors is associated with a higher absolute retail margin, making the newer generation FDCs more attractive to pharmacists.

Thirdly, the market for each drug class is connected to the plain metformin market in a different way. Suppliers of sulfonylurea-metformin FDCs have on average a smaller stake in the plain metformin market. However, the percentage of firms that offers plain metformin is higher (54.2% compared to 30.8%). Thus, suppliers of DPP4i-metformin

FDCs are either very connected to the plain market or not connected at all.

Next, I have plotted metformin sales over time to identify any temporal trends in commercial performance. Figure 1 depicts the market shares of SDFs, sulfonylurea-metformin FDCs and DPP4i-metformin FDCs for the period of analysis. The sales value of metformin combinations have exceeded plain metformin sales for the entire duration of the sample. I do not observe a sudden decrease in sales of SDFs after the implementation of the 2013 price controls (indicated by the vertical red line). Therefore, I conclude that the evasion of price controls can be ruled out as a major cause of the proliferation of metformin FDCs[2]. Interestingly, the sales trends of the two FDC drug classes are mirrored. This could imply that sulfonylureas are gradually being replaced by DPP-4 inhibitors in the second-line treatment. I explain how I control for such temporal trends in Section 5.

Figure 1. Market shares of plain metformin (solid line), sulfonylurea-metformin (upper dotted line) and DPP4i-metformin (lower dotted line)



[2] Background information about the 2013 price controls and the use of FDCs to mitigate their impact can be found in Appendix A2.

5. Methodology

In this section, I present the empirical method and specifications employed in the panel analysis.

Since our data is structured the same way, I follow the estimation strategy of Bhaskarabhatla et al. (2017) in regard to regression method, fixed-effects selection and clustering of the standard errors. Regressions are run using the ordinary least squares method. All specifications include company, state and month fixed-effects to control for heterogeneity across firms, regions and time. The company fixed-effects allow me to compare brands of different firms without bias arising from differences in product quality between firms. State and month fixed-effects are added to avoid that results are explained away by regional characteristics or temporal trends. Lastly, I correct the standard errors by clustering observations at the firm-region level to account for serial correlation.

In the empirical specifications, I exploit the variation within formulations (combination - dosage strength - delivery type - pack size). Formulation fixed-effects allow me to directly compare the sales performance of different brands. The obvious downside of this approach is that I cannot measure competition between brands of different combinations. However, brand loyalty is less likely to be a major factor at this level, as I will explain in Section 8. I estimate the following equation in order to examine the effect of brand loyalty on sales performance:

$$ln(Y)_{ijkt} = \beta_0 + \beta_1\, ln(RetailMargin)_{ijkt} + \beta_2 BrandAge_{ijt} + \beta_3 CsharePlain_{jkt} + \beta_4 HHI_{kt} + \omega + \theta_j + \kappa_k + \tau_t + \varepsilon_{ijkt} \quad (1)$$

In the above equation i indexes the brand, j the firm, k the region and t the month. ω captures product fixed-effects to control for formulation-specific factors. θ_j, κ_k and τ_t indicate the firm, region and month fixed effects. The dependent variable (Y_{ijkt}) and retail margin variable ($margin_{ijkt}$) are included as natural logarithm to facilitate interpretation

and comparison between formulations. I use *SalesUnits* and *WholesaleMargin* as dependent variable in separate regressions. In accordance with the first hypothesis, I expect a positive coefficient estimate for β_1, indicating that a higher retail margin is associated with better sales performance. I expect β_2 to be positive, indicating that older brands – which have had more time to build up brand loyalty – sell more than younger brands. I expect β_3 to be positive, implying that a higher market share in the plain metformin market translates to more sales in the FDC market. In sum, I cannot reject hypothesis 1, 2 and 3 if the coefficient estimates of β_1, β_2 and β_3 are all positive and significant.

Next, I deepen the base model by incorporating the underlying relationships between the explanatory variables related to brand loyalty. I add an interaction term for each relation, amounting to a total of three interaction terms. This allows me to investigate which vertical control practices complement each other and which do not. I estimate the following equation:

$$\begin{aligned} ln(Y)_{ijkt} = \beta_0 + \beta_1\, ln(RetailMargin)_{ijkt} + \beta_2 BrandAge_{ijt} + \beta_3 CsharePlain_{jkt} + \beta_4 HHI_{kt} \\ + \beta_5\, ln(RetailMargin)_{ijkt} * BrandAge_{ijt} + \beta_6 BrandAge_{ijt} * CsharePlain_{jkt} \\ + \beta_7\, ln(RetailMargin)_{ijkt} * CsharePlain_{jkt} + \omega + \theta_j + \kappa_k + \tau_t + \varepsilon_{ijkt} \end{aligned} \quad (2)$$

The coefficient estimate of β_5 shows whether the effectiveness of granting high retail margins increases ($\beta_5 > 0$) or decreases ($\beta_5 < 0$) with brand age. β_6 indicates whether market power in the plain market is levered more easily to new FDC brands ($\beta_6 < 0$) or more established FDC brands ($\beta_6 > 0$). Lastly, β_7 indicates whether granting high retail margins has more effect for companies that lack market power in the plain metformin market ($\beta_7 < 0$) or have strongly positioned themselves in that market ($\beta_7 > 0$).

In addition, I examine the results of equation (1) in relation to the degree of market concentration. I interact each of the brand loyalty variables with the Herfindahl-

Hirschman Index to find out how competition between firms influences the extent to which brand loyalty pays off. This is specified in the following equation:

$$\begin{aligned} ln(Y)_{ijkt} = \beta_0 + \beta_1\, ln(RetailMargin)_{ijkt} + \beta_2 BrandAge_{ijt} + \beta_3 CsharePlain_{jkt} + \beta_4 HHI_{kt} \\ + \beta_5\, ln(RetailMargin)_{ijkt} * HHI_{kt} + \beta_6 BrandAge_{ijt} * HHI_{kt} \\ + \beta_7 CsharePlain_{jkt} * HHI_{kt} + \omega + \theta_j + \kappa_k + \tau_t + \varepsilon_{ijkt} \end{aligned} \quad (3)$$

Negative coefficients of β_5, β_6 and β_7 indicate that granting high retail margins, being an established brand or having market power in the plain market has more effect on sales when competition is fierce. Conversely, a positive coefficient implies that brand loyalty has more impact in concentrated markets.

6. Results

In this section, I present the empirical results regarding the effect of brand loyalty on sales performance. The effects on sales units are discussed first, followed by the effects on wholesale margins. In both cases, I find positive effects of brand loyalty on sales performance, thus supporting my hypotheses. The effects of brand age and market power in the plain metformin market are higher in more competitive markets across all models. Lastly, I compare the results between the two drug classes. The same results are found for sales units, however the ability of brands to charge extraordinary wholesale margins is weaker in the market for FDCs with DPP-4 inhibitors.

6.1. Quantity analysis

The results of equation (1) are shown in column 1 of Table 2. The coefficient estimates of *RetailMargin, BrandAge* and *CsharePlain* are all statistically significant and positive. This indicates that a brand is being sold more when it offers a higher absolute retail margin, when it is older, and when it belongs to a firm with a relatively high market share in the plain metformin market. All three effects are consistent with the hypotheses. Based on the magnitudes of the coefficients, I reckon that age and retail margin are the key

factors. Keeping other variables fixed, an age difference of one year is associated with a sales difference of 11.9% on average. Increasing the absolute margin with 1% is associated with increased sales of 0.6%. Thus, a firm would have to increase its retail margin by roughly 20% to overcome a competitive disadvantage of only one year. Market share in the plain metformin market has less of a profound effect on sales. An increase of 1 percentage point in market share is associated with increased sales in the FDC market of 4.8%. For the really big players this effect is substantial and can be considered a key advantage, however three quarters of the mixed bundling firms only have a market share in the plain metformin market below 3%.

The results of equation (2) are shown in column 2. Every coefficient estimate is statistically significant. The coefficient of *RetailMargin*BrandAge* is negative, indicating that the positive effect of granting a high retail margin becomes less as a brand ages. Hence, new brands can slightly compensate for their age by increasing their retail margin. The coefficient of *CsharePlain*BrandAge* is positive, indicating that market power in the plain metformin market is better leveraged to older FDC brands. As expected, it takes time to transfer brand loyalty from the plain to the combination market. The negative coefficient of *CsharePlain*RetailMargin* suggests that the positive effects of a high retail margin and market power in the plain metformin market cancel each other to some extent.

The results of equation (3) are shown in column 3. The coefficient of *RetailMargin*HHI* is statistically significant and positive, while *RetailMargin* has lost its significance. This indicates that the positive effect of a high retail margin is strongly dependent on the market structure. More specifically, a higher retail margin contributes more to sales in concentrated markets. In contrast, the negative coefficients of *CsharePlain*HHI* and *BrandAge*HHI* indicate that market power in the plain metformin market and brand age become less important factors when markets are concentrated. I report the full model, including the variables from columns 2 and 3 in column 4. The

results remain broadly similar and consistent with the hypotheses. The results are also robust to the inclusion of PTR as a control variable (output table can be found in Appendix A3). PTR may be a second-order criteria for pharmacists in the choice between brands. From a profit-maximising standpoint, it would be optimal to maximise the absolute retail margin and minimise purchase price.

Table 2. Effects of brand loyalty on sales units

D.V. = ln_SalesUnits	1	2	3	4
ln_RetailMargin	0.628***	0.922***	0.108	0.405***
	[0.067]	[0.095]	[0.113]	[0.143]
BrandAge	0.122***	0.136***	0.162***	0.175***
	[0.008]	[0.010]	[0.014]	[0.015]
CsharePlain	0.047***	0.027***	0.092***	0.077***
	[0.009]	[0.011]	[0.011]	[0.015]
HHI	-0.433***	-0.416***	-0.182	-0.140
	[0.112]	[0.112]	[0.147]	[0.149]
ln_RetailMargin x BrandAge		-0.042***		-0.032***
		[0.009]		[0.009]
CsharePlain x BrandAge		0.005***		0.003***
		[0.001]		[0.001]
CsharePlain x ln_RetailMargin		-0.019***		-0.020***
		[0.004]		[0.004]
ln_RetailMargin x HHI			0.812***	0.736***
			[0.146]	[0.149]
BrandAge x HHI			-0.067***	-0.068***
			[0.016]	[0.016]
CsharePlain x HHI			-0.079***	-0.069***
			[0.015]	[0.016]
Constant	9.906***	9.811***	9.819***	9.732***
	[0.417]	[0.422]	[0.465]	[0.468]
Observations	433,287	433,287	433,287	433,287
R-squared	0.528	0.530	0.531	0.532

All specifications include formulation, firm, state and month fixed-effects.
Firm-region clustered standard errors in brackets.
*** p<0.01, ** p<0.05, * p<0.1

6.2. Pricing analysis

The results of the specifications regarding wholesale margins are shown in the same order as before in Table 3. The significance of the variables in the base model alters when interaction terms are added. This implies that the findings are very context specific. I proceed straight to the interpretation of the full model, as it takes all contexts into account.

Table 3. Effects of brand loyalty on wholesale margins

D.V. = ln_WholesaleMargin	1	2	3	4
ln_RetailMargin	0.559***	0.355***	0.616***	0.366***
	[0.028]	[0.034]	[0.042]	[0.049]
BrandAge	0.018***	0.001	0.025***	0.008**
	[0.003]	[0.003]	[0.004]	[0.004]
CsharePlain	-0.001	-0.001	0.006**	0.012***
	[0.001]	[0.001]	[0.003]	[0.004]
HHI	0.025	0.028	0.155***	0.123***
	[0.028]	[0.027]	[0.035]	[0.035]
ln_RetailMargin x BrandAge		0.035***		0.035***
		[0.003]		[0.003]
CsharePlain x BrandAge		0.000		-0.000
		[0.000]		[0.000]
CsharePlain x ln_RetailMargin		-0.002		-0.003**
		[0.001]		[0.001]
ln_RetailMargin x HHI			-0.101**	-0.012
			[0.041]	[0.040]
BrandAge x HHI			-0.012***	-0.010**
			[0.005]	[0.004]
CsharePlain x HHI			-0.011**	-0.020***
			[0.005]	[0.005]
Constant	1.746***	1.811***	1.641***	1.745***
	[0.121]	[0.126]	[0.127]	[0.129]
Observations	406,327	406,327	406,327	406,327
R-squared	0.848	0.852	0.849	0.852

All specifications include formulation, firm, state and month fixed-effects.
Firm-region clustered standard errors in brackets.
*** p<0.01, ** p<0.05, * p<0.1

The coefficient estimate of *RetailMargin* is positive, indicating that brands granting a higher retail margin can also permit to set a higher wholesale margin. The coefficients of *RetailMargin*Age* and *CsharePlain*RetailMargin* show that this effect becomes larger with brand age and smaller for companies with a relatively high market share in the plain metformin market. The coefficients of *BrandAge* and *CsharePlain* are both positive, while they are negative when interacted with *HHI*. This suggests that brand age and market power in the plain metformin market contribute towards the ability of firms to price above their marginal costs. However, these effects loose in strength as markets become more concentrated. The few firms that operate in these markets, all have the power to set high margins, as indicated by the positive coefficient of *HHI*. All in all, the results are consistent

with the hypotheses, albeit primarily in competitive markets. Retail margins are the exception to this rule, for which the results remain consistent across all models. Increasing the retail margin by 1% is associated with an increase in wholesale margin by 0.6% on average, ceteris paribus.

6.3. Subsample analysis

The estimation results of the full model for the separate drug classes are shown in Table 4. Columns 1 and 3 concern the sulfonylureas and columns 2 and 4 concern DPP-4 inhibitors.

Table 4. Effects of brand loyalty for each drug class

D.V.	ln_SalesUnits		ln_WholesaleMargin	
	1	2	3	4
ln_RetailMargin	0.364**	5.038***	0.362***	-0.635
	[0.153]	[0.871]	[0.054]	[0.582]
BrandAge	0.195***	5.452***	0.009**	1.137***
	[0.016]	[0.453]	[0.004]	[0.083]
CsharePlain	0.055***	0.256*	0.012***	0.392
	[0.015]	[0.140]	[0.004]	[1.192]
HHI	0.007	-2.948**	0.126***	0.632
	[0.151]	[1.143]	[0.036]	[0.458]
ln_RetailMargin x BrandAge	-0.043***	-1.187***	0.035***	-0.485***
	[0.009]	[0.123]	[0.003]	[0.053]
CsharePlain x BrandAge	0.002***	0.013***	-0.000	0.020***
	[0.001]	[0.003]	[0.000]	[0.003]
CsharePlain x ln_RetailMargin	-0.009**	-0.142***	-0.003**	-0.217
	[0.004]	[0.051]	[0.001]	[0.572]
ln_RetailMargin x HHI	0.848***	2.404***	-0.007	-0.272
	[0.165]	[0.789]	[0.048]	[0.239]
BrandAge x HHI	-0.089***	-0.136	-0.011**	0.004
	[0.017]	[0.157]	[0.004]	[0.009]
CsharePlain x HHI	-0.029	-0.032	-0.021***	0.023*
	[0.020]	[0.073]	[0.006]	[0.013]
Constant	9.602***	0.484	1.744***	2.994***
	[0.477]	[1.636]	[0.129]	[1.004]
Observations	423,776	9,511	401,574	4,753
R-squared	0.531	0.593	0.852	0.959

All specifications include formulation, firm, state and month fixed-effects.
Firm-region clustered standard errors in brackets.
*** p<0.01, ** p<0.05, * p<0.1

I start by comparing the effects of brand loyalty on sales units. Based on the same sign of each pair of variables except *HHI,* I conclude that the same mechanisms of brand loyalty apply across drug classes. The magnitude of the coefficients in the second column are higher, but this does not necessarily imply that brand loyalty plays a bigger role in the sales performance of DPP-4 inhibitors. The number of sales units of DPP-4 inhibitors is generally much lower. Relative effects expressed by the natural logarithm will therefore always be higher. That said, the reduced significance of *CshareePlain* in column 2 reflects that market power in the plain metformin market has less impact on sales for the newer generation FDCs. Moving on to the specifications regarding wholesale margins, the results for sulfonylureas are similar to the main findings in Table 3. There is little variation in the wholesale margins of DPP-4 inhibitors, and most of it is absorbed by the fixed-effects. This suggests that brand loyalty plays a negligible role in the ability of firms to set a higher wholesale margin. Nonetheless, the coefficient of *BrandAge* is statistically significant and positive, indicating that older brands can appropriate more of the vertical margin.

7. Discussion and implications

In this section, I discuss the results of the empirical analysis. Overall, the results provide evidence for a considerable role of brand loyalty in the use of FDCs. The proliferation of FDCs is driven by brands which grant a higher retail margin, are older and are connected to firms with a high market share in the plain metformin market. Consequently, I formulate specific policy recommendations targeted at containing the diffusion of FDCs in the future.

I start by reflecting the main empirical findings on the existing literature. Firstly, brands which offer a higher retail margin perform better in terms of sales performance. I compare brands of different firms for the same formulation, controlling for possible quality differences using company fixed-effects. Bhaskarabhatla (2018) comes to similar results for different brands of the same manufacturer. He shows that a manufacturer sets the

same MRP across brands, but decreases its PTR on some of them to make them more attractive to pharmacists. The firm shares part of its profit with the retailer in return for retailer's loyalty, a practice known as resale price maintenance (Asker and Bar-Isaac, 2014). Instead of a shift in vertical profits from manufacturer to retailer, I find that higher retail margins are associated with higher wholesale margins. Thus, resale price maintenance is employed to increase total industry profits at the cost of consumers.

Secondly, brands which are older perform better. An established brand is sold more frequently at a higher wholesale margin. This result is more likely to be related to prescription behaviour of physicians than the dispensing behaviour of pharmacists. Pharmacists are more sensitive to brief sales promotions, reflected by their interest in receiving regular information about bonus schemes by sms (Srivastava et al., 2014). Physicians develop trust in a medicine based on repetitive product usage (Bednarik, 2005). Since most drugs are sold under brand names in India, physicians could identify their trust in a certain medicine with the brand they have been prescribing (Blackett and Harrison, 2001). Once physicians have formed their preference for a particular medicine, or in this case a brand of medicine, it is very hard to change. The drug choice is strongly dependent on the previously prescribed drugs (Janakiraman et al., 2008). As a result, older brands are likely to have a competitive advantage over newer brands.

Thirdly, a brand that is sold by a firm with a high market share in the plain metformin performs better in terms of sales performance. International guidelines strongly advise to start with plain metformin as first-line treatment, and move on to combination therapy when metformin monotherapy proves to be ineffective. A firm could transfer its market power from the plain to the FDC market, using physician's loyalty as leverage. Although the context is quite specific, the same mechanism could apply to other pharmaceuticals when progressive treatment stages are in order. Physicians tend to describe the drugs of the same company if the company has a history of effective drugs

(Wright and Lundstrom, 2004). Yet Kannan et al. (2015) suggest that Indian physicians usually skip plain metformin and prescribe a FDC right away. This would undermine the described mechanism, in which case the finding is more likely to be related to general corporate reputation (Moss, 2001; Narendran and Narendranathan, 2013).

Fourthly, brands generally tend to play a bigger role in competitive and mature markets. This finding is consistent with the literature on pharmaceutical branding. In the mature market of sulfonylurea-metformin FDCs, product performance differences are likely to be minimised and competition is fierce. Especially under this situation, brand loyalty becomes effective (Moss and Schuiling, 2004). Brands play an important role in differentiation as a large number of drugs is available to physicians (Chandler and Owen, 2002). As illustration, there exist 163 brands of regular tablets of the glimepiride-metformin FDC. Which brand should a physician choose? Strong brands help physicians differentiate between two identical products. In return, brand loyalty reduces the vulnerability to competitive action (Panchal et al., 2012; Sanyal et al; 2013).

Next, I broaden my scope and reflect on the role of firms in the proliferation of metformin FDCs in India. As argued above, I am convinced that corporate branding contributes to the abundance of medically controversial FDCs for the sake of profit-maximisation. While these are without doubt unethical practices in itself, they are partly the result of a failure of the entire system. As the patent protection of medical products is limited in India, there are mostly generic drugs on the market (Fink, 1999; Sanyal et al; 2013). In the absence of patent protection, branding has become an important tool for firms to recoup costs of research and development (R&D). This creates a toxic landscape, where unbranded generics are not competitive anymore. Moreover, firms acquire market power through brands due to the demand generated by physicians and pharmacists. Physicians tend to choose drugs based on brand familiarity, while pharmacists push the demand for expensive brands in order to earn higher retail margins.

In order to contain the diffusion of FDCs, the aforementioned system failures have to be addressed. I suggest the following policy considerations. Firstly, India could review the balance between access to affordable drugs and patent protection. In the current system, there may be more competition in newly marketed products, leading to lower prices than would be the case in a patent-induced monopoly. But instead of focussing on real product innovations, this policy has incentivised the launch of irrational formulations and combinations of existing drugs which have no additional therapeutic value (Nigam et al., 2013; Evans et al., 2018). The strengthening of intellectual property rights in 2005 is a step in the right direction, as it has been associated with higher private returns on R&D investment (Arora et al., 2008). However, this effect appears to be highly concentrated in the most technologically progressive Indian firms. De-branding generics would force more firms to innovate by substantially decreasing prices of essential drugs (Injeti, 2014). Secondly, the drug distribution system could be reformed. The retail trade organisation controls the entire flow of medicines and acts as a cartel, hindering downstream competition (Bhaskarabhatla et al., 2016). Promoting competition among pharmacists is likely to reduce vertical margins and the demand for expensive FDCs. Thirdly, one could develop clearer guidelines for physicians. Poorly trained physicians are a major problem in India (Kaushik et al, 2008), and play a key role in prescribing irrational FDCs (Bhaskarabhatla and Chatterjee, 2017). Physicians need to be better educated on the chemical content of FDCs and the action of individual components. In this way, they are more likely to base their drug choice on rational considerations about cost-effectiveness rather than emotional value.

8. Limitations and future research

There are several limitations to my research that need acknowledging.

A key limitation of the methodology is that I only compare brands within the same formulations. There is a distinction to be made between intra-molecular and inter-

molecular competition between brands (Ellison et al., 1997). Intra-molecule competition involves the substitutability of different molecules for the same therapeutic therapy, whereas inter-molecule competition involves substitutability amongst drugs that contain the same molecule but differ in brand. For example, there exists intra-molecule competition between a glimepiride-metformin brand and gliclazide-metformin brand, and there is inter-molecule competition between two glimepiride-metformin brands. Ellison et al. (1997) find that demand for inter-molecular substitutes is more price elastic. This means that physicians are more likely to prescribe a different brand of the same molecule than a completely different molecule. Since I study brand loyalty in an inter-molecular setting, the results cannot just be generalised to competition between different drugs. Rather than explaining why a FDC is chosen initially, I offer an explanation why FDCs are purchased repeatedly, hence the term loyalty. Both actions contribute to the proliferation of FDCs in a different way. Future research could therefore examine brand competition across drugs. It would be especially interesting to investigate whether plain metformin is substituted by FDCs in first-line treatment, as suggested by Kannan et al. (2015). Additionally, a lack of data prevents me from incorporating the SDF market for the supplementary agents used in metformin combination therapy. This might provide new insights into the different bundling strategies of firms.

Furthermore, the empirical examination is limited to a sample of five metformin FDCs. They account for a large proportion of the sales value of metformin FDCs, yet the popular combinations of glimepiride-pioglitazone-metformin and glipizide-metformin are not included (Evans et al., 2018). The two combinations with DPP-4 inhibitors make up for about a quarter in sales value due to their high prices, but they only represent a small fraction of sales volume. Nonetheless, I reckon that brand loyalty plays a similar role for other anti-diabetic FDCs. The results may also apply to other medicine markets, as FDCs and pharmaceutical branding are widespread issues in India (Bhaskarabhatla, 2018;

Nigam, 2013). However, caution should be taken when generalising the results. Type 2 diabetes is a chronic disease and metformin is only available by prescription. The effect of brand loyalty is likely to be stronger in this case, since purchases are repeated over a long time and are induced by physicians who are probably less price sensitive than the final consumer. Future research could compare chronic with acute disorders and prescription drugs with over-the-counter medicines. This would provide different perspectives to brand loyalty research due to a varying degree of influence from physicians and pharmacists. Finally, the results are specific to the context of India, where the regulatory system and brand profiling are different from other countries.

9. Conclusion

This study examines the economic drivers behind the proliferation of FDCs in India. I focus on the role of pharmaceutical branding, as this has enabled firms to acquire considerable market shares in the past. Based on the bundling literature, I argue that a firm markets new FDCs under new brand names to create variety, which in turn increases consumer demand. The loyalty of physicians and pharmacists to attractive brands contributes to the diffusion of FDCs after their introduction. Using panel data from 2007 to 2015 on five popular metformin FDCs, I find evidence for large differences in sales volume and wholesale margin across brands within the same medicine formulation. Pharmacists push the demand for brands with a higher retail margin, while physicians are more likely to prescribe older brands. Furthermore, a firm can transfer market power from a successful SDF brand to a FDC brand, using loyalty as leverage. Firms exploit this situation by increasing their wholesale margins at the cost of consumers.

The proliferation of controversial FDCs has become a major health policy concern in India. While most of the research on this topic has focused on medical attributes, adequacy of prescribers and regulatory approvals, this paper points towards the role of pharmaceutical branding. The findings imply that public policy makers should take brand

loyalty seriously in order to contain the mushrooming of FDCs. This requires a closer assessment of all parties involved, including firms, pharmacists and physicians. Otherwise India might end up in a viscous circle, where new brands are marketed to increase variety, leading to overcrowded therapy areas where brand value becomes the primary tool to differentiate between identical products.

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APPENDIX

A1. List of abbreviations

DDP4i *or* DPP-4 inhibitors - dipeptidyl peptidase-4 inhibitors: anti-diabetic drug used in combination with metformin

FDC – Fixed-dose combination: medicine for which each pill contains two or more plain molecules

MRP – Maximum retail price: maximum price a pharmacist is allowed to charge to consumers by a manufacturer

PTR – Price to retailer: price at which a manufacturer sells a product to a pharmacist

SDF – Standard-dose formulation: medicine for which each pill contains a single molecule

A2. Potential use of FDCs to evade price regulation

In 2013, the Indian government imposed price controls on over 300 drugs in an effort to make essential drugs more affordable. The Drug Price Control Order 2013 (DPCO 2013) has shown to be of limited effectiveness as a result of a ponderous policy process and only partial regulation of some of the formulations of each medicine (Bhaskarabhatla et al., 2017). Pharmaceutical industry associations have deployed numerous non-market strategies to manipulate the public policies. Evidence has been found for lobbying (IDMA Annual Report, 2011), price coordination (Bhaskarabhatla et al., 2017), and cartel punishment of cheating firms by organizing boycotts (Bhaskarabhatla et al., 2016). In the case of metformin, India only defined the 500mg SDF as being an essential drug in accordance with the World Health Organisation's guidelines at the time. The price regulation left the 850mg and 1000mg SDFs as well as the FDCs unregulated. Pharmaceutical firms might try to evade the effects of the price controls by shifting their sales from the plain to the FDC market. Based on the tremendous power of industry associations and their unethical actions from the past, this is a very plausible scenario.

For instance, Bhaskarabhatla et al. (2018) found for paracetamol that efforts are diverted from the regulated 500mg segment into the unregulated 650mg segment.

A3. Robustness check of quantity analysis

D.V. = ln_SalesUnits	1	2	3	4
ln_RetailMargin	0.468***	0.782***	-0.065	0.277*
	[0.083]	[0.107]	[0.120]	[0.149]
BrandAge	0.119***	0.136***	0.158***	0.175***
	[0.008]	[0.010]	[0.014]	[0.015]
CsharePlain	0.047***	0.026**	0.094***	0.077***
	[0.009]	[0.011]	[0.011]	[0.015]
HHI	-0.414***	-0.396***	-0.167	-0.118
	[0.112]	[0.112]	[0.146]	[0.149]
ln_PTR	0.493***	0.563***	0.513***	0.554***
	[0.139]	[0.139]	[0.137]	[0.138]
ln_RetailMargin x BrandAge		-0.050***		-0.040***
		[0.009]		[0.009]
CsharePlain x BrandAge		0.005***		0.003***
		[0.001]		[0.001]
CsharePlain x ln_RetailMargin		-0.017***		-0.018***
		[0.004]		[0.004]
ln_RetailMargin x HHI			0.821***	0.721***
			[0.148]	[0.151]
BrandAge x HHI			-0.082***	-0.071***
			[0.014]	[0.016]
CsharePlain x HHI			-0.067***	-0.068***
			[0.016]	[0.016]
Constant	8.381***	8.051***	8.235***	7.995***
	[0.622]	[0.621]	[0.649]	[0.651]
Observations	433,287	433,287	433,287	433,287
R-squared	0.529	0.531	0.532	0.533

All specifications include formulation, firm, state and month fixed-effects.
Firm-region clustered standard errors in brackets.
*** p<0.01, ** p<0.05, * p<0.1