Competition and Innovation: A Structural Model using the Pharmaceutical Market.*

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Abstract

How do pharmaceutical companies react to their competitors' R&D decisions? How do firms' characteristics affect their profitability from innovations and their ability to compete with other firms? Answering these questions can have important policy implications for antitrust or for designing incentives to promote pharmaceutical innovations. I build a structural model on pharmaceutical innovation using a data set of clinical trials, to estimate a game of incomplete information between firms. I show that firms who innovate in many markets are better equipped to benefit from their rivals. I also show that firms' size has a positive effect on the profitability from innovation.

1 Introduction

Understanding the determinants of innovation is one of the most important, enduring problems in economics. The "perennial gale of Creative Destruction" idealized by Schumpeter (1976) was driven by new consumer goods and new technologies: but what are the conditions that lead to such innovation? For Schumpeter, the opportunity to capture monopoly profits, joined with large firms' financial capacity to invest in research, were the keys. Arrow (1962) argued, in contrast, that it is competition that generates stronger incentives to innovate, because competitive firms need not be concerned about cannibalizing current profits. Arrow (1962) pioneered theoretical models

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that analyzed product and price competition when there is R&D collaboration between firms. These early models, which were later elaborated by Spence (1986), provide the key insight that incentives to invest in R&D are reduced by the presence of technology spillovers. But strategic interaction among firms within an industry includes both a technology spillover effect and a product rivalry effect. While technology (or knowledge) spillovers can increase the productivity of other firms that operate in similar technology areas, innovation by product market rivals has a negative effect on a firm's value due to business stealing. If the former dominates the latter effect, then the net effect of innovation on other firms will be positive (Jaffe, 1986).

This selective tour through the economic history of innovation highlights several key questions addressed by this paper. What is the net effect of product market competition on innovation? How important is firm size? Can we say whether the technology spillover effect dominates the product rivalry effect in specific circumstances? We attempt to answer these questions within the pharmaceutical industry.

The pharmaceutical industry offers a particularly attractive observatory for examining the economics of innovation for several reasons. First, this industry is a perennial high spender on research and development: R&D spending averages 17% of revenues. Second, within the industry there are many markets that are segmented, and large firms compete in varying subsets of those markets. Third, clinical trials represent a particularly meaningful measure of R&D spending. Clinical trials represent the majority of total R&D expenditures for pharmaceutical companies, and are an unavoidable part of getting a product approved and onto the market (DiMasi et al., 2016). Moreover, trials are disease-specific and corporate sponsorship is public. Thus, not only is innovation in the pharmaceutical industry of great intrinsic interest, but it also offers a set of features that makes it possible to identify some of the interactions between innovative firms.

Assessing the effect of product-market competition and the spillovers on innovation, however, is quite challenging. Firms simultaneously decide how much to innovate, but their decisions affect each other. This is an obvious concern for the identification of any model of innovation. This calls for a structural model that endogenizes competitors' decisions. Parameters of interest in such a structural model can however be identified by using exogenous variation in player-specific observable regressors that are excluded from competitors' payoffs.

In this paper, I focus on the large players in the pharmaceutical industry and measure the net effect of each big firm's innovation choices on those of other big firms. I limit this analysis to the top 20 pharmaceutical companies in terms of innovation. In this game each player decides how many clinical

trials to conduct for each disease. I use the firms' history of innovation in each market as a variable that satisfies exclusion restrictions for identifying the model.

Using this model, I show that if firms are present in many markets, the positive spillover effect will dominate the negative competition effect more. This indicates that firms who innovate in fewer markets will be more vulnerable to competition, compared to firms who have a more diverse portfolio of innovations. I also show that the size of a firm, in terms the total revenue, is positively correlated with the profit from innovation. This suggests that despite the extensive history of mergers in this industry over the past 30 years there remain further gains to be harvested through growth.

Determining the net effect of a firm's innovation on the other players in the market can have important policy implications. For example, an estimate of the net effect of one firms' investment in innovation on others could help assess whether there is over-investment or under-investment in R&D. For such an assessment, we need to compare social and private rates of return to R&D. The conventional wisdom is that if product market rivalry effects dominate technology spillovers, then there is under-investment in R&D from a welfare perspective (Bloom et al., 2013). Other possible uses for this model include the ability to predict how mergers between firms will affect innovation; how changes in the cost of trials will affect innovation; and how changes in prices would affect investment in innovation.

The rest of the paper is organized as following: Section 2 introduce a discrete choice model of incomplete information, which I will use to explain firms decisions on innovation. In Section 3, I show how this model can be estimated, using suitable data. I give a brief description of pharmaceutical industry and the process for drug development in Section 4. Section 5 details the data used for estimation of the model. Section 6 presents the result of the estimation.

2 Model

Here I introduce a game in which each player simultaneously chooses one action from a finite and discrete set of possible decisions to model firms' decisions on innovation. I use $i \in \mathbb{I} = \{1, ..., I\}$ to index players. Each player simultaneously chooses a single action y_i from a set $\mathbb{Y} = \{0, .., J\}$ in each market. A player's payoff depends on its competitors' actions. I use $-i$ to show all of player i's competitors and y_{-i} to show their actions in each market.

A firm's action in each market is based on two types of state variables.

First, a vector of state variables $x_i \in X$. These are common knowledge to all players and the econometrician. Some of these variables are market-specific and some of them are both market-specific and firm-specific. Second, players' private information denoted by $\varepsilon_i(y_i)$. This private information can, for example, include the firm's cost of operations in each market or its marketing or distribution capacity. Although this private information is not known to competitors, they can form beliefs about its realization. I also assume that all players and the econometrician know its cumulative distribution. Additionally, I assume that players' private information sets are independent.

Given all these variables, we can show player i's payoff from choosing y_i as $\pi_i(y_i, y_{-i}, x_i, \varepsilon_i(y_i))$. In this paper the firms' actions are their level of innovation in each market. So these actions are naturally ordered. In such cases an ordered-response model is an appropriate option for defining players' payoffs (Marcoux, 2019; Aradillas-López and Gandhi, 2016; Bresnahan and Reiss, 1991). I impose some restrictions on the payoff function to ensure that it is globally concave in y_i and s_i. I assume that $\varepsilon_i(y_i)) = \varepsilon_i$ and that the payoff function follows the following form:

$$\pi_i(y_i, y_{-i}, x_i, \varepsilon_i) = y_i[\zeta_i(y_{-i}, s_i) + \varepsilon_i] - \bar{c}(y_i). \tag{1}$$

We can interpret $\bar{c}_i(y_i)$ as part of the cost that is choice specific and not visible to the econometrician. This variable may be visible for the other players. So, we can perceive them as choice-specific unobservables. Here $y_i[\zeta_i(y_{-i}, x_i) + \varepsilon_i]$ is capturing the rest of the cost and the revenue. This part of the payoff is a function of state variables and other players' decisions, which means that it can capture the strategic interaction between firms.

I show the conditional choice probability (CCP) of player i choosing y_i at a given realization of the common-knowledge state variables x by $P_i(y_i|x)$. Note that the CCP of a firm is a function of the state variables of rival firms via their choices. So here $x = \{x_1, ..., x_I\}$ is a vector of all the players' state variables. We show the conditional choice probability (CCP) of a firm's competitors as $P_{-i}(y_{-i}|x)$, and define the expected revenue of the index function $\zeta_i(y_{-i}, x)$ as:

$$\zeta_i^p(x) \equiv \sum_{y_{-i}} P_{-i}(y_{-i}|x)\zeta_i(y_{-i}, x).$$

Thus we can write the expected profit of firm i as:

$$\pi_i^p(y_i, x, \varepsilon_i) = y_i[\zeta_i^p(x) + \varepsilon_i] - \bar{c}(y_i). \tag{2}$$

We define the marginal value of choice specific unobservables as $c(j) \equiv \bar{c}(j+1) - \bar{c}(j)$. Given this variable and Equation 2, we can see that player i

makes choices as follow:

$$\begin{cases} y_i = 0 & \text{if } \zeta_i^p(x) + \varepsilon_i \leq c(1) \\ y_i = j \ (0 < j < J) & \text{if } c(j) < \zeta_i^p(x) + \varepsilon_i \leq c(j+1) \\ y_i = J & \text{if } c(J) < \zeta_i^p(x) + \varepsilon_i \end{cases}$$

I denote the cumulative distribution of the private function variable by $\Lambda(e)$. I assume that this variable follows a logistic distribution, so that $\Lambda(e) = \frac{\exp(e)}{1+\exp(e)}$. As we can see, the vector of values $c = \{c(1), ..., c(J)\}$ acts as a set of thresholds in this model. We treat them as parameters to be estimated. Given this distribution, the CCPs should have the following form:

$$P_i(j|x;c) = \begin{cases} \Lambda(c(1) - \zeta_i^p(x)) & \text{if } j = 0 \\ \Lambda(c(j+1) - \zeta_i^p(x)) - \Lambda(c(j) - \zeta_i^p(x)) & \text{if } 0 < j < J \\ 1 - \Lambda(c(J) - \zeta_i^p(x)) & \text{if } j = J \end{cases} \tag{3}$$

If we show the right-hand side of Equation 3 by $\varphi_i(j, x, P_{-i}; c)$, the pure strategy Bayesian Nash Equilibrium (BNE) of the game will be a vector of CCPs which satisfy the following equations:

$$P_i(j|x;c) = \varphi_i(j, x, P_{-i}; c)$$

for any $y_i \in \mathbb{Y}$ and $i \in \mathbb{I}$. Therefore a BNE of this game is a fixed point of the best response mapping, such that each player's beliefs are consistent with their competitors'.

3 Estimation

Our main objective is to estimate the index function $\zeta_i(y_{-i}, x)$ and estimate firms' response to their competitors' level of innovation. To avoid the problems that a relatively small sample size can impose on estimating $\zeta_i(y_{-i}, x)$ non-parametrically and to make the interpretation of the results more straightforward, I use the following parametric specification for the index function:

$$\zeta_i(y_{-i}, x; \theta_i) = x'\beta + \delta_i \sum_{n \neq i} y_n, \tag{4}$$

where $\theta_i = [\beta', \delta_i]'$. The firm plays this game in many different markets. I index each market by m and show the number of all the market where the game is repeated with M. So the data available to the econometrician can be

summarized as: $y_{im}, x_{im} : m = 1, ..., M$. We can thus write the conditional choice probability of player i in market m as:

$$P(j|x_m; \theta_i, c) = \varphi(j, x_m, P_{-i}; \theta_i, c). \tag{5}$$

One can use this equation and the maximum likelihood method to estimate θ_i. But this can be computationally cumbersome, since that requires one to calculate the equilibrium solution in each step of maximization, making the estimation process resource intensive and time consuming.

However, we can estimate CCPs directly from the data. I show these estimated values by $\hat{P}_i(j|x_m)$. If we substitute these estimation in the right hand side of Equation 5, we do not need to find the BNE equilibrium in every step, rendering the estimation of the model much simpler. Therefore I use the pseudo maximum likelihood method to the estimate θ_i in this paper (Tamer, 2003). Using such a method means I estimate the model in two steps: first, I estimate the reduced form CCPs directly from the data; and second, I use the estimated CCPs to estimate the payoff parameters.

3.1 CCP Estimation

I use a parametric approximation to recover CCPs directly from the data. More precisely, I use a flexible ordered logit to parameterize an estimator and use the Expectation-Maximization (EM) algorithm to estimate the parameters of the estimator. Let $h(x; \phi)$ be a simple first-order polynomial function of the state variable x_{im} with a vector of parameters ϕ:

$$h(x_{im}; \phi) = x'_{im}\phi.$$

I also define a vector of threshold parameters $\eta = \{\eta(1), ..., \eta(J)\}$, such that the reduced-form choice probability of player i with state variable x_{im}, choosing option $y_i = j$ will be

$$P(j|x_{im}; \phi, \eta) = \begin{cases} \Lambda(\eta(1) - h(x_{im}, \phi)), & \text{if } j = 0 \\ \Lambda(\eta(j) - h(x_{im}, \phi)) - \Lambda(\eta(j-1) - h(x_{im}, \phi)), & \text{if } 0 < j < J \\ 1 - \Lambda(\eta(J) - h(x_{im}, \phi)), & \text{if } j = J \end{cases}$$

where $\Lambda(e)$ is the logit function. Given this probability function and a vector of observed choices as $y = \{y_1, ..., y_I\}$, we can write the likelihood function for the data as follows:

$$L(y|x) = \prod_{m=1}^{M} \prod_{i=1}^{I} \prod_{j=0}^{J} P(j|x_{im}; \phi, \eta)^{1\{y_{im}=j\}}.$$

Using maximum likelihood, we can estimate $\hat{\phi}$ and $\hat{\eta}$ from the data. As we can see, the model used here is similar to the model described in Section 2, without the interaction terms for different firms. This means that the estimated parameters in this section will not have any economic meaning, though we can still use them to consistently approximate CCPs. To do that, we substitute the estimated parameters into the estimator and calculate the approximated value of CCPs as follow:

$$\hat{P}_i(y_i|x_{im}) \equiv P(y_i|x_{im}; \hat{\phi}, \hat{\eta}).$$

After estimating the reduced form CCPs directly from data, we can start estimating the payoff parameters.

3.2 Estimation of the payoff parameters

Given the estimated $\hat{P}_i(y_i|x)$, we can calculate the expected values of the index function as following:

$$\zeta^{\hat{P}}(x; \theta_i) = x_i'\beta + \delta_i \sum_{n \neq i} \sum_{j=0}^{J} \hat{P}_n(j|x) j. \tag{6}$$

Therefore the conditional choice probability of player i choosing $y_i = j$ in market m will be:

$$P(j|x_m; \theta_i, c) = \begin{cases} \Lambda(c(1) - \zeta_i^{\hat{p}}(x_m; \theta_i)), & \text{if } j = 0 \\ \Lambda(c_i(j) - \zeta_i^{\hat{p}}(x_m; \theta_i)) - \Lambda(c_i(j-1) - \zeta_i^{\hat{p}}(x_m; \theta_i)), & \text{if } 0 < j < J \\ 1 - \Lambda(c_i(J-1) - \zeta_i^{\hat{p}}(x_m; \theta_i)), & \text{if } j = J \end{cases}$$

We can use these probabilities to define the maximum likelihood of the observed data as follows:

$$L(y|x) = \prod_{m=1}^{M} \prod_{i=1}^{I} \prod_{j=0}^{J} P(j|x_m; \theta_i, c)^{1\{y_{im}=j\}}.$$

We can maximize this likelihood function with respect to its parameters to estimate $\hat{\theta}_i$ and $\hat{c}$.

3.3 Identification

Here I briefly summarize the identification argument for estimating this model. We want to know that θ_i are uniquely identifiable from the available

data set. Marcoux (2019) presents an identification argument for a similar model. The identification argument of Marcoux uses variation in some player-specific regressors excluded from competitors' payoffs to estimate the parameters of the model. This is similar to many identification arguments available in the literature. The paper argues that given a vector of exogenous variables $z_{im} \subseteq x_{im}$ which shift a players' payoff without affecting its competitors' decisions directly, one can recover the parameters of the model uniquely.

The difference between the model presented in this paper and the model in Marcoux (2019) is that he could not observe a variable satisfying the exclusion restriction. So he used a predetermined outcome, realized before the start of the game, to estimate a market-specific and firm-specific unobservable. He then used the estimated unobservable as a variable satisfying the exclusion restriction to make the estimation of the model viable. However, in this paper, I can directly observe a variable that satisfies the execution restriction. So the estimation of the model will be more straightforward.

We should keep in mind that the empirical game presented in this paper may have multiple equilibria, which can make the estimation of the parameters more complicated. To avoid this problem, I assume that each player in the game uses the same equilibrium strategy when equilibria exist. This is a common assumption in the literature for similar situations (Aguirregabiria and Mira, 2007; Bajari et al., 2010; Aradillas-Lopez, 2012). This assumption means that, even though the model allows for multiple equilibria, I am forcing a unique equilibrium through the assumption of symmetric strategies.

4 The Pharmaceutical Industry

The innovative pharmaceutical industry is not only important to the economy, but intimately touches the lives of almost everyone in the world. The industry is complex and sophisticated, and operates in a highly regulated environment. The large pharmaceutical firms that are the subject of this paper engage in several core activities: they develop, manufacture and market new drugs. These activities combine both fierce competition and the exercise of monopoly power. The companies compete aggressively to advance new drugs to the market, but once approved, price competition is typically quite limited. The price sensitivity of patients is mitigated by the presence of insurance; and the physicians who prescribe drugs are obliged to prescribe the best drug for their patient's health, which does not normally involved too close a consultation about price. The key competitive advantage of a firm is therefore in having patented drugs that treat some patients better than any

other therapy. This means that innovation is in many ways the main area of competition in the pharmaceutical industry.

Innovation, of course, is itself tremendously complex: launching a new drug into the market is both lengthy and very expensive. The process of bringing a new drug to market typically involves multiple steps. Generally, basic science often done in universities elucidates interesting targets, for example a protein to be blocked. This prompts a search for possible molecules that may address the target. Once the bench science identifies feasible molecules, they may be tested in the lab and are eventually trialed in animals. These initial steps are not very expensive but they are almost always unsuccessful. In many cases, these initial steps are performed by a university spin-off, a small biotech. If the animal trials are successful, additional funding will be sought for further chemical work, to refine the drug, and following regulatory approval, Phase 1 tests for safety in healthy humans are performed. Phase 1 trials cost an average of about $25m per drug, and about 40% of drugs fail at this stage. (All numbers on clinical trial costs are taken from (DiMasi et al., 2016).)

If successful in Phase 1, the drug may be advanced to Phase 2 , to see if it has the desired effects in patients with the disease or condition it is supposed to treat. Phase 2 is also an opportunity to determine how much of the drug is needed. Phase 2 clinical trials are typically considerably more costly because it is necessary to find the right patients and to control carefully how the drug is used over a longer period of time. In many cases, there are multiple Phase 2 trials for a single drugs. Phase 2 trials cost an average of about $57m per drug, and about 65% of drugs entering Phase 2 fail at this stage.

Successful drugs then may advance to Phase 3 trials, which tend to be longer and have a larger number of patients, to identify less common adverse effects. Usually the Phase 3 trials provide the main evidence required by regulators to permit the drug to be sold on the market. The price tag increases again, averaging about $255m per drug, and about 39% of drugs entering Phase 3 fail at this stage.

Finally the innovator submits the drug for regulatory approval. In the US, about 10% of drugs submitted are not approved, which means that there is only about an 11% rate of successes for drugs starting Phase 1 to advance to regulatory approval. The timelines are quite long, with the average successful drug taking about 10 years to go from the start of Phase 1 to approval, and the overall costs very substantial. One widely used estimate places the cost per new drug at around $2.6bn per drug, after accounting for the costs of failures and the cost of capital (DiMasi et al., 2016). Most of this cost is attributable to the clinical trials.

Because Phase 2 and 3 clinical trials are so costly, small biotechs cannot

usually obtain the financing to advance the drug to the point of approval, and instead aim to sell the compound or the entire company to a "big pharma" firm – such as the 20 firms that form the data for the present study – that has the deep pockets and expertise in capital allocation. If a big pharma firm does a Phase 1 trial, it is usually because that firm advanced the molecule through its own bench science. In such a case, we could say that the firm was truly "innovating" in the market as opposed to buying its way in.

Once a firm has an approved drug, that drug will effectively compete only in the market for a given disease. Not surprisingly, we see that firms often specialize to some extent in their fields of operation. For example, Roche has a focus on oncology. Table 1 shows the Herfindahl index (Hf) across disease areas for each of the 20 firms studied here. Note that this is a measure of concentration by the firms into particular therapeutic focus, not any kind of competition measure in this situation. More specifically, if $s_{im} = \frac{y_{im}}{\sum_m y_{im}}$ shows the proportion of firm i's clinical trials in market m, Hf for each firm is defined as: $Hf_i = \sum_m s_{im}^2$. This table also shows the size of each firm in term of global revenues in 2017. The financial data for each firm is available in their annual financial reports. Also, the last 5 columns of the table shows in how many markets each firm made each of the choices. For example, $Y_0 = 37$ for Roche means this firm made the choice $y_{im} = 0$ in 37 of the studied market. I provide more details about the definition of these choices in the next section.

5 Data

Since I am trying to investigate big pharmaceutical companies' decisions about innovation and how their actions affect their rivals behavior in a market, the number of Phase I clinical trials is a natural choice for a proxy for innovation. Given that these trials are so expensive, firms would only invest if they highly value the inventions embodied in those drugs. Therefore we can see them as a key stage in innovation competition between big pharmaceutical companies.

I used IMS R&D Focus as my primary source for information on drug development. This data set is widely used by industry to help understand the competitive environment. The records in this data set are drug projects. Each drug can target multiple indications and several pharmaceutical firms could be involved in its development. This data set includes all the known drug projects from the mid-1980s to the present, regardless of their success or failure in clinical trials or pre-clinical studies. Since it takes, on average, a decade to bring a new drug to the market, I focused on the number of

Players	*Revenue*	Hf	Y_0	Y_1	Y_2	Y_3	Y_4
Johnson & Johnson	71.9	0.012	49	45	70	29	0
Roche	55	0.014	37	39	42	31	44
Pfizer	52.8	0.012	32	23	41	46	51
Novartis	49.4	0.015	66	34	42	32	19
Bayer	42	0.016	82	35	29	44	3
Sanofi	41.7	0.012	48	44	61	38	2
Merck & Co	39.8	0.013	32	37	58	49	17
GlaxoSmithKline	37.7	0.012	36	36	45	57	19
AbbVie	25.6	0.015	62	42	42	41	6
Amgen	23	0.015	74	33	42	37	7
AstraZeneca	23	0.012	38	39	28	44	44
Lilly	21.2	0.014	64	22	40	42	25
Boehringer Ingelheim	20.1	0.012	62	38	64	29	0
Bristol-Myers Squibb	19.4	0.014	61	32	45	41	14
Takeda	17	0.013	65	28	40	57	3
Allergan	14.6	0.014	74	78	40	1	0
Astellas	12.9	0.014	48	49	37	53	6
Otsuka	10.6	0.017	64	80	15	34	0
Daiichi Sankyo	9.3	0.015	50	62	35	44	2
Eisai	5.2	0.012	61	61	63	8	0

Table 1: The specification of the players in this model. Revenue is in $US billions.

Phase 1 clinical trials between 2008 to 2017 as the measure of innovation. As mentioned before, some drugs have multiple clinical trials at each stage. Therefore, some of the projects in this data set have multiple recorded Phase 1 clinical trials in different time periods. In those cases, I counted them only if the *first* record of Phase 1 clinical trials for that drug happened during the relevant time period.

The next step is to define the market for these drugs. I chose each disease group defined by the Global Burden of Disease (GBD) study as a separate market for the drugs (GBD Collaborative Network, 2017). The Global Burden of Disease Study (GBD) is a comprehensive worldwide observational epidemiological study that describes mortality and morbidity from major causes of health lost. I limited causes to those for which there is a plausible pharmacological intervention (excluding categories for different types of injuries). Most of the profit from developing drugs comes from their sale in wealthy countries. Therefore I used the total burden of disease in countries categorized as wealthy in the GBD study. The burden of disease is measured as disability-adjusted life-years (DALYs), and we can use them as a proxy for the potential market size. I denote this variable by h in this paper. DALYs, as measured by the GBD, include both years of life lost to disease and years lived with disability. In the jargon of GBD, "disability" indicates a reduction in health. For example, chronic pain, depression, or any loss of function would be disabilities. The GBD uses weights to for different types of disability, with those considered more serious having a larger weight.

This market definition is useful only if I can connect each drug project in IMS database to the corresponding diseases in the GBD study. All of the projects in the IMS database have at least one Anatomical Therapeutic Classification (ATC) and some of the projects at the later stage of development have a CAS Registry Number. On the other hand, most of the causes in GBD are mapped to the International Classification of Diseases (ICD-10). Using the DrugCentral database, which is a comprehensive drug information resource for approved drugs, I map ATC codes and CAS Registry Numbers in IMS data set to the ICD-10 codes. I further enhance this mapping using MIA, an open source website with mappings between ICD-10 codes and ATC codes. Given a correspondence between ATC and ICD-10, I can connect each drug project in the IMS database to the causes in GBD.

Excluding the injury-related categories, I had 263 causes from GBD, 256 of which mapped to the ICD-10 codes. I identified 4833 drug projects in the IMS data that had their first Phase I clinical trial between 2008 and 2017. Using the mapping protocol described above, I connected 4619 of those projects to 193 causes in GBD. 1400 (%33) of the mapped projects were undertaken by one of the 20 large pharmaceutical firms in this study

Choices (y)	Number of Clinical Trials (CT)	Frequency
0	$CT = 0$	1105
1	$1 \leq CT < 4$	857
2	$4 \leq CT < 12$	879
3	$12 \leq CT < 33$	757
4	$33 \leq CT$	262

Table 2: Definition of choices for the model.

(or their subsidiaries). I chose the top 20 pharmaceutical firms with highest number of drug in pipeline at 2017 as the key players in this paper (Lloyd et al., 2017).

I used a log transformation of the number of phase I clinical trials by each firm in different markets (CT_{im}) to define the choice set. More specifically, to have a discrete set of choices, I rounded $1 + CT_{im}$ to the nearest integer and used it as the variable y_{im} in the model. Only 9 out of 3860 of these choices had a value bigger that 4. I changed their values into 4 to eliminate the need to try to estimate this infrequent outcome. The exact definition of those choices and their frequency in the data is summarized in Table 2.

It is common to use firms' incumbency status as the player-specific and market-specific variable that satisfies the exclusion restriction needed for identification. In similar spirit, I used each companies' number of Phase 1 clinical trials in each market in the past as such a variable. More precisely, if we denote the number of Phase 1 clinical trials between 1993 to 2007 by $\bar{CT}_{im}$, the exclusion variable is defined as: $z_{im} = \ln(1 + \bar{CT}_{im})$.

Markets themselves have differing levels of innovation, with some markets attracting many competitive entrants and some few. So we can imagine some market specific characteristic that affects the choices all firms in a market. A technological breakthrough can be an example of this kind of characteristic. The sequential nature of drug development can help us to control for such an unobservable. I use the total number of pre-clinical studies during the considered time period for this purpose. We can imagine any factor, which makes a market more attractive to all of the the players, would also encourage

pre-clinical studies in that market as well. I denote this explanatory variable by μ in the following sections.

Another possible factor affecting players' payoffs is their size. We use the revenue of each firm as a measure of its size r. This completes the list of the variables used in this paper. To summarize, we can write: $x = \{h, \mu, z, r\}$. To be consistent with our definition of y and z, we use the logarithmic transformation of variables h, μ and r for the rest of the paper.

6 Results

First, I ignore the heterogeneity between firms to try estimate the average effect of their decision for innovation on each other. In this case we have $\delta_i = \delta$ for all of the players. We can see the estimated coefficients of this model in Table 3. As we can see the δ is positive and significant. This indicated that, on average, the spillover effect dominates the competition effect for these firms. They compete with each other on drug sale, but they also learn from each others' failures and successes in working on different molecules to develop new drugs for diseases. This results show that on average the positive effect they have on each others in the research field dominates the negative effect they may have on each others investment through rivalry in the market following approval. We also see that the coefficient on health lost (h) is not significant, though this is perhaps not surprising since I employed the explanatory variable μ that can effectively control for any market specific heterogeneity. Indeed, it is straightforward to show that the effect of h on μ is positive and significant.

Notably, the coefficient for the size of the firms (r) is positive and significant in Table 3. However, the meaning is unclear since by assuming a constant δ, we could be forcing r to capture all the heterogeneity between firms. So the next step is to write δ_i as a function of the firms' characteristics and to see whether that changes the estimated parameters. I specifically assume that the interaction term for each firm can be function of its Herfindahl index (Hf): firms with smaller Hf are concentrating their resources in fewer markets, which can make them more vulnerable to competition. Therefore I assume the following functional form for δ_i:

$$\delta_i = \delta_0 + \delta_1(Hf).$$

As long as we have variation on Hf and P_{-i} separately, all of these variables can be estimated. In fact the Table 4 shows the result of estimating this version of the model. As we can see in this table, δ_1 is negative and significant. This suggests that firms who concentrate their resources into

variable	Coefficients	[0.025	0.975]
h	-0.01	-0.04	0.01
μ	0.37	0.21	0.53
z	1.39	1.28	1.50
r	0.20	0.08	0.32
δ_0	0.07	0.05	0.08
c_0	4.58	3.78	5.38
c_1	7.35	6.51	8.18
c_2	10.06	9.21	10.91
c_3	13.03	12.16	13.90

Table 3: Constant δ for all firms.

innovating in fewer markets are less well equipped to deal with competition. For consistency, I used the logarithmic transformation of the Herfindahl index for the estimation. Considering that this index is between zero and one, the negative interception (δ_0) is not surprising.

We can also estimate δ_i nonparametricly for each firm. This can make the estimation of the coefficients less accurate, but we can obtain a more specific estimation of δ for each firms and their ability to deal with competition. We can see all the coefficients (except δ) of this estimation in Table 5. As we can see here, the results are in general agreement with the previous estimates.

I also reported the results of nonparametricestimation of δ_i in Table 6. These variables can in principle be used to simulate the effect of a firms' exit or simulation of a merger, in which having a firm specific estimation of δ_i can be beneficial.

6.1 Alternative definition of market

In this section I try to check the robustness of my results by trying a different definition for drugs market. In previous section I assumed that each causes in GBD study is a distinguished market for the drugs and firms compete within each of those markets. An alternative way would be defining market as each ATC code in the IMS data, rather than using the GBD data.

I chose the 3-digit ATC as separate market, meaning if a drug was reported in more detail categories, I only count it in its parent group. With this approach, I have more markets (270), which means I observe fewer trials for each firm in each market. This can decrease the accuracy of our estima-

variable	Coefficients	[0.025	0.975]
h	-0.01	-0.04	0.01
μ	0.36	0.19	0.52
z	1.35	1.24	1.46
r	0.19	0.07	0.31
δ_0	-0.05	-0.12	0.02
δ_1	-0.03	-0.04	-0.01
c_0	4.49	3.69	5.29
c_1	7.26	6.43	8.10
c_2	9.98	9.13	10.83
c_3	12.96	12.09	13.84

Table 4: δ_i as a function of the firms' characteristics.

variable	Coefficients	[0.025	0.975]
h	-0.024	-0.051	0.002
μ	0.087	-0.067	0.242
z	0.996	0.849	1.142
r	-0.048	-0.289	0.194
c_0	2.838	1.806	3.870
c_1	5.774	4.711	6.837
c_2	8.937	7.866	10.007
c_3	12.857	11.775	13.938

Table 5: coefficients model with Firm specific δ_i.

Firms	*Revenue*	δ_i	[0.025	0.975]
Johnson & Johnson	71.9	0.117	0.099	0.136
Roche	55	0.188	0.166	0.209
Pfizer	52.8	0.205	0.181	0.229
Novartis	49.4	0.126	0.106	0.146
Bayer	42	0.115	0.097	0.133
Sanofi	41.7	0.106	0.086	0.126
Merck & Co	39.8	0.158	0.138	0.178
GlaxoSmithKline	37.7	0.154	0.133	0.175
AbbVie	25.6	0.126	0.107	0.144
Amgen	23	0.12	0.101	0.138
AstraZeneca	23	0.194	0.173	0.215
Lilly	21.2	0.164	0.144	0.183
Boehringer Ingelheim	20.1	0.125	0.108	0.143
Bristol-Myers Squibb	19.4	0.134	0.115	0.154
Takeda	17	0.13	0.111	0.149
Allergan	14.6	0.077	0.060	0.093
Astellas	12.9	0.145	0.126	0.164
Otsuka	10.6	0.112	0.094	0.129
Daiichi Sankyo	9.3	0.128	0.108	0.147
Eisai	5.2	0.093	0.074	0.113

Table 6: Firm specific δ_i.

variable	Coefficients	[0.025	0.975]
μ	0.80	0.66	0.94
z	1.00	0.82	1.17
r	0.30	0.14	0.47
δ_0	-0.06	-0.13	0.01
δ_1	-0.03	-0.06	-0.01
c_0	5.77	5.13	6.40
c_1	8.56	7.87	9.25
c_2	11.05	10.20	11.90

Table 7: δ_i as a function of the firms' characteristics for alternative definition of the market.

tion. I needed to decreases the number of thresholds from 4 to 3 in this case. But we would not need the mapping to GBD, which can help us to avoid any errors arising from improper correspondence mappings. The results are reported in Table 7 and we can see that it is in general agreement with our previous results.

7 Discussion

As we can see in table 6, for most of the firms the interaction term (δ_i) is positive and significant. This means that the spill over effect is dominating the competition effect for those firms. They learn from each other through out the development process of the drugs. It seems the value of this learning, in absolute term, is bigger than the negative effect of competition. As I mentioned in Section 1, the positive estimate of these terms can be interpret as over-investment in R&D from a welfare perspective.

The result also shows that the estimation of δ_1 is negative and significant. This means that if Hf increases, the probability that firms chose to have higher level of innovation decreases more with the presence of rivals in the markets. We know from definition that higher Hf means the firm has most of its innovation in fewer markets. Therefore we can conclude that firms are more vulnerable to competition if they concentrate their effort in fewer markets.

Additionally, we can see from the results that the coefficient of z is around one or slightly higher. We should keep in mind that I used logarithmic

transformation for all the variables. So estimating one for the coefficient of z means that the level of innovation for each firm in a market is linearly correlated with its experiences in that market. For example, if a firm already had twice as many innovation in a market compare to a rival, the probability that the former firm chooses a higher lever of innovation in the future is twice as likely as the later one.

The model estimated here also can be used to identify the key firms in the industry: those firms whose exit would reduce innovation the most (König et al., 2014). Due to the positive or negative effects firms have on each other, if a firm were to exit, the net impact on the industry's total is ambiguous. This paper provide the empirical framework for ranking the key firms in pharmaceutical industry in terms of their contribution to total innovation.

Additionally, the model estimated in this paper can be extended to investigate the effect of mergers on innovation. In most merger cases, the antitrust authority has tried to assess potential impacts on innovation but found little guidance in the economics literature (Igami and Uetake, 2019). Mergers in innovative industries represent an opportunity to kill competition and acquire talent. Beyond the trade-off between market power and efficiency, the merger's effect on other firms' innovation should be considered. Previous studies on the effect of mergers on innovation in pharmaceutical industry have numerous flaws. Most importantly, they are unable to address the endogeneity of merger decisions. Moreover, they ignore the effect of mergers on other firms in the market and their innovation. One can overcome this issue by using the estimated model in this paper to simulate the effect of a merger on innovation.

8 Conclusion

This paper presents a structural econometric model of "big pharma" companies' investments in innovation for different diseases, using data on clinical trials. This paper shows that, if firms concentrate their resources in fewer markets, there is an increased chance that the knowledge spillover effect dominates the competition effect. This paper has also shown that firms' size has a positive effect on the profitability of innovation.

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