Entry and Investment Decisions in the Pharmaceutical Industry

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Abstract

The pharmaceutical industry is different from most industries where entry has been studied as it involves a time intensive research process with most of the interesting dynamics and firm interactions occurring pre-launch. This paper asks the question: do firms respond to the actions of their competitors in the R&D stages? Measuring the impact of competition on firms' investment decisions has significant implications on the impact of a faster FDA approval process - something most pharmaceutical companies are pushing for. While a faster approval process incentivizes firms to invest in disease markets due to the quicker realization of profits it also intensifies competition. Which effect dominates depends on the degree of competition. To this end, I first estimate a dynamic entry and investment model while accounting for firm interactions and market heterogeneity using a panel dataset on firm entry and exit decisions at the research phase level in various markets. I then solve for the equilibrium firm responses under the counterfactual of a faster FDA approval process.

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1 Introduction

Pharmaceutical firms spend a significant portion of their time and investment in the research phase testing and proving the safety and efficacy of their drugs. The profits are realized only upon launch of the product, so drugs which fail part way through the process generate no revenues to offset the substantial costs accumulated over the development process. Finally, unlike most industries, even after significant investment and results the launch of a firm's product in a market is not certain. This is because the Food and Drug Administration (FDA), the regulatory authority that oversees the entire R&D testing, can approve or reject a firms petition to launch in the market. The outcome of this regulatory process is fairly uncertain with unpredictable review times.[1] Pharmaceutical firms view this process as delaying marketing of their new drugs and deterring innovation[2]. This effect is further exacerbated by the short remaining patent life of most drugs[3].

Many firms, investors and industry lobbyists have repeatedly called for a faster FDA approval process. However, it is unclear if this is necessarily beneficial for firms. From the perspective of a focal firm, an early launch is beneficial because 1) the firm gets more years on its patent to market the drug and 2) profits are realized sooner. However, the possibility of an early launch makes the market lucrative to other firms as well, potentially leading to a more crowded market reducing the focal firm's profits[4]. Thus, while a faster approval process can increase the NPV of profits, it can also intensify competition among firms leading to lower per-firm profits. Which effect dominates depends on the extent to which firms are impacted by competition. The theoretical literature does not provide a clear direction of this impact: on one hand competition can encourage innovation if the potential innovator is able to usurp market share from the incumbent with its new product but on the other hand the presence of competition can deter the incentive to innovate if the potential innovator is able to take only a share of the total industry profits[5].

Using observed data to empirically measure this impact is hard because observed market structure and innovation rates are equilibrium responses and hence co-determined. The ideal way to measure the impact of competition on innovation is by observing market structure change due to exogenous reasons. Empirical work that uses this strategy include Aghion

[1] Firms quote this uncertainty as a disclaimer in their forward-looking press release statements.

[2] For example "In recent years, Mr Pharma will complain, the FDA's approval process has become slower", Big Pharma's gripes about the FDA, Economist, July 2011 and "FDA approval of new products is deterring new investment in innovation," Medtronic chief rues US approval process, Oct 2011, Financial Times

[3] Grabowski and Kyle (2007) estimate that market exclusivity periods range from 10-15 years, compared to the 20-year patent term awarded

[4] This is similar to a lowering of the entry threshold described in Bresnahan and Reiss (1991)

[5] See Gilbert (2006) for a review of the theoretical and empirical literature on competition and innovation.

et al (2004) who use changes in market structure caused by government policy changes and MacDonald (1994) who uses changes in import policies. However, exogenous variation of market structure in most industries is scant. For example, Cockburn and Henderson (1995) using detailed investment data at the drug discovery level find that investment is weakly correlated across firms after controlling for technological opportunity. However, as they point out, this could be the case simply because observed investments are equilibrium responses. This calls for a structural model that endogenizes market structure and innovation taking into account industry-specific features (e.g. Goettler and Gordon 2011). I use both approaches to measure this impact, relying on the structural parameters to evaluate the counterfactual of a faster FDA approval process.

First, I exploit the unique feature of the pharmaceutical industry - the uncertainty of the FDA approval process – to measure if firms respond to competitors' states. While firms might know the average approval probabilities in expectation, the exact outcome of the FDA review process is uncertain, i.e. FDA approvals and rejections conditional on filing are fairly exogenous. Using this in a reduced form regression, I find evidence that firms respond to competitors' states: specifically a firm's probability to continue investment reduces if the firm's competitor received an FDA approval and increases if the competitor received an FDA rejection.

Second, I build a structural model that accounts for the endogeneity of market structure and innovation. Using a dataset on firm entry and investment decisions in Phase 3 clinical trials across different markets in the pharmaceutical industry, I estimate a structural model to measure the impact of competition on firms' continuation decisions. Closest in this regard is Goettler and Gordon (2011) who estimate a structural model that endogenizes innovation to evaluate the counterfactual if Intel would innovate more in the absence of AMD. Unlike their setting where the market structure is fixed at two firms, I observe varying market structures both within and across markets. Relatedly, Finger (2008) uses data on firms' R&D expenditures and their patenting activities to measure the impact of the government funded tax credit in the Chemicals Industry and Kryukov (2010) looks at firms' decisions to continue R&D investments in the category of Infection drugs to estimate the impact of policy interventions aimed at increasing the number of drugs. Unlike Kryukov (2010), I allow the duration a drug remains in research to be endogenous.

The structural model takes four main aspects of the pharmaceutical industry into account: the forward-looking behavior of firms, their strategic decision making, market heterogeneity and the uncertainty of the FDA approval process. As firms incur huge costs in the research phase which can take up to 10-12 years and as profits are realized only upon successful launch of the product, it is the forward-looking nature of firms that justifies investing large

amounts in the research phase. Thus it is important to account for dynamics to model this industry. Second, the model should be able to account for equilibrium responses of firms. For example, a firm may exit a market while in the research phase if it observes that one of its competitors has launched. This is because if the share of profit of the focal firm decreases with the number of launched firms it no longer justifies continued investments in the research phase. Third, one needs to account for the fact that some markets can be more lucrative than others by accommodating the presence of unobserved heterogeneity in markets. Lastly, the launch outcome is not determined by the firm but by the FDA review process. I thus estimate a dynamic model of oligopoly with permanent unobserved heterogeneity.

I estimate the model using the underlying approach outlined in Arcidiacono and Miller (2011) allowing for two types of markets. The estimates indicate a significant impact of competition on firms' investment decisions. I then simulate the effect of a faster FDA approval process by reducing the probability that a drug remains in-review but keeping overall approval and rejection rates the same. The results indicate that in this counterfactual, the increase in expected profits arising from the reduced time in-review dominates the decrease in profits due to competitive intensity although competition lowers per-firm profitability conditional on a launch.

Broadly this paper contributes to the literature on the pharmaceutical industry which has answered questions on topics related to the role of the physician and the patient (see Manchanda et al 2005 for a review), the effect of potential market size on pharmaceutical innovation (Acemoglu and Linn 2004) and questions surrounding health insurance markets (e.g. Einav et al 2013) to name a few.

The paper is organized as follows. Section 2 gives an overview of the pharmaceutical industry, describes the data and highlights a few empirical regularities in a reduced-form setting, Section 3 builds the structural model, Section 4 discusses the estimation strategy and Section 5 presents the results. Section 6 evaluates the counterfactual of a faster approval process to answer the question posed above and Section 7 concludes.

2 Industry Background and Data

Drug development is a time-intensive and expensive process. Firms vying to enter a market after discovery of a chemical compound have to perform pre-clinical, Phase I, Phase II and Phase III trials before they can launch their product. Getting to the final launch phase is a low probability event - for every 250 compounds that enter preclinical testing only 1 wins

FDA approval.[6]

Pre-clinical trials for the drug involve testing the compound on animals. Based on the findings firms may decide to file an Investigational New Drug filing with the FDA which can either approve or reject the filing. If approved, the drug has to pass successfully through three more phases – Phase I which involves testing on a small group of healthy individuals, Phase II which involves testing on a small group of patients with the disease to prove that the drug has the intended effects on the patients and Phase III which involves testing on a large-scale to establish safety and efficacy of the drug. Figure 1 illustrates the various phases a pharmaceutical firm needs to go through before final launch and the approximate time it takes to complete each phase.

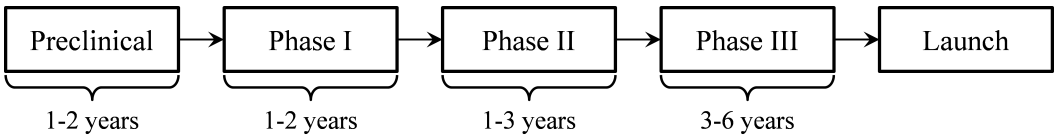


Figure 1: Pharmaceutical research and development process

To answer the questions posed in this paper we need firm actions in the R&D stages prior to a New Drug Application (NDA) as well as FDA-determined launch outcomes at the market-firm-year level. I focus on drug development efforts post-Phase 2 clinical trials. This is because Phase 3 is by far the most expensive of all four research phases (DiMasi et al 2003) and because these data are largely publicly available as the FDA requires that all drugs in controlled clinical investigation other than Phase 1 trials be registered on a publicly-available database. The dataset used in the paper comes from Adis R&D insight - an aggregator that collects this information across all firms and markets over time.

Specifically, an observation in the data consists of the date a firm entered Phase 3 clinical trials in a particular disease indication and the date if it exited, filed or launched. The data consists of a total of 294 disease indications[7] in the period 1995-2008. The pharmaceutical industry is characterized by four main features: forward-looking firms, heterogenous markets, uncertainty in FDA outcomes and strategic firms. I provide evidence of each of these characeteristics in the data below:

[6]Source: Pharmaceutical Research and Manufacturers of America citing data from the Tufts University Center for the Study of Drug Development

[7]To ease the computational burden I restrict the considered drugs to those affiliated with the top 15 firms by sales. I further consider only the first drug that a firm entered a market with (thus potentially ignoring complementarities within a market). This brings down the number of markets from 513 to 294.

Forward-looking firms

Firms spend an average of 4.6 years in Phase 3 clinical trials. Figure 2 shows the number of years spent in research by various firms across different markets. During this period the firm does not earn any profits. Investments are made in expectation of profits if and when a firm's drug launches in the market. This is clear evidence of firms' forward-looking behavior and warrants a model that takes these dynamics into account.

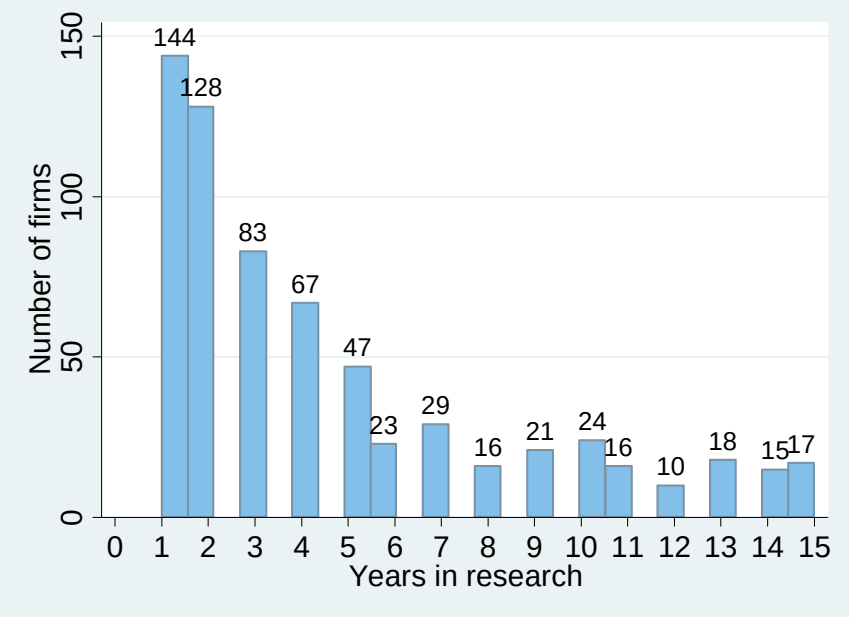


Figure 2: Distribution of years spent in research across all firms and markets

Heterogenous markets

The number of drugs in Phase 3 trials per market ranges from 1 to 10: the table below shows the distribution of number of drugs per market. 52% of markets have just 1 drug that has entered Phase 3 in that indication while few markets have more than 4 drugs that entered the market. This is an indication of substantial market-specific heterogeneity: some markets see more firms investing in them while others see relatively fewer firms[8].

This market-specific heterogeneity is also evidenced in the number of launched firms per market shown in Figure 3. The average number of launched firms in a market is 0.57 with 176 markets having no launched product during the time-span in the data, 88 markets having

[8]The data is left-truncated at the year 1995. This implies that I do not observe drugs which have launched pre-1995 and this will lead me to over-estimate the impact of competition. For example, the analysis will infer a firm's response to exit when there is 1 launched competitor while in reality there might exist 4 competitors. I plan to control for this by collecting information on launched drugs pre-1995 from FDA's Orange Book database.

1 firm that has launched successfully, 20 markets with 2 launched firms and 10 markets with greater than 3 launched firms.

The R&D investment data is further supplemented with market-specific descriptives such as prevalence and whether the indication disproportionately affects people of a specific age, race or gender. Lastly, data from MedTrack which tracks realized sales of launched products, provides a crude measure of the indication-specific market-size in dollar amounts. These figures are observed only conditional on launch - however, by averaging across all drugs and years of realized sales within a disease-indication this gives an approximate measure of the market potential specific to a given indication. Table 2 provides the summary statistics of these market descriptives.

No. of drugs per market	***No. of markets***	***% of markets***
1	152	52%
2	56	19%
3	35	12%
4	21	7%
5	8	3%
6	7	2%
7	4	1%
8	6	2%
9	2	1%
10	3	1%

Table 1: Number of drugs in research per market

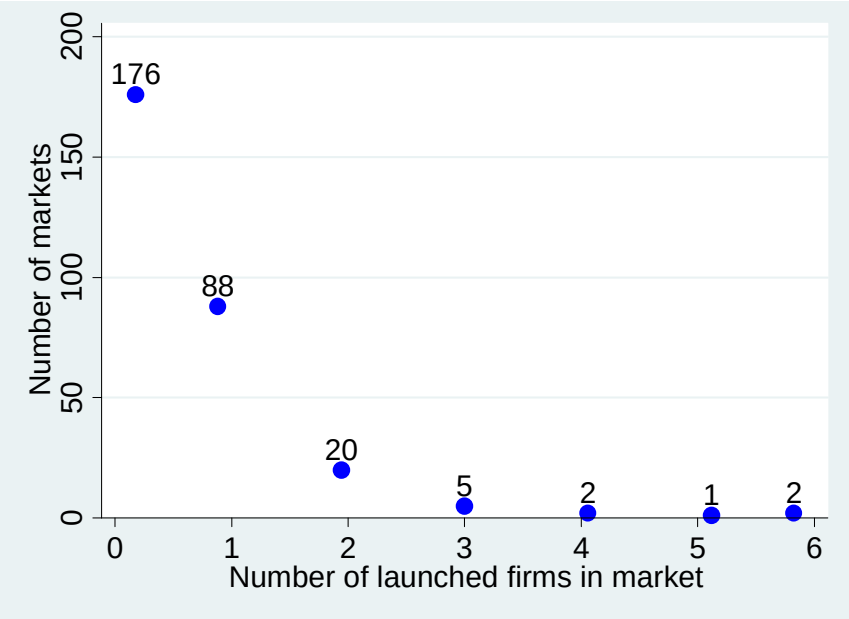


Figure 3: Number of launched firms per market

Table 2: Market Characterisitcs

	Mean	Std. Dev	Percentiles 10th	50th	90th	N Obs
Prevalence (per 10,000)	628	1,056	0.74	130	2,000	158
Varies with						
Age	0.25	0.43	0	0	1	215
Race	0.41	0.49	0	0	1	215
Gender	0.53	0.50	0	0	1	215
Market size ($ millions)	$ 468	$ 438	$ 41	$ 349	$ 1,054	213

Uncertain FDA Approval process

After entering Phase 3 clinical trials, a firm in a market can take one of three actions - continue investment (i.e. remain in Phase 3), exit the market or file for an NDA. After a firm files with the FDA, whether the firm's petition is approved, rejected or remains in further review is entirely determined by the FDA. The table below summarizes the transitions between phases across all drugs, markets and time. The second row of the table is indicative of firms' endogenous actions: 86.9% of the time an incumbent continues on in its R&D efforts, 7.6% of the time it files for an NDA and 5% of the time it decides to exit the market. The third row is indicative of the FDA determined exogenous outcomes: of those that are filed, 26.2% are approved, 2.3% are rejected by the FDA and 71.6% continue to remain in the filed

status. Both this and Figure 4 which shows the distribution of years spent in review across all firms in the data, indicate that 1) approval on filing is not guaranteed and 2) realization of the outcome is not always quick. Conditional on an outcome (approval/rejection) the average time spent in review is 1.49 years.

Table 3: Phase Transitions across all drugs, firms, market and years

	Not entered	**Entered P3**	**Filed NDA**	**Launched**	**Exited**	**N Obs**
Not entered	84.7%	15.3%	0%	0%	0%	3,912
Entered P3	0%	86.9%	7.6%	0.6%	5.0%	3,045
Filed NDA	0%	0%	71.6%	26.2%	2.3%	573
Launched	0%	0%	0%	100%	0%	1,213
Exited	0%	0%	0%	0%	100%	1,188

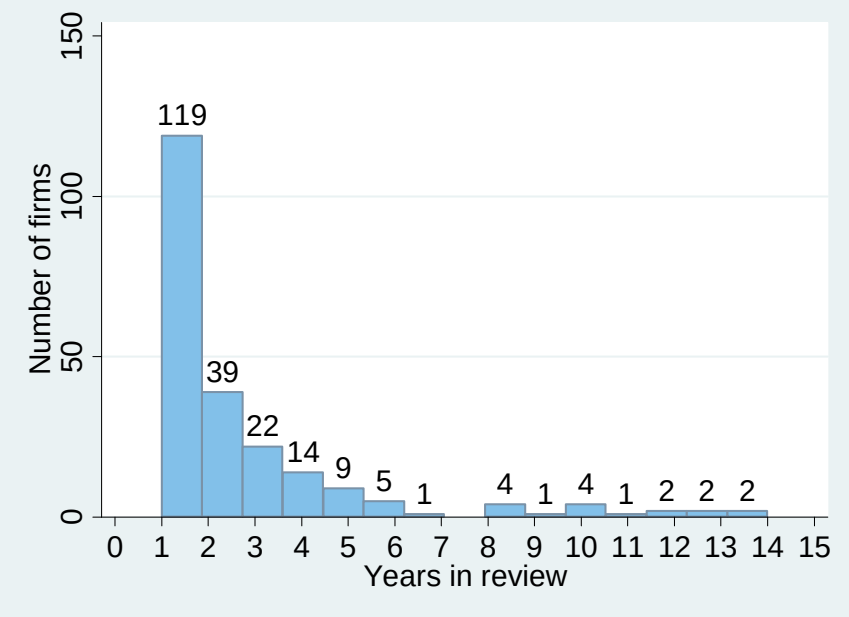


Figure 4: Distribution of Years in FDA review across all firms and markets

Strategic interactions between firms - Reduced form evidence

I now provide reduced-form evidence showing the impact of competitor's states on a firm's investment decisions. Table 4 regresses the decision to continue or exit on the firm's own state as well as the competitor's state controlling for market-, firm- and time- fixed effects. The first set of results under the column Endogenous actions show that a firm is more likely to continue investment if a competitor has exited the market and this probability increases as the number of competitors that have exited the market increases. The second column

includes the FDA determined outcomes of launches and rejections. The results indicate that a firm is less likely to continue investment in R&D when a competitor has launched successfully in the market with more competitors having an increasingly negative effect. The results also indicate that endogenous as well as FDA-determined exits have a similar effect on a firm's decision to continue investment.

Endogeneity concerns stem from two sources 1) firm-determined outcomes are equilibrium responses and 2) an omitted variable, such as a scientific discovery specific to a disease-market, can lead to biased estimates. Concerns related to (1) are mitigated by the regression on FDA-determined outcomes. To the extent that the firm files only if it expects a positive outcome, this can still be at best interpreted as a correlational regression. To overcome this concern, I turn to a structural model in Section 3 that explicitly endogenizes firm actions. Concerns related to (2) should lead us to underestimate the effect of competition leading to a conservative estimate. To see this, a market-time specific event, such as a scientific discovery that makes Phase 3 clinical trials easier for all firms, will likely cause us to see more launched firms in the market and more firms investing in R&D efforts. This will lead to a positive coefficient on the Number of competitors launched coefficient, while the estimated coefficient reported in Table 4 is significantly negative.

Table 5 shows a similar regression but on the decision to enter Phase 3 clinical trials or not. Here we see a negative impact of the number of exits and number of firms in research on the focal firm's decision to enter Phase 3 with the probability further declining as the number of competitors that have exited or are in research increases. Including the FDA-determined outcomes, we see that an FDA-determined exit reduces the probability of entry much more than an endogenously determined exit. Launched firms have an increasingly negative effect on a firm's decision to enter.

Table 4: Decision to continue or exit as a function of competitor's states

Continue/Exit	Endogenous actions		FDA outcomes	
	Coefficient	t-stat	Coefficient	t-stat
Number of competitors exited				
1	3.05	6.96	3.23	7.00
2	4.72	6.64	4.76	6.68
3	4.84	5.00	5.29	5.07
4	4.60	2.93	4.43	2.89
5	6.42	4.88	5.28	3.71
6	7.59	4.71	4.99	2.87
7	21.12	0.01	17.20	0.02
Number of competitors in research				
1	0.17	0.48	0.06	0.15
2	0.30	0.61	0.00	0.00
3	0.35	0.53	-0.26	-0.36
4	1.11	1.29	0.94	0.94
5	-0.63	-0.52	-1.74	-1.34
6	-1.71	-1.23	-3.05	-1.96
7	0.00	0.00	0.00	0.00
Number of competitors in filed status				
1	-0.62	-1.53	-0.72	-1.55
2	-1.25	-1.28	-0.53	-0.51
3	13.20	0.00	12.22	0.01
Number of competitors exited due to FDA				
1			3.21	2.71
Number of competitors launched				
1			-0.77	-1.42
2			-1.35	-1.66
3			-1.85	-1.81
4			-4.42	-2.62
5			9.00	0.00
6			-7.69	-3.40
Own state (Reference: Research Year>4)				
Research year 1	1.26	2.95	1.16	2.68
Research year 2	0.71	1.78	0.62	1.54
Research year 3	0.51	1.27	0.34	0.83
Research year 4	0.64	1.48	0.63	1.42
Fixed-effects	Market, Firm, Time			
Log likelihood	-233.88		-222.49	
N obs	1299		1299	

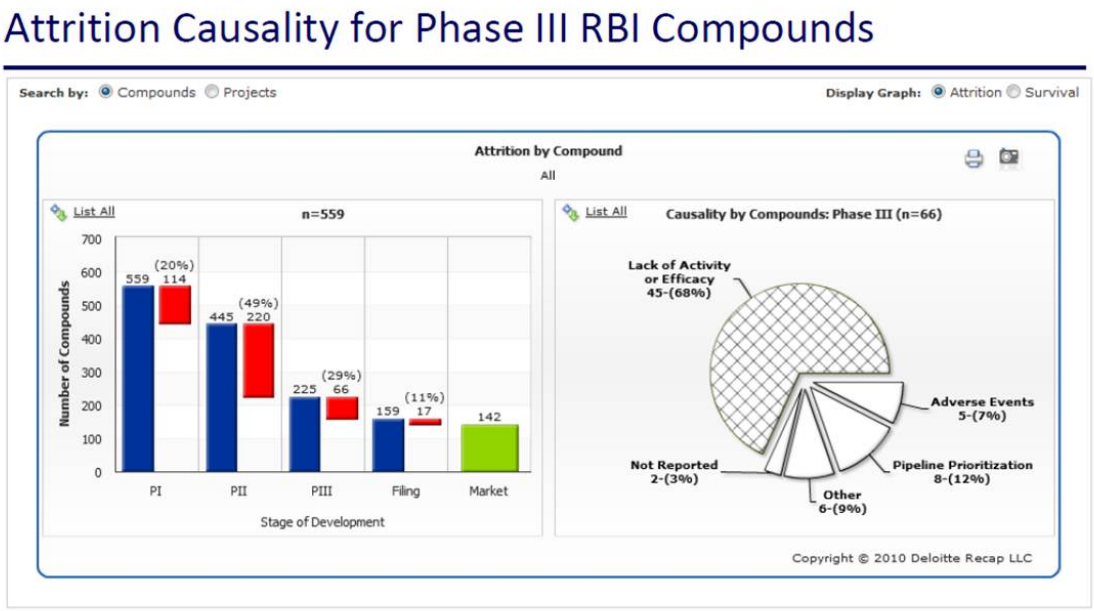
Table 5: Decision to enter Phase 3 or not as a function of competitor's states

Enter/Not enter	Endogenous actions		FDA outcomes	
	Coefficient	t-stat	Coefficient	t-stat
Number of competitors exited				
1	-1.33	-4.65	-1.35	-4.59
2	-1.64	-3.68	-1.84	-4.00
3	-2.75	-2.95	-2.96	-3.48
4	0.00	0.00	0.00	0.00
5	-3.14	-2.23	-3.32	-2.25
6	-4.14	-2.40	-3.88	-2.11
7	0.00	0.00	0.00	0.00
Number of competitors in research				
1	-0.61	-3.21	-1.18	-5.86
2	-1.51	-5.62	-2.30	-8.05
3	-1.75	-4.69	-2.52	-6.45
4	-1.60	-3.31	-2.73	-5.60
5	-2.64	-3.17	-3.32	-4.33
6	-2.12	-0.47	-2.75	-1.05
7	-1.21	-1.06	-2.76	-2.38
Number of competitors in filed status				
1	-0.45	-1.97	-1.03	-4.22
2	0.23	0.45	-0.42	-0.88
3	-13.17	-0.02	-12.24	-0.04
Number of competitors exited due to FDA				
1			-3.31	-5.72
Number of competitors launched				
1			-2.27	-7.48
2			-2.97	-6.64
3			-2.57	-3.88
4			-4.06	-3.96
5			-4.53	-3.23
6			0.00	0.00
Fixed-effects	Market, Firm, Time			
Log likelihood	-896.38		-839.32	
N obs	3874		3874	

Strategic interactions between firms - Anecdotal evidence

Figure 5 taken from Recap, a company that provides insights for the biopharmaceutical industry, sheds some light into the causal reasons why firms abandon their compounds in late-stage clinical trials. The figure shows that of the 66 compounds (out of 559 compounds in Recap's Bioportfolio Index which contains only biotech companies) that abandoned clinical trials in Phase 3, 12% state "Pipeline prioritization" as their reason for leaving Phase 3. This

includes market and competitive dynamics like market size and level of market saturation.



Source: "Is Biotech Beating Big Pharma on Approval Success Rates?", Deloitte Recap *LLC*, www.recap.com

Figure 5: Evidence suggesting competitive considerations account for 12% of Phase 3 clinical trials abandonment

While this provides preliminary evidence of the impact of competition on firm's decisions, I next develop a model that explicitly endogenizes innovation and market structure taking into account the specifics of the industry as described above.

3 Model

I now describe the model that governs a firm's decision to enter Phase 3 clinical trials or not; and conditional on entry to continue investment in these clinical trials, file for a NDA or exit the market. These decisions are influenced by 1) the structural parameters which include the cost to enter Phase 3 clinical trials, continuation costs of research and profitability by market type, 2) the firm's own state 3) the competitors' states and 4) privately observed shocks (e.g. adverse side-effects in clinical trials can cause the firm to exit). The payoff is positive only if a firm launches its product in the market. Payoffs in the investment stages reflect the cost of continuing research.

Outcomes which are not in the firm's control include Approval and Rejection by the FDA, i.e. once a firm has chosen to file for an NDA the outcome after this step is determined by the FDA.

I now briefly go over the reasons a firm can exit the market and explain how these are captured in the model. A firm can exit the market due to one of three reasons 1) adverse effects of the drug on the patient population that are discovered during research 2) pipeline prioritization arising from competitive considerations or 3) FDA rejection after the firm has filed for an NDA.

Adverse effects

If a firm's drug has adverse effects on its desired patient population, the firm will have to withdraw testing and exit the market. This effect is captured through the error term ε_{ex} present in the utility from exiting the market. A large positive shock captures the effect of an adverse event while a negative shock captures the effect of a windfall. Competitors are assumed to know these error shocks only in expectation.

Pipeline prioritization

This captures a firm's decision to endogenously exit or continue investment in the clinical trials as influenced by its competitors states and actions. This influence is captured through the state space in the firm's consideration - the extent of this influence is empirically estimated.

FDA rejection

A firm, when it is reasonably confident that it has all the data to justify a launch, submits the relevant documents to the FDA who then reviews them. Based on its review the FDA may reject the petition of the firm to launch in the market. I capture this as a probability pr_e associated with exit conditional on filing. These probabilities are directly inferred from the data, and conditional on filing are assumed to be exogenous.

3.1 States and State Transitions

The state space consists of those variables that are observed to the researcher x_t and those that are unobserved to the researcher s. Both variables are known to the firm. The unobserved state allows for market-specific heterogeneity. A market's type is assumed to be fixed over time, i.e. it cannot transition from one state to another. Firm i's observed state in period t is denoted by x_{it} where $x \in \{0, 1, 2, 3, 4, 5, \text{Exit}, \text{File}, \text{ExitFDA}, \text{Launch}\}$. 0

indicates that the firm has not yet entered the market, 1...5 denote the research year[9] the firm is in, Exit indicates the firm has exited the market, File indicates that the firm has filed for an NDA and is waiting to hear of an outcome from the FDA, ExitFDA indicates that the FDA rejected the firm's NDA while Launch indicates that the firm won FDA approval. Note that Exit, ExitFDA and Launch are all absorbing states, i.e. once a firm has reached this state it continues to remain in this state. Next I describe the state transitions that determines a firm's next period state given its current state and action.

If a firm has not yet entered Phase 3 in year t it can choose action d_{it} where $d \in \{\text{ne,e}\} \equiv \{\text{Not Enter, Enter}\}$. Its next period state is then given by

$$x_{it+1} = (x_{it} + 1) .1 (d_{it} = \text{e}) + 0.1 (d_{it} = \text{ne})$$

where $1(.)$ is the indicator function.

If a firm is an incumbent it can choose action d_{it} where $d \in \{\text{c,f,ex}\} \equiv \{\text{Continue,File,Exit}\}$. Its next period state is given by

$$x_{it+1} = \begin{array}{c} x_{it} + 1 \text{ if } d_{it} = \text{c} \\ \text{File if } d_{it} = \text{f} \\ \text{Exit if } d_{it} = \text{ex} \end{array}$$

Once a firm's state changes to File, its next period state is determined exogenously by the FDA, i.e.

$$x_{it+1} = \begin{array}{c} \text{Launch with probability } pr_l \\ \text{ExitFDA with probability } pr_e \\ \text{File with probability } pr_f = 1 - pr_l - pr_e \end{array}$$

where pr_l and pr_e are exogenous launch and exit probabilities directly informed by the data.

A firm's transition conditional on entry into Phase 3 is captured in the schematic below.

[9] to limit the state space, I assume that once a firm has reached state 5 it continues to remain in state 5 until it exits or files.

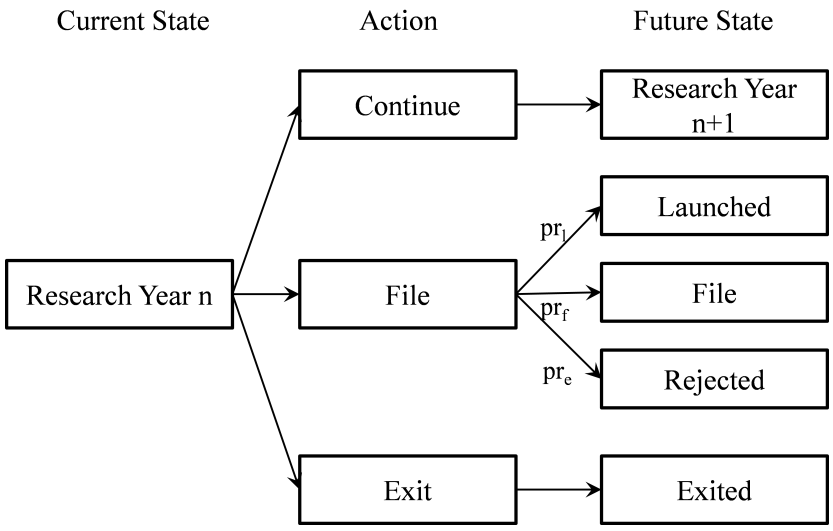


Figure 6: Schematic of a firm's transition from a research year to the next state

3.2 Per-period utility

I now specify the current-period payoffs associated with each possible action a firm can take. For an entrant with two possible choices, the per-period utility of staying out of the market and entering the market are given by Equations 1 and 2 respectively.

$$u_{ne} = 0 + \varepsilon_{ne} \tag{1}$$

$$u_e = -c_{enter} + \varepsilon_e \tag{2}$$

For an incumbent with three possible choices, the utility from continuing research, filing for an NDA and exiting the market are given by Equations 3-5.

$$u_c = -c_r + \varepsilon_c \tag{3}$$

$$u_f = -c_f + \varepsilon_f \tag{4}$$

$$u_{ex} = 0 + \varepsilon_{ex} \tag{5}$$

If the firm has reached the launch phase, it gets a profit which depends on the number of competitors who are also in the launch stage. I assume the following form of the profit function

$$u_l = \pi + \delta N \tag{6}$$

where N is the total number of competing firms in the launched state.

The structural parameters $\theta = \{c_{enter}, c_r, c_f, \pi, \delta\}$ consist of the costs c_{enter}, c_r, c_f associated with entering Phase 3, continuing research and filing respectively, π the profitability of a market and δ the impact of additional competitors on profits.

3.3 Value functions

The choice-specific value functions if a firm is a potential entrant can be given by the following equations:

$$V_{ne}(x_t, s) = u_{ne} + \beta \sum_{x_{t+1}=1}^{X} \text{Emax}_{\varepsilon'}\left(V_{ne}(x_{t+1}, s), V_e(x_{t+1}, s)\right).f_{ne}(x_{t+1}|x_t)$$

$$V_e(x_t, s) = u_e + \beta \sum_{x_{t+1}=1}^{X} \text{Emax}_{\varepsilon'}\left(V_c(x_{t+1}, s), V_f(x_{t+1}, s), V_{ex}(x_{t+1}, s)\right).f_e(x_{t+1}|x_t)$$

The summation is over all the possible states $\left(\dim \prod_{-i} |x_{-i,t+1}|\right)$ that all of firm i's competitors can be in, in the next time-period. The probability of each of these states occurring is given by $f_j(x_{t+1}|x_t)$ if j was the action chosen by i in period t. i's own state in the next period can be determined from the state transition equations described above.

The choice-specific value functions for an incumbent firm is given by the following equations:

$$V_c(x_t, s) = u_c + \beta \sum_{x_{t+1}=1}^{X} \text{Emax}_{\varepsilon'}\left(V_c(x_{t+1}, s), V_f(x_{t+1}, s), V_{ex}(x_{t+1}, s)\right).f_c(x_{t+1}|x_t)$$

$$V_f(x_t, s) = u_f + \beta \sum_{x_{t+1}=1}^{X} \left(pr_l.V_{lFDA}(x_{t+1}, s) + pr_e.V_{exFDA}(x_{t+1}, s) + pr_f.V_{fFDA}(x_{t+1}, s)\right).f_f(x_{t+1}|x_t)$$

$$V_{ex}(x_t, s) = 0$$

Once a firm has filed with the FDA the corresponding value functions are (Note: although these are subscripted for launch, file and rejection these are not choice-specific as these

outcomes are not determined by the firm)

$$V_l(x_t, s) = u_l(x_t, s) + \beta \sum_{x_{t+1}=1}^{X} V_l(x_{t+1}, s) f(x_{t+1}|x_t)$$

$$V_{fFDA}(x_t, s) = 0 + \beta \sum_{x_{t+1}=1}^{X} (pr_l.V_{lFDA}(x_{t+1}, s) + pr_e.V_{exFDA}(x_{t+1}, s) + pr_f.V_{fFDA}(x_{t+1}, s)).f(x_{t+1}|x_t)$$

$$V_{exFDA}(x_t, s) = 0$$

3.4 Equilibrium

Firms are assumed to be symmetric in their actions and their strategies are assumed to be Markov Perfect. A firm chooses that action that maximizes its value function conditional on the current state space and its expectation of other firms strategies.

$$V(x_t, s|d^*_{it}, d_{-i}) \geq V\left(x_t, s|d^{'}_{it}, d_{-i}\right)$$

4 Estimation

The parameters are recovered using the EM Algorithm described in Arcidiacono and Miller (2011). For estimation, if a market contains more than four incumbents, I use only the first four firms that entered the market[10]. I first specify the likelihood of the data and how to obtain the conditional choice probabilities (CCPs) from the data and then list the steps used in estimation.

4.1 Likelihood

Assuming the ε's follow a Type-1 i.i.d extreme-value distribution the choice-specific value functions for an incumbent can be written as

$$v_c(x_t, s; \theta) = -c_r + \beta \sum_{x_{t+1}=1}^{X} (\Gamma + ln[exp(v_c(x_{t+1}, s; \theta)) + exp(v_f(x_{t+1}, s; \theta)) + exp((v_{ex}(x_{t+1}, s; \theta)))]).f_c(x_{t+1}|x_t) \tag{7}$$

[10]This is for computational simplicity. I plan on performing robustness checks on this assumption.

$$v_f(x_t, s; \theta) = -c_f + \beta \sum_{x_{t+1}=1}^{X} \left(pr_l . V_{lFDA}(x_{t+1}, s; \theta) + pr_e . V_{exFDA}(x_{t+1}, s; \theta) + pr_f . V_{fFDA}(x_{t+1}, s; \theta)\right) . f(x_{t+1}|x_t) \tag{8}$$

$$v_{ex}(x_t, s; \theta) = 0 \tag{9}$$

where $v(.) = V(.) - \varepsilon$

We can further simplify the above by using the fact that exiting the market is a terminal action (Ellickson, Misra and Nair (2012), Arcidiacono and Miller (2012)). To see this, writing down the conditional choice probabilities associated with equations 7-9

$$p_c(x_t, s; \theta) = \frac{exp(v_c(x_t, s; \theta))}{exp(v_c(x_t, s; \theta)) + exp(v_c(x_t, s; \theta)) + exp(v_c(x_t, s; \theta))} \tag{10}$$

$$p_{ex}(x_t, s; \theta) = \frac{exp(v_{ex}(x_t, s; \theta))}{exp(v_c(x_t, s; \theta)) + exp(v_c(x_t, s; \theta)) + exp(v_c(x_t, s; \theta))} \tag{11}$$

Equation 7 can thus be re-written as

$$v_c(x_t, s; \theta) = -c_r + \beta \sum_{x_{t+1}=1}^{X} \left(\Gamma + ln \frac{[exp(v_{ex}(x_{t+1}, s; \theta))]}{p_{ex}(x_{t+1}, s; \theta)}\right) . f_c(x_{t+1}|x_t) \tag{12}$$

But $p_{ex}(x_t, s; \theta)$ is the conditional choice probability of exiting the market and can be estimated directly from the data. Replacing $p_{ex}(x_t, s; \theta)$ with $\hat{p}_{ex}(x_t, s)$, equation 13 simplifies to

$$v_c(x_t, s; \hat{p}, \theta) = -c_r + \beta \sum_{x_{t+1}=1}^{X} \left(\Gamma - ln(\hat{p}_{ex}(x_{t+1}, s))\right) . f_c(x_{t+1}|x_t) \tag{13}$$

which requires computation of only one-period ahead conditional choice probabilities.

Note that the same simplification cannot be applied to $v_f(x_t, s; \theta)$ because once the firm has filed with the FDA it no longer has a choice to make - all further decisions are made by the FDA. To compute this, I simulate out V_{lFDA} and V_{fFDA} using $\hat{p}$ for T time periods and use this to compute $v_f(x_t, s; \hat{p}, \theta)$.

Similarly, the choice-specific value functions for an entrant can be written as

$$v_e(x_t, s; \hat{p}, \theta) = -c_{enter} + \beta \sum_{x_{t+1}=1}^{X} \left(\Gamma - ln(\hat{p}_{ex}(x_{t+1}, s))\right) . f_e(x_{t+1}|x_t) \tag{14}$$

$$v_{ne}\left(x_t, s; \hat{p}, \theta\right) = 0 + \beta \sum_{x_{t+1}=1}^{X} \left(\Gamma + ln\left[exp\left(v_e\left(x_{t+1}, s; \theta\right)\right) + exp\left(v_{ne}\left(x_{t+1}, s; \theta\right)\right)\right]\right) .f_{ne}\left(x_{t+1}|x_t\right) \tag{15}$$

$$= \beta \sum_{x_{t+1}=1}^{X} \left(\Gamma + ln\frac{\left[exp\left(v_e\left(x_{t+1}, s; \theta\right)\right)\right]}{p_e\left(x_{t+1}, s; \theta\right)}\right) .f_{ne}\left(x_{t+1}|x_t\right)$$

$$= \beta \sum_{x_{t+1}=1}^{X} \left(\Gamma + v_e\left(x_{t+1}, s; \theta\right) - ln\left(p_e\left(x_{t+1}, s; \theta\right)\right)\right) .f_{ne}\left(x_{t+1}|x_t\right)$$

$$= \beta \sum_{x_{t+1}=1}^{X} \left(\Gamma - c_{enter} + \beta \sum_{x_{t+2}=1}^{X} \left(\Gamma - ln\left(\hat{p}_{ex}\left(x_{t+2}, s\right)\right)\right) .f_e\left(x_{t+2}|x_{t+1}\right) - ln\left(p_e\left(x_{t+1}, s; \theta\right)\right)\right) .f_{ne}\left(x_{t+1}|x_t\right)$$

which requires evaluation of two-period ahead CCPs.

The likelihood of the data for an incumbent and an entrant is given by equations 16 and 17 respectively.

$$l_{imts}\left(y_{imt}|x_t, s; \hat{p}, \theta\right) = \frac{exp\left(v_c\left(x_t, s; \theta\right)\right) .1\left(y_{imt} = \text{c}\right) + exp\left(v_f\left(x_t, s; \theta\right)\right) .1\left(y_{imt} = \text{f}\right) + 1.1\left(y_{imt} = \text{ex}\right)}{exp\left(v_c\left(x_t, s; \theta\right)\right) + exp\left(v_f\left(x_t, s; \theta\right)\right) + 1} \tag{16}$$

$$l_{imts}\left(y_{imt}|x_t, s; \hat{p}, \theta\right) = \frac{exp\left(v_e\left(x_t, s; \theta\right)\right) .1\left(y_{imt} = \text{e}\right) + exp\left(v_{ne}\left(x_t, s; \theta\right)\right) .1\left(y_{imt} = \text{ne}\right)}{exp\left(v_e\left(x_t, s; \theta\right)\right) + exp\left(v_{ne}\left(x_t, s; \theta\right)\right)} \tag{17}$$

$$l_{ms}\left(y_m|x, s; \hat{p}, \theta\right) = \prod_{i=1}^{I} \prod_{t=1}^{T} l_{imts}\left(y_{imt}|x_t, s; \hat{p}, \theta\right)$$

$$l\left(y|x; \hat{p}, \theta\right) = \sum_{m=1}^{M} \sum_{s=1}^{S} q_{ms} ln\left(l_{ms}\left(y_m|x, s; \hat{p}, \theta\right)\right) \tag{18}$$

4.2 CCP estimation

I use the data to estimate the conditional choice probabilities. I estimate θ_{CCP} which is used to parametrically approximate $\hat{p}$. For incumbents, I estimate a logit on the probabilities of continuing, filing and exiting the market and for entrants, I estimate a logit on the

probabilities of entering and not entering. The continuation function is specified as a linear combination of

$$\left(1, \sum_{-i}\left(x_{-imt}=\text{Exit}\right), \sum_{-i}\left(x_{-imt}\in\{1,...,5\}\right), \sum_{-i}\left(x_{-imt}=\text{File}\right), \sum_{-i}\left(y_{-imt}=\text{ExitFDA}\right), \sum_{-i}\left(y_{-imt}=\text{Launch}\right), x_{imt}\right).$$

The function for the filing choice probabilities is specified as a linear combination of

$\left(1, 1.\left(x_{imt}=1\right), 1.\left(x_{imt}=2\right), 1.\left(x_{imt}=3\right), 1.\left(x_{imt}=4\right), 1.\left(x_{imt}=5\right)\right)$ and the entry probabilities are specified using

$$\left(1, \sum_{-i}\left(x_{-imt}=\text{Exit}\right), \sum_{-i}\left(x_{-imt}\in\{1,...,5\}\right), \sum_{-i}\left(y_{-imt}=\text{File}\right), \sum_{-i}\left(y_{-imt}=\text{ExitFDA}\right), \sum_{-i}\left(y_{-imt}=\text{Launch}\right)\right).$$

q_{ms} are used as weights in the logit likelihood as each market m has a probability q_{ms} of being type s.

4.3 EM Algorithm

I operationalize the EM algorithm with starting values $\pi_s^1, \theta_{CCP}^1, \theta^1$ where the superscript denotes the lth iteration of the EM algorithm. Update $q_{ms}, \pi_s, \theta_{CCP}, \theta$ as follows

1. $q_{ms}^{l+1} = \frac{\pi_s^l l_{ms}\left(y_m|x,s;\theta_{CCP}^l,\theta^l\right)}{\sum_{s=1}^S \pi_s^l l_{ms}}$
2. $\pi_s^{l+1} = \frac{\sum_{m=1}^M q_{ms}^{l+1}}{M}$
3. Obtain θ_{CCP}^{l+1} using the specification in Section 4.2 and q_{ms}^{l+1} as weights.
4. $\theta^{l+1} = \underset{\theta}{\text{argmax}} \sum_{m=1}^M \sum_{s=1}^S q_{ms}^{l+1} ln\left(l_{ms}\left(y_m|x,s;\theta_{CCP}^{l+1},\theta\right)\right)$

4.4 Identification

Here I briefly go over the identification of the second stage parameters $\theta = [c_{enter}, c_r, c_f, \pi, \delta]$. As the revenues of each market are not observed, one of the parameters needs to be normalized. I normalize π to \$4 units for estimation.

The observed rate of entry identifies the entry cost c_{enter}. If we observe fewer entries in a market with high expected profits, it must be that the entry cost is high. The continuation rate identifies the cost of research c_r relative to the cost of exiting. If firms exit sooner after entry into a market it implies high continuation costs. Similarly, the observed filing rate identifies the cost of filing c_f. The profit parameter δ is identified based on firm's responses to launched competitors. If we observe more exits when there are more launched competitors it implies a negative effect of competition on profitability.

5 Results

The estimation algorithm recovers $q_{ms}, \pi_s, \theta_{CCP}, \theta$. The CCP estimates θ_{CCP} for continuation and filing for incumbents and entering for entrants are shown by type of market in Table 6 . Table 7 presents the structural parameter estimates θ. Type-1[11] markets include indications like cerebral ischaemia, cystic fibrosis and melanoma. These markets see fewer launched firms. These translate into a higher negative impact of an additional competitor, reflected in the higher values of for Type-1 markets. The negative research costs indicate that conditional on entry, firms are more likely to continue than exit the market. The sign of these research costs is driven by the fact that a large number of markets have 0 launched firms: the only way to justify firms' continued investments to rationalize the data is through a positive term in the utility from continuing research[12].

The FDA approval probabilities (Table 8) are recovered directly from the data. Conditional on being in review a firm has a 26.2% chance of receiving approval, 71.6% chance of remaining in review and 2.3% chance of receiving rejection. This translates to an ex-ante in-review probability curve shown in Figure 8.

[11] I define a market as Type-1 if $q_{ms=1} > 0.5$

[12] Since the data is right-truncated at 2009, I do not observe actual launches for some markets. 176 out of 294 markets have 0 launched firms. To verify this is the cause of the negative research costs, I re-run the estimation for the data using only markets where there are a positive number of launched firms. However, this is a selected sample which will bias δ towards 0. In this sample, I find the estimates of research costs are positive and δ is negative but has a lower magnitude as expected. Simulating out the path until termination or until an outcome is determined to get around the right-truncation issue is currently work in progress.

Table 6: CCP Estimates

	Type - 1		Type - 2	
	Coefficient	t-stat	Coefficient	t-stat
Incumbent (base outcome: exit)				
Continue				
Constant	4.33	15.25	0.360	1.279
Number of competitors exited	-0.07	-0.19	1.535	1.922
Number of competitors exited due to FDA	-0.05	0.00	0.280	1.190
Number of competitors launched	-0.33	-1.27	-1.780	-14.673
Number of competitors in research	-0.51	-2.84	1.587	1.898
Number of competitors in filed status	0.47	0.79	2.528	5.966
Own state: Research Year 1	-1.80	-4.26	0.598	2.815
Own state: Research Year 2	-1.21	-2.09	-0.366	-1.883
Own state: Research Year 3	-1.43	-2.72	0.361	1.141
Own state: Research Year 4	-1.54	-2.98	1.882	0.216
File				
Constant	-0.76	-1.82	-1.24	-3.13
Entrant (base outcome: not enter)				
Enter				
Constant	-0.82	-1.84	-1.79	-13.26
Number of competitors exited	0.43	2.28	0.65	1.95
Number of competitors launched	-0.17	-0.30	0.57	2.10
% Type-m	52%		48%	
Log likelihood	2414.04			
Number of markets	294			

Table 7: Structural Parameter Estimates

		Market Type-1		Market Type-2	
		Coefficient	t-stat	Coefficient	t-stat
Entry cost	c_{enter}	12.35	60.41	14.32	67.18
Research cost	c_r	-1.79	-89.24	-2.91	-60.93
Profit ($100 m)	π	3.06	N/A	3.73	N/A
Competitive impact	δ	-2.31	-47.85	-0.81	-15.55
% Type-m		52%		48%	
Log likelihood		-1399.63		-1514.95	

Table 8: FDA Approval Probabilities conditional on Firm's filing for an NDA

	pr_f	pr_l	pr_e
Current FDA	71.60%	26.20%	2.30%

Impact of competition on expected profits

Using the estimates for the Type-1 market and the model in Section 3, I simulate out the equilibrium responses of firms for T=20 periods to evaluate the impact of competitors on a firm's profits conditional on launching. Figure 7 shows that the number of competitors that have entered Phase 3 clinical trials does not have a significant impact on the NPV of profits - this is because firms know that after entry the competitor still has many years remaining before it will launch in the market. However, if the competitor has filed there is a 26.2% probability that it will get approved and this causes the NPV to decline. Lastly, as the number of competitors that have launched increases the profits decline.

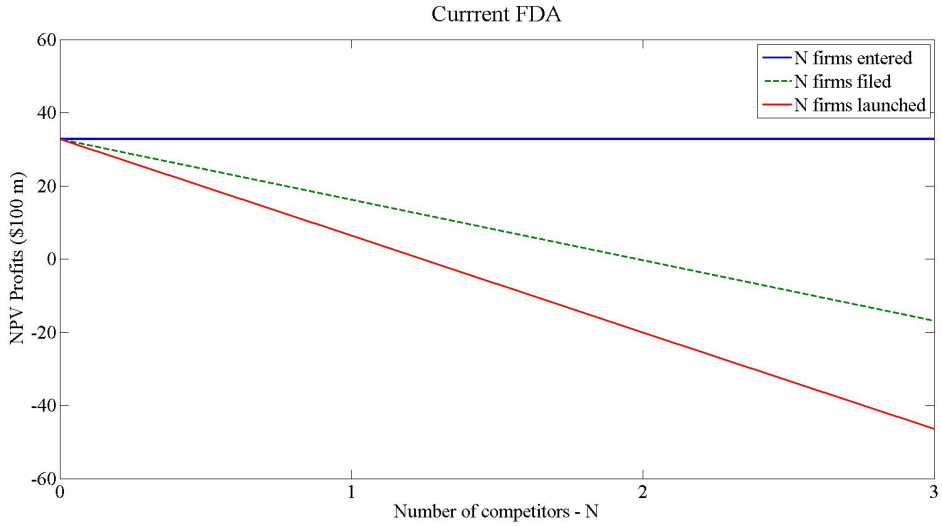


Figure 7: Impact of competition on profits conditional on launching

6 Counterfactual

Effect of a Faster FDA Approval Process

To measure the possible effect of a quicker FDA approval process I modify the FDA's probability of approval so that the in-review time is effectively reduced. Table 8 presents the current FDA probabilities as well as the probabilities used in this counterfactual evaluation. In the data, the probability of a firm staying in the File state is 71.6% while in the counterfactual this is reduced to 31.6%. I adjust the per-period approval probability to 62.9% to ensure that overall approval and rejection probabilities are the same over a span of 20 years, i.e. $\sum_{t=1}^{T} pr_f^{t-1}.pr_l = \sum_{t=1}^{T} pr_{f,faster}^{t-1}.pr_{l,faster}$ where $pr_{f,faster}$ is the in-review probability in the counterfactual of a faster FDA approval.

Table 9: FDA Approval Probabilities conditional on Firm's filing for an NDA

	Filed NDA (remains in review)	Approved	Rejected
Current FDA	71.60%	26.20%	2.30%
Faster FDA Approval	31.60%	62.99%	5.41%

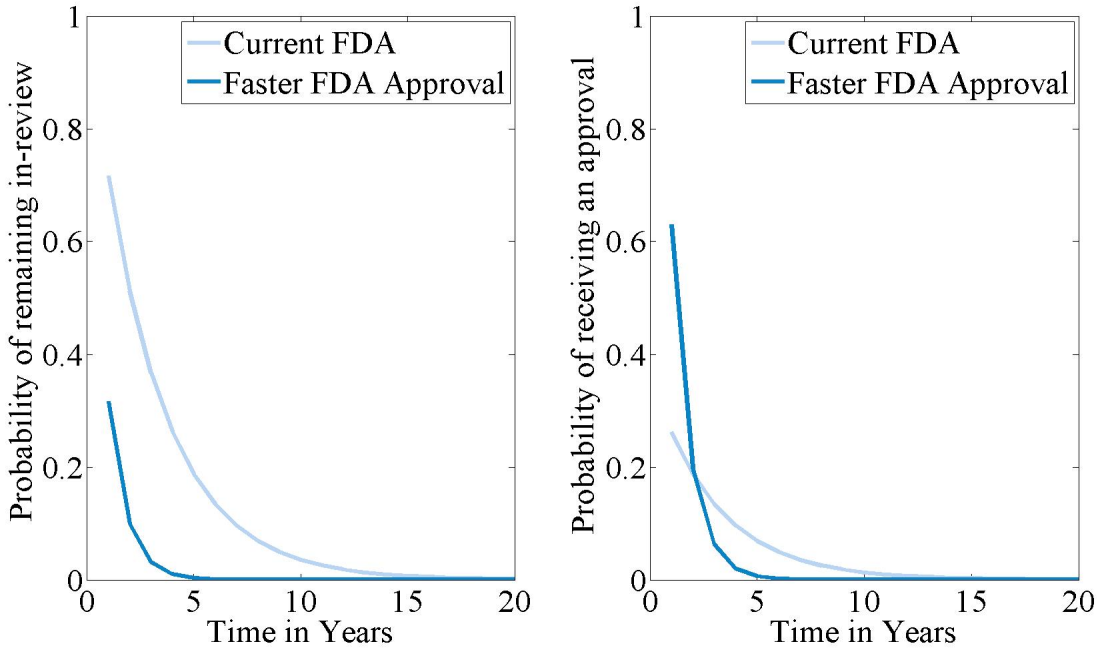


Figure 8: Ex-ante probabilities of remaning in-review and approval

The model presented in Section 3 is used to evaluate the equilibrium response of firms. Using the structural estimates in Table 7 for the Type-1 market and assuming a finite time-horizon of T=20 periods, I backward-solve for the equilibrium firm responses and value functions at every time period.

First, I compare the impact of competition on profits across the two scenarios: current FDA approval rates and a faster FDA approval. Figure 9 shows that the absolute values of the NPV decline much more quickly in the counterfactual of a faster FDA approval process when competitors are in the filed state: this is because unlike in the current FDA, competitors remain in-review for shorter periods of time.

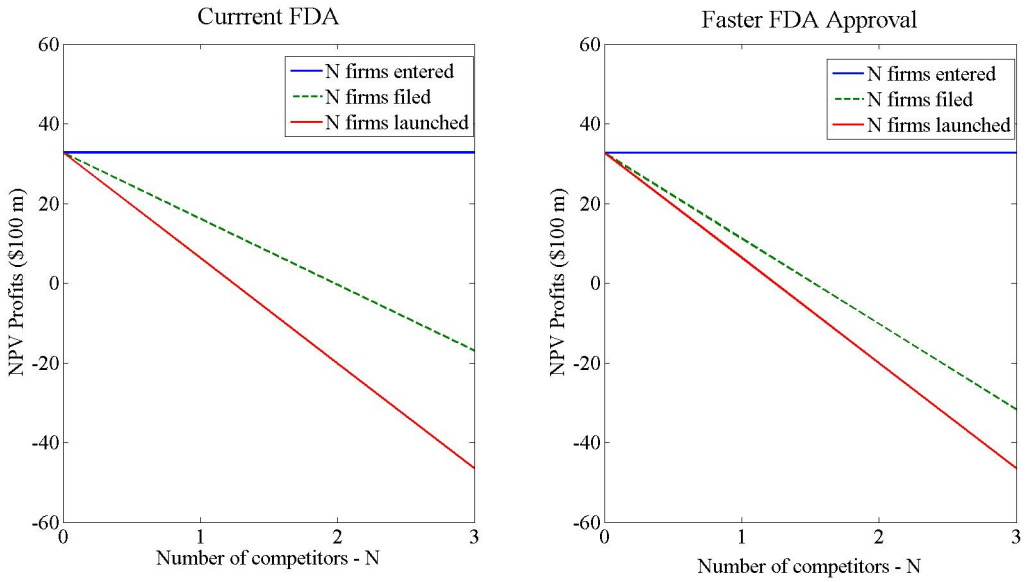


Figure 9: Impact of competition on profits - faster FDA approval reduces NPV of profits when competitors have filed

Quantifying the effects: Competitive intensity vs. reduced time to market

To quantify the extent to which each effect dominates, I evaluate firm profits by solving the dynamic equilibrium under a faster FDA approval process and comparing it to the profits if firms acted without any strategic behavior, i.e. ignored the states of their competitors. Figure 10 plots the continuation value under the 2 scenarios along with the base case scenario of the current approval process. Under the estimates for the Type-1 market, the increase in profits due to an expedited approval process is $532m. The bias, if firms did not consider their competitor's strategic responses, is in the order of $80m.

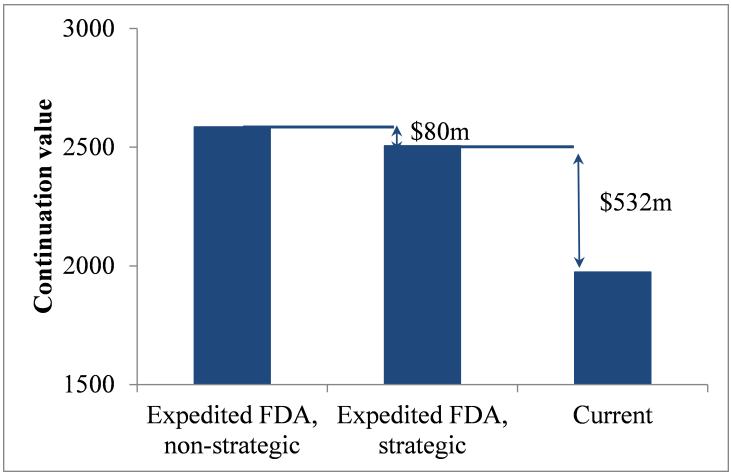


Figure 10: Increase in profits due to reduced time to market dominates decrease due to competition

7 Conclusion

The main objective of this paper was to answer the question if a faster FDA process, something pharmaceutical firms are pushing for, is beneficial. While the reduced time to profits can increase the NPV of the flow of profits, this makes the market more attractive thus intensifying competition which can exert a downward pressure on firm profits. Using a dataset on Phase 3 clinical trial entry, continuation and filing decisions and FDA outcomes at the firm-market-year level a dynamic model of oligopoly was estimated accounting for unobserved heterogeneity in markets. The structural parameters that govern a firm's entry and continuation decisions in the complex and time-intensive R&D stage of the pharmaceutical industry were recovered using the two stage Expectation-Maximization algorithm.

The counterfactual simulation using the estimated parameters show that the gains in per-firm profits due to a faster launch dominates the decline in profits due to increased competitive intensity.

This paper focused only on the Phase 3 stage of R&D. Acquiring data on the earlier Phases of research can further shed light on the dynamics that occur in this industry. It was also assumed that conditional on being in a research state, all firms are equal. While this assumption seems reasonable given that these firms constitute the top 15 firms in the US pharmaceutical indsutry, relaxing this assumption and accounting for firm heterogeneity is a direction for future work.

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