Entry and Investment Decisions in the Pharmaceutical Industry

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PRELIMINARY - WORK IN PROGRESS

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. The profits are realized only upon launch of the product, so drugs which fail part way through the research process generate no revenues to offset the substantial costs accumulated over the development process. I study this industry to answer questions from the perspectives of firms’ development activities and social welfare. To this end, I estimate a dynamic entry model while accounting for firm interactions and market heterogeneity. I use a panel dataset on firm entry and exit decisions at the research phase level in various markets. The estimates indicate that firms are strategic in their behavior taking into account the actions of their competitors. I conduct a counterfactual that reduces FDA approval rates to understand the impact of increased regulatory scrutiny, a potential outcome of increased emphasis on comparative effectiveness research. I also evaluate the impact of targeted research grants that decrease research costs for incumbents.

∗This is a very preliminary version, all comments are welcome.
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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 research process generate no revenues to offset the substantial costs accumulated over the development process. Business development managers want to invest their R&D budget on compounds that are likely to be successful and profitable and want to know the right time to stem investment in a product.

As expected product profitability is a key driver of investment certain markets can be under-invested in because of their low revenue generating capacity. This raises the concern that firms are investing in predominantly blockbuster drugs and lucrative life-style drugs as opposed to life-saving drugs and drugs with smaller patient populations. This paper determines the extent of incentives to be given to firms to enhance entry in less-profitable but critical markets.

The recent Health Care Reform talks about establishing an institute that incorporates comparative effectiveness research. This information will be used to indicate how effective and tolerable one drug is compared to another for the same disease indication thus providing the best treatment options to patients. Currently the US FDA requires that firms prove the safety and efficacy of their drug in comparison to a placebo. One of the possible effects of such an additional requirement to show comparative effectiveness, if mandated by the FDA, is lower approval rates. I evaluate a counterfactual where FDA approval rates during the early years of a firm’s research in Phase 3 are lower than the current rates. Ideally we would like to see only entry (and not continuation) rates decreasing, because reduced continuation rates would imply huge time- and cost- investment losses to firms that have successfully made it all the way to Phase 3 clinical trials.

To answer these questions this paper builds a structural model that incorporates forward-looking behavior, strategic decision making of firms and market heterogeneity.

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. Secondly, firms respond to actions taken by their competitors. 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 the more the number of launched firms the smaller the share of profit the focal firm would have, thus no longer justifying continued investments in the research phase. This warrants a model
that accounts for equilibrium responses of firms. Thirdly, 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. I thus estimate a dynamic model of oligopoly with permanent unobserved heterogeneity.

The model is built using a unique dataset that comprises of firm entry into clinical trials and subsequent launch and exit decisions for several markets. I observe the path of a drug from the date it enters clinical trials until the date it launches or exits the market.

The estimation strategy builds on the underlying approach outlined in Arcidiacono and Miller (2008) and Bajari, Benkard and Levin (2007). These modeling strategies, to name a few, have been applied by Finger (2007) in analyzing the chemicals R&D industry and by Ryan (2005) in the cement industry.

The paper is organized as follows. Section 2 gives an overview of the pharmaceutical industry, Section 3 describes the data, Section 4 builds the structural model, Section 5 discusses the estimation strategy and Section 6 presents the results. Section 7 presents counterfactuals to answer the questions posed above and Section 8 concludes.

2 Industry Background

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.\footnote{Source: Pharmaceutical Research and Manufacturers of America citing data from the Tufts University Center for the Study of Drug Development}

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 Food and Drug Administration (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.
Table 1 extracted from DiMasi et al (2003) gives a brief idea of the average costs for each research phase. Phase III is by far the most expensive of all four research phases.

<table>
<thead>
<tr>
<th>Testing Phase</th>
<th>Mean cost</th>
<th>Median cost</th>
<th>Standard Deviation</th>
<th>N*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>15.2</td>
<td>13.9</td>
<td>12.8</td>
<td>66</td>
</tr>
<tr>
<td>Phase II</td>
<td>23.5</td>
<td>17.0</td>
<td>22.1</td>
<td>53</td>
</tr>
<tr>
<td>Phase III</td>
<td>86.3</td>
<td>62.0</td>
<td>60.6</td>
<td>33</td>
</tr>
<tr>
<td>Long-term animal</td>
<td>5.2</td>
<td>3.1</td>
<td>4.8</td>
<td>20</td>
</tr>
</tbody>
</table>

* Number of compounds with full cost data for the phase.

Table 1: Average costs for drugs under investigation in millions of 2000 dollars (DiMasi et al, 2003)

At each phase, pharmaceutical firms can decide to take their product forward or not based on the findings of the studies as well as the competitive environment. Moreover, at each phase the pharmaceutical firm’s petition to move to the next phase can be rejected/approved by the FDA. As this paper examines the effect of competition on firm’s decisions I provide anecdotal evidence to indicate that firms are likely to be affected by their competitive environment.

Deloitte Recap’s Development Optimizer, a biopharmaceutical intelligence tool, provides attrition analysis along with evidence for the cause of project termination. This tool is intended for firms to make informed strategic decisions. Their analysis shows high late-stage attrition rates - 29% of 559 compounds analyzed fail in Phase III. Further, they record that while 68% stop due to lack of efficacy and 7% due to adverse events, 12% of failed compounds in Phase III mention ‘Pipeline Prioritization’ as the reason for stopping further investment. This indicates that there are likely other factors beyond drug efficacy and safety that affect exit decisions.

Secondly, most press releases of pharmaceutical firms are accompanied by statements such as “This press release contains ”forward-looking statements” [...] based on current expectations of future events. Risks or uncertainties include, but are not limited to, general industry conditions and competition; economic factors, such as interest rate and currency

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2Press release: Deloitte Recap Launches New Solution for Clinical Development. Development optimizer supports biopharmaceutical clinical development decisions

exchange rate fluctuations; technological advances and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approvals; domestic and foreign health care reforms and governmental laws and regulations; trends toward health care cost containment; and increased scrutiny of the healthcare industry by government agencies.”

Thus, pharmaceutical firms are clearly forward-looking and take into account the actions of their competitors in their entry and investment decisions.

3 Data

To answer the questions posed in this paper I need a panel dataset that captures the entry and exit decisions of pharmaceutical firms at the market level. The data, obtained from Wolters Kluwer Pharma Solutions, consists of entry and exit observations from 1995-2008 at the market (disease indication) - firm - phase - date level. Thus, the date a firm enters a research phase in a market is observed. The date if it exited or launched in the market is also observed. A firm can exit the market in any phase. Note that investment data is not observed as firm R&D costs per project are not made public.

This paper focuses on entry decisions of firms into Phase 3 clinical trials and exit/launch following Phase 3 entry. Entry and investment decisions at the earlier phases is ignored for three main reasons. First, the available data is punctuated with missing information pre-Phase 3 as the U.S. Public Law does not make it mandatory to report pre-clinical and Phase I trials. Firms are not likely to disclose their intentions early on in the product pipeline (pre-clinical, Phase I and II) to maintain their competitive edge. Second, when a drug has been approved for treating a particular disease indication and the firm decides to enter another market with the same compound, the FDA requires it to repeat only Phase 3 trials to prove safety and efficacy for the new disease indication. Third, the Business Development group of firms usually acquires compounds that are in the later stages of development.

I also limit the analysis to the first four big entrants in a market⁵. Big entrants are defined as those that were classified as the top 15 corporations by U.S. sales, ranked by IMS Health. Entrants can and do differ by market. If a firm enters a market with more than one drug product, the first product it entered with is chosen. The dataset consists of 91 markets where each market is a disease-indication. Alzheimer’s disease, bipolar disorders, chronic


⁵This is done to avoid the state space from becoming unreasonably large. Implications of such an assumption on the estimates is discussed in the Results section. Robustness checks relaxing this assumption are also performed.
lymphocytic leukaemia and type 2 diabetes mellitus are examples of disease indications in
the data.

Table 2 summarizes the data. On average 1.63 firms enter a market and it takes an entered
firm an average of 3.39 years before it either exits the market or successfully launches its
product in the market. There are 28 exits observed across all 91 markets leading to an
average exit rate of 0.31. These 28 exits are confined to 23 markets with the remaining 68
markets having no exits in the time period observed.

<table>
<thead>
<tr>
<th></th>
<th>Number of markets</th>
<th>Average</th>
<th>Std Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of entered firms</td>
<td>86</td>
<td>1.63</td>
<td>1.06</td>
</tr>
<tr>
<td>Number of years in research</td>
<td>91</td>
<td>3.39</td>
<td>2.67</td>
</tr>
<tr>
<td>before exit/launch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of exited firms</td>
<td>91</td>
<td>0.31</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Table 2: Summary Statistics

4 Model

The goal of the estimation process is to recover the costs of entry, the continuation costs of
research and profitability by market type. Costs of entry in this context should be thought
of as the cost it takes a firm to make it successfully to Phase 3 - this includes the cost to
enter pre-clinical trials in the market, cost of conducting research in the pre-clinical, Phase 1
and Phase 2 stages and the cost of failure in any of these stages. Recovering these structural
parameters enables me to perform counterfactual experiments to determine the effect of
government intervention and changes in FDA regulation policies. In this section I build a
structural model aimed at capturing the dynamics involved in firm entry, continuation and
exit decisions as well as accounting for the equilibrium responses of firms.

The pharmaceutical industry is characterized by simultaneous entry, exit and investment
decisions of firms in each market (disease indication). A successful path of a firm that has
completed Phase 2 trials consists of conducting the required research in Phase 3 clinical trials
to establish the safety and efficacy of the drug and launching upon FDA approval. However,
many firms do not make it through the complete path and exit mid-way either due to failure
(e.g. severe adverse effects) in clinical trials or due to realization that profit margins are no
longer lucrative.

Incumbents decide whether to continue investing in the research process or exit while
potential entrants decide whether to enter or stay out of the market. Note that an entrant
here is a firm that not only has entered the market but also has successfully made it through
all of the previous phases. The payoff is positive only if a firm launches its product in the
market. Payoffs in the investment stages are negative and reflect the cost of continuing research. Markets are assumed to be independent.

States

A firm in the model can be described by two state variables 1) $s$ - the stage of research a firm is in and 2) $M$ - the market type. $s$ can take on 8 possible values: 0 if the firm has not entered the market, 1 if the firm has just entered the market, 2...5 if the firm is in research year 2 through 5 or longer\(^6\), Launch if the firm has launched successfully in the market and Exit if the firm has exited from the market. $M$ can take on 2 values, markets can either belong to the High type or Low type indicating their degree of profitability. The market type is unobserved to the researcher and is treated as permanent unobserved heterogeneity. Firms are assumed to know the market type.

Current Period Payoff

Utility of staying out of the market

If a firm has not entered the market yet, it gets a per-period payoff

$$U_0 = 0 + \varepsilon_{notenter}$$ (1)

Utility of entering the market

The cost of entering a market reflects the cost of successful entry into and completion of the pre-clinical, Phase1 and Phase 2 phases of the research process.

$$U_{enter} = -c_{enter} + \varepsilon_{enter}$$ (2)

Utility of continued research

Every year the firm decides to continue research it is assumed to bear the research cost of investment.

$$U_r = -c_r + \varepsilon_{cont}$$ (3)

\(^6\)To limit the state space, it is assumed that once a firm has reached state 5 it continues to remain in state 5 until it exits or launches. This translates to the assumption that the probability of launch remains the same year 5 onwards.
Utility of exiting the market

If the firm decides to exit the market at any given stage, it gets a scrap value that period

\[ U_{exit} = \phi + \epsilon_{exit} \]  

(4)

Utility of launching

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

\[ U_{launch} = \pi + \delta N \]  

(5)

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

State Transitions

Entrant

An entrant can take one of two possible actions \{Enter, NotEnter\}. If a firm decides to enter in time period \( t \), its state in the next time period is given by

\[ s_{t+1} = s_t + 1 \quad \text{if } s_t = 0 \text{ and } a_t = \text{Enter} \]  

(6)

If the firm decides not to enter, it continues to remain at \( s_t \)

\[ s_{t+1} = s_t \quad \text{if } s_t = 0 \text{ and } a_t = \text{NotEnter} \]  

(7)

Incumbent

An incumbent can take one of two possible actions \{ContinueInvestment, Exit\}. If an incumbent firm, in research year \( r \), decides to continue investment in research, it is assumed that it launches with probability \( p_r \) and moves on to the next year of research with probability \( 1 - p_r \), i.e. if the firm does not launch it moves up a research phase. \( p_r \) is informed from the data - at each research state \( r \), it is the proportion of observed launches relative to the observed continuation decisions. This probability of launch conditional on a research state is exogenously determined by the FDA. Conditional on being in the same research state, all firms are symmetric, i.e., it is not possible for a firm to put in more investment resources in a research year compared to another firm in the same research year to increase its chances of
approval\textsuperscript{7}. The number of years in research is the only way a firm can put in more resources compared to another firm.

\begin{equation}
 s_{t+1} = \begin{cases} 
 s_t + 1 & \text{with prob } 1 - p_r = s_t \\
 \text{Launch} & \text{with prob } p_r = s_t
\end{cases} \text{ if } s_t = r \text{ and } a_t = \text{ContinueInvestment}
\end{equation}

Research year 5 is handled slightly differently to keep the state-space reasonably small. If an incumbent is in research year 5, it is assumed that if it does not launch it continues to remain in research year 5 with probability $1 - p_r$

\begin{equation}
 s_{t+1} = \begin{cases} 
 s_t & \text{with prob } 1 - p_r = s_t \\
 \text{Launch} & \text{with prob } p_r = s_t
\end{cases} \text{ if } s_t = 5 \text{ and } a_t = \text{ContinueInvestment}
\end{equation}

If an incumbent firm decides to exit, it reaches the exit state after which it cannot re-enter the market.

\begin{equation}
 s_{t+1} = \text{Exit} \text{ if } s_t = r \text{ and } a_t = \text{Exit}
\end{equation}

**Market type**

The market type $M$ is assumed to be fixed, i.e. it cannot transition from one state to another. The market type is known to firms but is unobserved by the researcher.

**Value Functions**

The market type $M$ is suppressed in the following equations.

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

\begin{equation}
 V_{\text{not enter}}(s_j = 0, s_{-j}) = 0 + \beta \sum_{s'_{-j}} E_{max} \epsilon' \left\{ \begin{array}{ll}
 V_{\text{enter}}(s') + \epsilon'_{\text{enter}} \\
 V_{\text{not enter}}(s') + \epsilon'_{\text{not enter}}
\end{array} \right\} dF(s'_{-j}|s)
\end{equation}

\textsuperscript{7}Incorporating the fact that some firms are capable of investing more resources than others would require us to incorporate firm heterogeneity. I assume firm homogeneity, which while not an innocuous assumption is likely justified as all firms in my analysis are big firms.
\[ V_{\text{enter}}(s_j = 0, s_{-j}) = -c_{\text{enter}} + \beta \sum_{s'_{-j}} E_{\text{max}} e' \left\{ V_{\text{cont}}(s') + \varepsilon'_{\text{cont}}, V_{\text{exit}}(s') + \varepsilon'_{\text{exit}} \right\} dF(s'_{-j}|s) \tag{12} \]

The summation is over all the possible states \((\text{dimension } |S| \times |S| \times |S|)\) that all of the firm’s competitors can be in, in the next time-period. The firm’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 can be given by the following equations:

\[ V_{\text{cont}}(s_j, s_{-j}) = -c_r + \beta \sum_{s'_{-j}} (1 - p_{s'}) E_{\text{max}} e' \left\{ V_{\text{cont}}(s') + \varepsilon'_{\text{cont}}, V_{\text{exit}}(s') + \varepsilon'_{\text{exit}} \right\} + p_s' V_{\text{launch}}(s') dF(s'_{-j}|s) \tag{13} \]

\[ V_{\text{exit}}(s_j, s_{-j}) = \phi \tag{14} \]

**Equilibrium Concept**

Firms are assumed to be symmetric in their action and their strategies are assumed to be Markov Perfect. For a potential entrant this can be written as

\[ V(s_j = 0|\sigma_j^*, \sigma_{-j}) \geq V(s_j = 0|\sigma_j', \sigma_{-j}) \]

where \(\sigma_j = \{\text{Enter, NotEnter}\}\)

For an incumbent this can be written as

\[ V(s_j|\sigma_j^*, \sigma_{-j}) \geq V(s_j|\sigma_j', \sigma_{-j}) \]

where \(\sigma_j = \{\text{ContinueInvestment, Exit}\}\)

**Discussion on the factors leading to exit**

A firm can exit in the research stage 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 and 3) FDA rejection. I discuss in this section how each of these three aspects of the pharmaceutical industry are captured in the model.
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 $\epsilon_{cont}$. A large negative shock captures the effect of an adverse event while a positive shock captures the effect of a windfall. Competitors are assumed to have limited knowledge of these shocks and they know these error shocks only in expectation.

Pipeline prioritization

A firm is likely to be influenced by its competitors action in all states. For example, if a competitor enters the market or a competitor successfully launches its product, the probabilities and actions of the focal firm are likely to be different. This influence is captured through the state space in the firm’s consideration - the focal firm’s value function is dependent on the state of its competitors. 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 can accept or reject the petition of the firm to launch in the market. I capture this as a probability associated with launch in every stage of research. For example, in year 1 of research the probability of successful launch might be very low while this probability might be very high in Year 3 of research. These probabilities are directly inferred from the data and are allowed to be market type-specific.

5 Estimation

The parameters are estimated using the two-step estimation procedure described in Bajari, Benkard and Levin (2007) and Arcidiacono and Miller (2008). In the first step the policy functions are recovered as a function of the relevant states and in the second step the structural parameters that govern firm decisions are recovered.

5.1 First stage estimation

The first stage recovers the policy functions as a non-parametric function of the relevant states. Due to the large number of possible states $dimension |S_j| \times \prod_{-j} |S_{-j}|$ (or, if the firms are treated symmetrically $dimension |S_j| \times \sum_{-j} |S_{-j}|$), I use a flexible parametric
approximation that is rich enough to explain the actions taken by a firm as a function of the states.

5.1.1 Parametric specification

The choice-specific value function for the decision to continue is parametrically specified\(^8\) as

\[
V_{cont}(s_j, s_{-j}, i; \alpha_m, \beta) = \alpha_m + \alpha_{m,\text{launch}} N_{\text{launch}} + \sum_{s_{-j}} \beta_{s_{-j}} N_{s_{-j}} + \beta_{s_j}s_j
\]

(15)

where \(N_{s_{-j}}\) denotes the number of competitors in state \(s_{-j}\) and \(N_{\text{launch}}\) denotes the number of competitors who have launched in the market.

\(\alpha_m\) is the type-specific market constant and \(\alpha_{m,\text{launch}}\) is the type-specific effect of launched competitors on the firm’s continuation value function.

Similarly, the choice-specific value function for the decision to enter is parametrically specified as

\[
V_{enter}(s_j, s_{-j}, m; \lambda_m, \gamma) = \lambda_m + \lambda_{m,\text{launch}} N_{\text{launch}} + \sum_{s_{-j}} \gamma_{s_{-j}} N_{s_{-j}}
\]

(16)

Specifying the firm’s action using the typical discrete-choice notation, the firm chooses to continue investment if its choice specific value function satisfies the following equation

\[
V_{cont}(s_j, s_{-j}, i; \alpha_m, \beta) + \varepsilon_{\text{cont}} \geq V_{exit}(s_j, s_{-j}, i; \alpha_m, \beta) + \varepsilon_{\text{exit}}
\]

(17)

Similarly, it chooses to enter, if its choice specific value function satisfies

\[
V_{enter}(s_j, s_{-j}, i; \lambda_m, \gamma) + \varepsilon_{\text{enter}} \geq V_{\text{notenter}}(s_j, s_{-j}, i; \lambda_m, \gamma) + \varepsilon_{\text{notenter}}
\]

(18)

\(V_{exit}(s_j, s_{-j}, i; \alpha_m, \beta), V_{\text{notenter}}(s_j, s_{-j}, i; \alpha_m, \beta)\) are normalized to 0.

5.1.2 Likelihood function

Assuming the \(\varepsilon’\)s to be Type 1 extreme value distributed, the likelihood of observing incumbent firm \(j\) in market \(i\) continuing in time period \(t\) can be written as

\[
p_{j,i,t}^{cont}(s_j, s_{-j}, i; \alpha_m, \beta) = \frac{V_{cont}(s_j, s_{-j}, i; \alpha_m, \beta)}{1 + V_{cont}(s_j, s_{-j}, i; \alpha_m, \beta)} I(\text{cont})
\]

(19)

The likelihood of observing firm \(j\) in market \(m\) entering in time period \(t\) can be written as

\(^8\)Many other specifications were tried. This was chosen as it described the data the best.
\[ p_{j,i,t}^{\text{enter}}(s_j, s_{-j}, i; \lambda_m, \gamma) = \frac{V_{\text{enter}}(s_j, s_{-j}, i; \lambda_m, \gamma)}{1 + V_{\text{enter}}(s_j, s_{-j}, i; \lambda_m, \gamma)} I(\text{enter}) \]  

(20)

where \(I(\text{cont})\) and \(I(\text{enter})\) are indicator functions for the firm’s continuation and entry decisions respectively.

Aggregating the probabilities over all observations of continuation and entry in a given market, the market-level likelihood is defined as

\[ p_i(\alpha_m, \beta, \lambda_m) = \prod_j \prod_t p_{j,i,t}^{\text{cont}}(\alpha_m, \beta) p_{j,i,t}^{\text{enter}}(\lambda, \gamma) \]  

(21)

The market type is not observed to the researcher. Thus, the log-likelihood that the observed actions occur in market \(i\) is the weighted average of the likelihoods across all market types and can be written as

\[ p_i(\theta) = \log \sum_{m=1}^{M} \tau_m p_i(\alpha_m, \beta, \lambda_m) \]  

(22)

where \(\tau_m\) is the percentage of Type \(m\) markets.

The overall log-likelihood across all markets can then be written as

\[ LL(\theta) = \sum_i p_i(\theta) \]  

(23)

where \(\theta = \{\tau_1, \alpha_1, \lambda_1, ..., \tau_M, \alpha_M, \lambda_M, \beta, \gamma\}\)

Maximizing this likelihood function is computationally difficult and I resort to the EM algorithm to recover \(\theta\).

### 5.1.3 EM algorithm

The EM algorithm (Dempster et al, 1977; Train 2008) is used to recover the underlying demand parameters. The EM algorithm solves for iteratively using the following recursion

\[ \theta^{k+1} = \arg\max_\theta \sum_i \sum_m q_{im}(\theta) \log \tau_m p_i(\alpha_m, \beta, \lambda_m) \]  

(24)

where \(q_{im}(\theta)\) is the conditional probability that market \(i\) is of type \(m\). The steps for estimation using the EM algorithm are given in Appendix A.
5.2 Second stage estimation

This stage recovers the structural parameters $\theta_2$ - the entry cost $c_{\text{enter}}$, research cost $c_r$, scrap value $\phi$ and profit parameters $\pi$ and $\delta$. The value function for any given firm $j$ and starting state $s_0$ can be re-written as

$$V_j(s_0, \sigma, \theta_2) = W_j(s_0, \sigma).\theta_2$$

(25)

where

$$W_j(s_0, \sigma) = E_{\sigma|s_0} \sum_{t=0}^{\infty} \beta^t \left[ 1(\text{enter}_j(s_t)), 1(\text{cont}_j(s_t)), 1(\text{Launch}_j(s_t)), 1(\text{Launch}_j(s_t)) N_{\text{launch}} \right]$$

(26)

and

$$\theta_2 = [c_{\text{enter}}, c_r, \phi, \pi, \delta]$$

$1(\text{enter}_j(s_t))$ is the policy function that determines if firm $j$ enters the market if the state is $s_t$

$1(\text{cont}_j(s_t))$ is the policy function that determines if firm $j$ continues research in the market if the state is $s_t$

$1(\text{Launch}_j(s_t))$ is the indicator function equal to 1 if the firm launched.

I follow the procedure outlined in Bajari, Benkard and Levin (2007) to simulate the vector of expected discounted actions $W_j(s_0, \sigma)$. To account for the unobserved heterogeneity, I simply treat the unobserved state vector as an observed state as the market-type is known after the first stage estimation. Starting at state $s_0$, I draw the vector of private shocks $\varepsilon_{\text{cont}}, \varepsilon_{\text{exit}}, \varepsilon_{\text{enter}}, \varepsilon_{\text{notenter}}$ for each firm over time per market. These shocks are assumed to be i.i.d extreme value across firms, market and time. I then calculate the specified action using the policy function estimated in the first stage for each firm $j$. Next, the state evolution can be determined using the state transitions outlined in the Model section. This procedure is repeated for $T$ (=30) periods.

For each starting state $s_0$ I simulate the path of play NSim (=100) times. Within each simulation step, I forward simulate $T$=30 periods for each firm and compute the expected discounted value functions. I perturb the policy functions slightly to create the alternative policy functions. The alternative policy functions are created so that they can be compared with the observed policy functions (generated from the first stage estimates). The intuition behind recovering the parameter vector is that the payoffs associated with the observed policy functions are optimal and hence should be higher than the payoffs associated with any alternative policy function. The value functions thus obtained must satisfy the following two inequalities. The first is an individual rationality constraint and the second is an incentive...
compatibility constraint.

\[ W_j \left( s_0, \sigma_j^*, \sigma_{-j} \right), \theta_2 > 0 \] \hspace{1cm} (27)

\[ W_j \left( s_0, \sigma_j^*, \sigma_{-j} \right), \theta_2 > W_j \left( s_0, \sigma_j', \sigma_{-j} \right), \theta_2 \] \hspace{1cm} (28)

where \( \sigma_j^* \) is the optimal policy and \( \sigma_j' \) is an alternative policy for firm \( j \).

Based on these equations, the following moments can be defined

\[ g_1 \left( s_0, \theta_2 \right) = \min \left( W_j \left( s_0, \sigma_j^*, \sigma_{-j} \right), \theta_2, 0 \right) \] \hspace{1cm} (29)

\[ g_2 \left( s_0, \sigma, \theta_2 \right) = \min \left( \left[ W_j \left( s_0, \sigma_j^*, \sigma_{-j} \right) - W_j \left( s_0, \sigma_j', \sigma_{-j} \right) \right], \theta_2, 0 \right) \] \hspace{1cm} (30)

The true parameter vector satisfies both the incentive compatibility as well as individual rationality constraints. In reality, we minimize the violations of the inequalities and try to achieve the zero of the objective function, i.e.

\[ Q(\theta_2^*) = \min \int G \left( s_0, \sigma, \theta_2 \right) dH \left( s_0, \sigma \right) \]

where \( G \left( s_0, \sigma, \theta_2 \right) = g' \left( s_0, \sigma, \theta_2 \right) g \left( s_0, \sigma, \theta_2 \right) \) and \( g \left( s_0, \sigma, \theta_2 \right) = \left[ g_1 \left( s_0, \theta_2 \right), g_2 \left( s_0, \sigma, \theta_2 \right) \right] \)

5.3 Identification

Here I briefly go over the identification of the second stage parameters \( \theta_2 = [c_{enter}, c_r, \phi, \pi, \delta] \).

As the revenues of each market are not observed, I normalize \( \pi \) to the market size of each type. \( \pi \) for the High Type markets is set at $180m based on the figure for the median annual sales for the top 500 drugs in 2000. \( \pi \) for the Low Type market is set at $40m - the cutoff for drugs that determines whether they are included in the top 500 or not.

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 \( c_r \). If firms exit sooner after entry into a market it implies high continuation costs. The profit parameter \( \delta \) is identified based on firm’s responses to launched competitors. If we observe more exits when there are more launched competitors it identifies the effect of competition on profitability. Lastly, as the firm’s decision to exit is captured in its decision to continue, the scrap value \( \phi \) is not separately identified from \( c_r \) and is normalized to 0.
6 Results

6.1 First stage parameter estimates

The first stage estimates accounting for permanent unobserved heterogeneity are presented in Table 3. From the estimates, we see clear evidence of heterogeneity. Type 2 (High Type) markets are more lucrative for entry and continuation as evidenced by the high values of $\alpha_2$ and $\lambda_2$.

We also see that as the number of launched competitors increases, the probability to enter as well as continue decreases in Type 1 (Low Type) markets. Similarly as the number of launched competitors in Type 2 (High Type) markets increases, the probability to continue declines.

However, the probability to enter in High Type markets increases as the number of launched competitors increases. This might be indicative of an element of learning in these markets, i.e., existence of more competitors may be indicative of higher profitability encouraging firms to enter these markets.

Some of the markets that fall under the High-type include depression, seasonal allergic rhinitis, insomnia and HIV infections which have gained higher public awareness recently either due to their recent increased prevalence or due to increased consumer awareness\textsuperscript{9}. Table 4 highlights a few of the markets that fall under Type 1 and Type 2.

6.2 Second stage parameter estimates

Table 5 presents the structural parameter estimates. The estimation is done separately for the high-type and low-type markets. DiMasi et al (2003) report the mean costs for Phase 1 and Phase 2 to be $15.2m and $23.5m respectively. The estimates for entry costs of $295m for the high type and $82.6m for the low type capture the cost of entering a market, the cost of conducting research in the pre-clinical, Phase I and Phase II stages as well as the costs of failure in any of these stages. In markets where there are likely to be more than 4 potential entrants the entry costs are likely to be underestimated as I assume that there are only 4 entrants.

The low research costs indicate that conditional on entry, firms are more likely to continue than exit the market. This ties in with the data where in the High type market we observe 12 exits out of 98 entered firms indicating a continuation rate of 88%. The Low type market has a lower continuation rate of 62% with 16 exits among the 42 entered firms thus tying with the higher research costs for the Low Type market.

\textsuperscript{9}Part of this awareness has been firm-generated through channels like DTC advertising.
As can be seen from the values of $\delta$ relative to $\pi$, the High Type market can support 3 firms on average and the Low type market 1 firm on average.

Figure 2 plots, for the Low Type market, the probability of a firm in Research Year 1 moving to the subsequent year as well as the probability that this firm Launches, as a function of its competitor’s states. The remaining probability is the probability that the firm exits. As can be seen, the probability of continuation is highest when competitor firms have either not entered or exited. Similarly, the probability of exit is highest when the competitor firms have already launched.

Figure 2: Continuation and Launch Probability for a Firm in Research Year 1 as a function of its competitor’s states, Low Type Market

7 Counterfactuals

7.1 Effect of Reduced FDA Approval Rates

The comparative effectiveness policy would require firms to prove how effective their drug is compared to existing treatment options. One of the possible effects of such a policy could be more stringent FDA approval rates when the firm is in its early years of Phase 3 research. To measure the possible effect of the introduction of this policy I modify the FDA’s probability of approval at each of the 5 research years to reflect a more stringent FDA. Table 6 presents the current FDA probabilities as well as the probabilities used in this counterfactual evaluation.

Figures 3 and 4 indicate that entry rates into Phase 3 decrease while continuation rates increase for those firms that have entered. As it is tougher to get approval, fewer firms enter
the market. However, conditional on entry the chances of getting approval are better as the firm progresses in research, thus justifying higher continuation rates. This indicates that while such a policy might deter entry, one of the possible benefits could be avoidance of wasteful investment and failures later on in the stage of development of the drug.

Figure 3: Entry rates under Comparative Effectiveness and Current FDA policies

Figure 4: Launch rates under Reduced and Current FDA approval rates
7.2 Effect of Providing Monetary Research Incentives

The National Institutes of Health (NIH) provides grants to firms and research institutions to enable them to conduct research and develop drugs relevant to public health needs. The estimates from the model can be used to determine the impact of such research budgets on firm's continuation and launch probabilities.

I compute the effect of providing incentives in the form of research budgets to firms in the Low Type market. I evaluate the equilibrium under the scenario where the research costs, as a result of exogenous intervention, are 10% lower than current costs.

Figure 5 plots the incremental launch probabilities arising from providing research grants. From Figure 2 we know that the launch (and continuation) probabilities are very low when the competitor's have either Launched or are in Research Years 2 and 3 (as these are the research stages when the competitor is most likely to launch). Providing research grants is most beneficial in increasing these probabilities.

This kind of evaluation can help NIH and other grant providing institutes determine the likely impact their grants will have.

8 Conclusions and Future Work

In this paper, a dynamic model of oligopoly was estimated accounting for unobserved heterogeneity in markets. The structural parameters that govern a firm's entry and continuation

\footnote{http://grants.nih.gov/grants/grant Basics.htm}
decisions in the complex and time-intensive R&D stage of the pharmaceutical industry were recovered using the two stage estimation procedure. We see that firms are strategic in their actions and take their competitor’s behavior into account. We also see clear evidence of heterogeneity in the types of markets with some markets supporting a larger number of firms than others.

This paper also examined the effect of reducing FDA approval rates which can help us better understand how incorporating comparative effectiveness can affect firm entry and investment rates. We saw that such a policy reduces entry rates, but conditional on entry increases continuation rates.

We also measured the effect on launch probabilities under reduced research costs. This can help us understand the effect of research grants on drug development.

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. We also assumed that conditional on being in a research state, all firms are equal. This assumption can be relaxed to account for firm heterogeneity where some firms have a higher likelihood of succeeding than others.
9 Tables

<table>
<thead>
<tr>
<th>Type 1 (Low Type)</th>
<th>Coefficient</th>
<th>t-stat</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>3.63</td>
<td></td>
</tr>
<tr>
<td>$\lambda_1$</td>
<td>-3.16</td>
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<td>$\alpha_{1,\text{launch}}$</td>
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<td>-2.20</td>
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<td>$\lambda_{1,\text{launch}}$</td>
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<td>-2.22</td>
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</table>

<table>
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<th>Type 2 (High Type)</th>
<th>Coefficient</th>
<th>t-stat</th>
</tr>
</thead>
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<td>$\alpha_2$</td>
<td>6.62</td>
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<tr>
<td>$\lambda_2$</td>
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<td>$\lambda_{2,\text{launch}}$</td>
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<tr>
<th>Homogeneous</th>
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</thead>
<tbody>
<tr>
<td>$\beta_{R1}$</td>
<td>-1.40</td>
<td>-1.73</td>
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<tr>
<td>$\beta_{R3}$</td>
<td>-0.99</td>
<td>-1.09</td>
</tr>
<tr>
<td>$\beta_{R4}$</td>
<td>-2.00</td>
<td>-3.26</td>
</tr>
<tr>
<td>$\beta_{R5}$</td>
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<td>-0.95</td>
</tr>
<tr>
<td>$\beta_{\text{exit}}$</td>
<td>0.02</td>
<td>0.03</td>
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<td>$\beta_s$</td>
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<td>$\lambda_{R1}$</td>
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<td>0.03</td>
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<tr>
<td>$\lambda_{\text{exit}}$</td>
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<td>1.25</td>
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Table 3: First stage Estimates of the Continuation and Entry Policy Functions

<table>
<thead>
<tr>
<th>Type 1 (Low Type)</th>
<th>Type 2 (High Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Acne</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Bipolar disorders</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>Depression</td>
</tr>
<tr>
<td>Squamous cell cancer</td>
<td>HIV infections</td>
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</table>

Table 4: Classification of (a subset of) markets based on First stage estimates
<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_{enter}$</td>
<td>Entry Cost</td>
<td>-295.1</td>
</tr>
<tr>
<td>$c_r$</td>
<td>Research Cost</td>
<td>-0.54</td>
</tr>
<tr>
<td>$\pi$</td>
<td>Annual Revenue (normalized)</td>
<td>180</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Impact of Launched competitors</td>
<td>-75.3</td>
</tr>
<tr>
<td>Objective Function</td>
<td></td>
<td>2.31e+7</td>
</tr>
</tbody>
</table>

Table 5: Second stage Parameter Estimates. Values are in $\text{}$millions

<table>
<thead>
<tr>
<th>Firm’s Research Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>17.4%</td>
<td>63.9%</td>
<td>50%</td>
<td>16.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Reduced FDA Approval Rates*</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Assumed probabilities for counterfactual evaluation

Table 6: FDA Approval Probabilities conditional on Firm’s research state
References


Appendix A: EM algorithm

The EM algorithm solves for \( \theta \) iteratively using the following recursion

\[
\theta^{k+1} = \arg\max_{\theta} \sum_i \sum_m q_{im} (\theta) \log \tau_m p_i (\alpha_m, \beta, \lambda_m, \gamma)
\]

(31)

\[
= \arg\max_{\theta} \sum_i \sum_m q_{im} (\theta^k) \log \tau_m + \sum_i \sum_m q_{im} (\theta^k) \log p_i (\alpha_m, \beta, \lambda_m, \gamma)
\]

(32)

where \( \theta = \{ \tau_1, \alpha_1, \lambda_1, \ldots, \tau_M, \alpha_M, \lambda_M, \beta, \gamma \} \). Define \( \mu_m = \{ \alpha_1, \lambda_1, \ldots, \alpha_M, \lambda_M, \beta, \gamma \} \)

As \( \tau_m \) enters only in the first part and \( \beta_m \) only in the second part, the maximization can be done separately

\[
\mu_m^{k+1} = \arg\max_{\mu_m} \sum_i q_{im} (\theta^k) \log p_i (\mu_m)
\]

(33)

\[
\tau_m^{k+1} = \arg\max_{\tau} \sum_i \sum_m q_{im} (\theta^k) \log \tau_m
\]

(34)

The following are the steps to arrive at the optimum value \( \theta^* \) that maximizes the likelihood of the data

1. Start with initial guess \( \theta^1 = (\mu_m^1, \tau_m^1) \)

2. Determine \( q_{im} (\theta^k) \) at the current guess of \( \theta^k \) as \( q_{im} (\theta^k) = \frac{\tau_m^k p_i (\mu_m^k)}{\sum_m \tau_m^k p_i (\mu_m^k)} \)

3. Perform the next iteration to determine \( \theta^{k+1} \) as

\[
\tau_m (\theta^{k+1}) = \frac{\sum_i q_{im} (\theta^k)}{\sum_m \sum_i q_{im} (\theta^k)}
\]

(35)

\[
\mu_m^{k+1} = \arg\max_{\mu_m} \sum_i q_{im} (\theta^k) \log p_i (\mu_m)
\]

(36)

4. Stop if \( ||\theta^{k+1} - \theta^k|| < tol \). Otherwise, set \( k = k + 1 \) and repeat steps 2-4.