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Dynamic R&D and the Effectiveness of Policy Intervention in the Pharmaceutical Industry

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Abstract

This study structurally estimates a dynamic model of drug development process in pharmaceutical industry, and uses counterfactual experiments to evaluate effects of various policy interventions aimed at increasing the introduction rate of new drugs within a specific therapeutic area. Advanced computational methods – such as continuous time and polynomial approximations – overcome the modeling difficulties that limited previous studies to one or two stages of development process, and allow the model to describe the progress of drugs through all three phases of clinical trials and FDA approval. The primary result is that most policies affecting earlier stages of drug development are less effective than those aimed at later stages. The reason for this finding is a strategic response to policy-induced changes in the number of drugs under development and on the market.

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1 Introduction

In 2005, The Bill and Melinda Gates Foundation have announced over $160 million in grants related to drugs and vaccines, covering every stage of their lifecycle, starting from initial discovery, following through clinical trials, and ending with sale subsidies. At the same time, the National Institutes of Health (NIH) have spent $2.9B on sponsoring clinical trials alone, which is more than 10% of spending by the firms in the industry. These numbers illustrate the effort that governments, NGOs and private charities exert to speed up the development of new treatments for various conditions, ranging from tropical diseases and AIDS to cancer.[1] In the vast majority of cases, these efforts aim to increase introduction of new drugs by profit-maximizing firms (as opposed to dedicated non-profit establishments).

This gives rise to the main question of this study – what is the best way to achieve the policy goal of increased output of new drugs? Is it best to finance the discovery of new substances with therapeutic potential? Or should a donor help offset the tremendous cost of the three stages of clinical trials that are required to determine whether the drug is sufficiently safe and effective? Or is it most efficient to expand markets for these drugs by subsidizing the sales? Yet another approach is to streamline and accelerate lengthy clinical trials and FDA review process.

In order to answer these questions, it is necessary to model the drug development process and the decisions made at each of several stages within it. Considering pre-clinical and clinical trials as well as FDA review, DiMasi, Hansen, and Grabowski (2003) estimate the average time to bring a single drug to the market at 12 years; in addition, only 1 out of 5 drugs survives the development process, bringing the

[1] This study will not deal with justification of such interventions, but accepts them as given. Common view is that targeted condition lack attention of Pharmaceutical companies due to lower profitability. Interested reader is pointed to Cockburn and Henderson (1996) for discussion of feasibility of public R&D funding.

total accumulated cost to $800 million. Faced by such long and uncertain return to investment, the decision to continue with each consecutive stage of development involves not only the medical viability of the drug, but also requires a conjecture about situation in the market several years into the future. The basis for this conjecture is formed by the current number of competing drugs at various stages of development, as well as beliefs about the evolution of these over time. The latter, in turn, depend on the decision rules used by the firms.

To accurately describe the features of this decision-making process, this study formulates a fully dynamic model using the framework established by Ericson and Pakes (1995). Unlike most recent empirical papers using this framework[2], the model is formulated in continuous rather than discrete time, as suggested by Doraszelski and Judd (2007). Broadly speaking, while the discrete time model assumes periodic and simultaneous decisions by all of the agents, continuous time assumes sequential decisions with random order of moves. This matches the actual decision-making process, and offers important methodological advantages (the model would be intractable if formulated in discrete time). Additional feature of the model is use of polynomial approximation to value and policy function (instead of more common discretization), which keeps the number of estimated parameters low, and again improves tractability.

The model is estimated structurally by means of Nested Pseudo-likelihood (NPL) method suggested by Aguirregabiria and Mira (2002) and Aguirregabiria and Mira (2007), which uses equilibrium conditions of the model to estimate costs of each stage of development process; a number of other parameters, such as the approval rate of FDA applications and average duration of each development stage, are estimated directly from data before structural estimation.

[2]See, for example Bajari, Benkard, and Levin (2006), Ryan (2005), Schmidt-Dengler (2005), Collard-Wexler (2005).

Once the model parameters and associated equilibrium are computed, it becomes possible to evaluate the impact of various policies through counterfactual experiments. Experiments consist of matching each policy intervention to a change in the appropriate model parameter, and computing the new equilibrium for this changed parameterization. These policy-affected equilibria, as well as the baseline estimate, are compared in terms of average flow of the new drugs through the development pipeline, with special emphasis on the new drugs entering the market.

The key finding is that interventions at later stages of a development process result in more new drugs entering the market than those at earlier ones. The reason for this is rooted in uneven distribution of positive and negative effects of a policy across the development stages. An increase in the number of drugs on the market and under development resulting from policy intervention necessarily reduces the value of each drug; to offset that, each policy offers a benefit of one sort or another. But the dynamic nature of the model means that negative effects affect all stages, while the policy benefit occurs only at a single stage.

Naturally, the increased flow of drugs through the pipeline is the strongest at the stage affected by the policy. Moreover, earlier stages also see an increase in activity as firms expect to collect the policy benefit in the future. But in the stages following the policy intervention, only the negative effect remains, discouraging the firms from continuing the development and causing the effect of the policy to weaken with each subsequent stage. Since policy interventions are set up to be comparable either in terms of average cost or direct impact on affected stage, earlier interventions seem to have lower impact on the number of drugs entering market – the final stage of a drug's life.

In order to make necessary assumptions, this study relies on a substantial body of existing work studying individual stages of drug development process. The Henderson-

Cockburn research programme (1994a, 1994b, 1996) develops a framework for describing initial ("discovery") research and finds such features as spillovers, economies of scale, and scope.

The literature on clinical trials includes such works as Danzon, Nicholson, and Pereira (2003), Guedj and Scharfstein (2004), Dranove and Meltzer (1994) and Cockburn and Henderson (2001). These papers document a number of non-medical factors that affect the decision to continue the development into the next phase – size and type of firm, experience, and the perceived earning potential of the drug.

The market for drugs has been extensively studied by Berndt, Bui, Reily, and Urban (1994, 1995) and Azoulay (2002) who document extensive advertising expense that plays at least as large a role as quality of the drug, and show that first-mover advantage is present but temporary; these results suggest that differentiation in drug markets is horizontal rather than vertical. Roberts (1999) finds correlation between market profitability and rate of new drug introduction, confirming presence of an economic factor in R&D decisions. Grabowski and Vernon (1994) combine revenue data with development cost estimates of DiMasi, Hansen, and Grabowski (2003) to show that average return on investment in pharmaceutical industry is on par with the economy average, which helped put to rest accusations of unjustifiably high drug prices.

This paper contributes to the literature on pharmaceutical industry by aggregating the existing research on individual stages into a dynamic model of the entire development process. While such a model is analytically intractable, recent developments in computational economics have made it possible to estimate the model parameters and solve for the equilibrium numerically.

The rest of the paper proceeds as follows: Section 2 starts by describing the pharmaceutical industry, Section 3 sets up the model of the drug development process,

Section 4 discusses available data and estimation approach, and Section 5 presents the results.

2 R&D in Pharmaceutical industry

Pharmaceutical industry is characterized by a high intensity of R&D effort, meaning that new products (drugs and other treatment methods) constantly enter the market, driving the older ones out. In many modern industries, the focus of innovation is on research, which results in evolutionary (or revolutionary) changes to product; development is a relatively straightforward process of setting up the production. Pharmaceutical R&D is different in the sense that development (in the form of several phases of trials) plays a much bigger role, taking considerable time and costing more than research. Moreover, US's Food and Drug Administration (FDA), or similar regulatory body in other countries) requires firms to go through the complete set of trials for each new drug, so it makes sense to describe the R&D process as the sequence of stages in the "lifecycle" of a drug.

The research stage is referred to as *Initial discovery*; it results in the new chemical entities (NCE's), i.e. compounds believed to have therapeutic potential. These are typically patented and/or described in academic publications. The costs are relatively minor, as the research is limited to the laboratory experiments and wide adoption of the scientific discovery method has largely eliminated need for extensive trial-and-error search[3].

The next development stage for NCE is know as the *Pre-clinical trials* which are conducted on animals and test the safety of the drug. They take around 2-3 years.

If pre-clinical trials are successful and the firm wants to proceed with the drug, it

[3]See, for example Cockburn, Henderson, and Stern (2001).

files *Investigational new drug* (IND) application to FDA. The application summarizes the results of pre-clinical trials and requests permission to start human (clinical) trials. The wait for this decision is relatively short as FDA has only 30 days to review the application and voice any objections.

Once the drug receives IND status, the firm can start the *Clinical trials* that are the central part of the development process, taking on average 9.7 years and consuming the bulk of the cost. They are conducted on human subjects. The FDA standards for these trials demand a control group that receives a placebo or an already approved treatment, random allocation of subjects to treatment and control groups, and a "double blind" requirement that this allocation is not known to either the subjects or the physicians evaluating their condition. The trials are grouped into three phases of increasing breadth and length:

- *Phase I* establishes basic safety of the drug and typically involves a small group of healthy subjects, since they are likely to suffer less harm than patients already weakened by the condition if drug turns out to be unsafe.

- *Phase II* evaluates the efficiency of the drug in treating patients who have the target condition, which typically requires a larger group of subjects than Phase I.

- *Phase III* checks for any long-term side effects, which necessarily takes a considerable time and requires a broad range of subjects covering all possible demographics.

Within each phase, pharmaceutical firms conduct several trials with varying dosages of the drug, delivery methods, etc. Trials continue until the firm collects enough information to reach a conclusion on whether the drug satisfies the objective of the

respective phase, and whether the drug shows enough promise to continue development into the next phase.

Once the trials are complete, and if the firm is happy with their results, a *New drug application* (NDA) is submitted to FDA, who reviews the results of clinical trials and decides whether the drug is allowed to enter the market. The review process typically takes almost 3 years. Like with the trials, the decision to file the NDA application is not costless – in addition to application fee, firms have to compile and format the application materials, follow up with FDA and answer any questions that arise during the review process.

If FDA approves the drug, it is launched on the *Market* though a heavy advertising campaign. Over-the-counter drugs are advertised directly to consumer; prescription drugs are "detailed" to physicians by sales representatives. Advertising expenses remain a sizeable fraction of sales even after the launch. Drugs are rarely withdrawn from the market (only in case of unexpected side-effects), but they are displaced over time by newer drugs or generics. First-mover advantage is considerable but not always permanent, as Azoulay (2002) demonstrates. Individual susceptibility of patients to drugs means that differentiation between drugs is horizontal rather than vertical.

The most common definition of market within the industry uses Anatomical-Therapeutic-Chemical classification, i.e. a market consists of drugs that treat similar conditions using a specific chemical mechanism. The definition of markets along geographical boundaries is less common since the costs of entering additional countries are small compared to the expense of initial clinical trials; low transportation costs lead to active international trade. Division along consumer income and other demographic characteristics is even less common since various private and public health insurance schemes make same drugs available to widely varying groups of people.

Patent expiration & generics are a major factor contributing to gradual decline

of profitability and eventual elimination of the drug from the market. While the patent application is filed early in the development process, as of 1994 the expiration countdown is reset when NDA is filed, with 20 years of protection granted to all drugs. After patent expires, a generic (unbranded) version of the drug promptly enters the market[4]. Typically, brand loyalty and risk aversion of physicians keep the sales of original drug way above the generic; recent development of HMO's and implementation of drug-substitution mechanisms at the pharmacy level are partially offsetting this advantage.

An important feature of the R&D process is the gradual elimination of the drugs as they go through the development stages. Anecdotal evidence suggests that out of 5000 NCE's, 20 enter the pre-clinical trials, 5 receive IND status and only one is approved by FDA. Besides the two stages of FDA approval, a major source of such selection are the pharmaceutical companies themselves, that can (and do) discontinue drugs at every stage of the development process. Based on interviews during the data collection process, the reasons for such decisions are not limited to poor results of clinical trial, but can include "strategic considerations" or lack of funds[5]. This suggest building an economic model to describe these decisions.

3 Model

This section models the decisions of a pharmaceutical firm regarding the progress of drugs through development pipeline as the optimal strategy in a fully dynamic game. Subsection 3.1 sets up basic notation and introduces model parameters, and subsection 3.2 defines the equilibrium.

[4]While a generic also requires an FDA registration, Waxman-Hatch act of 1984 make it sufficient to demonstrate bioequivalence with the original drug, essentially reducing the entry barrier to zero.

[5]Financing constraits can be ingnored here, since it is common practice for small firm to sell drugs it cannot develop to a larger company.

3.1 Assumptions and notation

As previous section described, progress of drug through the development pipeline is a sequence of decisions to continue to the next stage or abandon the drug (here and below, word "stage" is used as a more general term than "phase of clinical trial", since stage can also include pre-clinical trial, FDA review and market.). This model will describe these decisions regarding an individual drug. Lacking data on clinical trial outcomes, the drugs are assumed to be identical (given same stage of development). This assumption is a "conservative" one, since it eliminates particularly good ("star") drugs from the model; it does not really affect underperforming drugs, since those are likely to be abandoned at previous stages of the development process.

The model assumes anonymous ownership of the drugs, essentially assuming that each drug is owned by a separate firm that has no other drugs, and is identical to any other firm on the market. This abstracts away from a possibility of a "large" firms that owns several drugs in each of development phases. While it is a realistic situation, and affects decision making in a meaningful way, but properly accounting for it would considerably complicate the model, and is not likely to generate any new insights since the decisions by both single- and multi-drug firms respond in similar way to outside factors.

Anonymous ownership also assumes away firms active on more than one market, but there is no evidence in industry literature to suggest use of multi-market strategies by Pharmaceutical firms, which is expected given sometimes widely different conditions and treatments that define each market.

The fundamental assumption of Ericson and Pakes (1995) modeling framework is that all the relevant information about an industry can be compressed into the few numbers of a state vector. "Relevant information" here refers to a maximum

information set that a firm within the industry can use to predict the actions of it's competitors and future development of the industry that it implies[6]. The solution concept is Markov-perfect equilibrium (MPE) that requires the firm's decisions to be optimal given current industry state, privately observed information and (rational) beliefs about the decision rules of competitors.

A consequence of such state-dependent strategies is that there is no history dependence, i.e. it does not matter how did the industry arrive at the present state. This prevents collusion (tacit or explicit) from being enforced by various punishment strategies. While allegations of price-fixing have been common during the 1990s, studies like Grabowski and Vernon (1994) demonstrated that proper computation of R&D expenses brings profitability of Pharmaceutical companies on par with other high-tech industries and it's own cost of capital.

In the model of this study, the state of a drug is given by it's current development stage, indexed by $s \in \{1:5\}$:

∘ $s = 1:3$ correspond to Phases I-III of clinical trials,

∘ $s = 4$ – drug submitted for FDA review, and

∘ $s = 5$ – drug on the market.

State of the industry is characterized by a vector $x \in \mathbb{Z}_+^5$; its component is denoted as x_s represents the number of drugs at stage s. A combined state of a single drug and the industry around it is (s, x); note that $x_s \geq 1$ since the singled-out drug is included into x.

Given a drug entering stage s, the duration of the stage is assumed to be random and distributed as Exponential with average duration $1/\mu_s$ years. This means that regardless of how long the drug has been in the stage, the hazard rate[7] of stage ending

[6] This development need not be deterministic, as the model incorporates purely random events (moves by "nature") and decisions based on privately observed random draws.

[7] Hazard rate refers to average number of events happening per a period of certain length. Here,

in the subsequent year remains μ_s. This is generally consistent both with observed data, and the industry practice of doing a series of trials[8] within each phase until the firm has enough information to make the decision.

The decision in question is whether to abandon the drug or move on to next phase of clinical trials. The information set for this decision includes the results of the trial (privately observed), number of competing drugs at every stage of other firms (x) and lump-sum cost of next phase R_s.

The results of the clinical trial is consist of $\varepsilon = (\varepsilon_0, \varepsilon_1)$ – a pair of independent type I Extreme Value random variables with standard error parameter σ_s. If the the drug is abandoned, the firm owning it receives ε_0 ($\varepsilon_0 < 0$ means that the firm pays the amount); if it advances to next stage – firm receives ε_1. Realizations of these ε are assumed to incorporate several unobserved factors, including (a) the difference between R_s and actual cost of continuing to next stage, (b) chance of FDA approval, (c) future earning potential of the drug, (d) "salvage value" of a drug, either for treatment of other conditions[9] or as a source of spillovers. Vector ε is private information because most of (a)-(d) cannot be observed from outside the company; the academic publications that follow the completion of a trials phase reveal only partial information, and are delayed in time.

Without observing the private results of the trial (as is the case with a firm considering possible actions of its competitors), the decision can be characterized by a probability of continuing to next phase. This probability will be endogenously determined in the model and is denoted as $p(s, x)$ – probability that drug will advance

the period is chosen to be year. Hazard rate can be interpreted as probability as long as it is no larger than one.

[8] The conditions of the trial – such as dosage, frequency, delivery methods, target demographics – are adjusted from one trial to the next in search of optimal performace.

[9] Pharmaceutical industry has numerous cases of drugs turning out to be effective in unintended roles, most famous of which is Viagra, which was originally developed as treatment for angina.

to phase s from $(s-1)$.

A drug submitted for FDA review ($s = 4$) has a constant and exogenous probability of advancing given by p_5. Keeping probability of FDA as constant reflects the assumption that unlike firm's decision, FDA's approval process is not affected by situation on the market, and is driven entirely by therapeutic considerations. There is anecdotal evidence that large established firms have easier time getting their drugs through FDA (both in terms of time it takes to reach a decision, and decision itself), and it is reasonable to assume that FDA would take a different approach for drugs in what it views as "priority" areas. Accounting for identity of drug owner is not possible under anonymity assumption; effect of changing FDA priorities requires additional data.

A drug on the market ($s = 5$) involves no decisions, but earns a steady stream of annual profits $R_5(x)$. Lacking meaningful information on quality of the drug, the functional form of $R_5(x)$ assumes the equal split of market by all drugs present on it.

$$R_5(x) = \frac{\pi M}{x_5},$$

where M is market size (in terms of total revenue), and $\pi < 1$ is the profit margin[10]. The assumption of equal market share does not negate first-mover advantage that is clearly a feature of drug markets, since first drug to reach the market starts earning profits earlier than others, these profits are larger, and increased number of drugs on the market discourages further entry.

Just like with previous stages, hazard rate $\mu_5 > 0$ gives the likelihood of the stage ending. In the case of a drug on the market, however, the end of stage means permanent exit of a drug from the industry. This assumption reflects gradual erosion

[10] π is defined as share of revenues left after deducting production, marketing, operating and research costs. Development costs are excluded since model incorporates them explicitly (as R_s)

of drug's profitability by more advanced substitutes and generics.

Having discussed progress of drugs through the pipeline and their exit, it remains to describe the process that puts new drugs into the pipeline. The assumption here is that every year an average of λ_0 drugs enter the Phase I trials ($s = 1$). This assumption eliminates the transition from pre-clinical to clinical trials from the model; it is unavoidable since the transition involves two separate decisions – IND application by the firm, and FDA response to it. As described in Section 4 below, available data do not allow to separate these two decisions, preventing any meaningful use of them in the model. This assumption also reflects the fact that a lot of discovery research is conducted in academic rather than commercial labs, so unlike development decisions, the intensity of research is not necessarily affected by situation in the market. Instead, one of policy experiments simulates increasing output of discovery research as the result of increased funding of a particular field, increased public attention or scientific relevance, etc.

3.2 Equilibrium

The decision to continue with development will maximize the present expected value of a drug, conditional on private information, development stage of the drug and industry state. The result of this optimization is called value function and denoted as $V(s, x)$.

Computing present expected value of a drug requires an assumption about the progress of time in the model. Common assumption in Ericson and Pakes (1995) framework was discrete time, with a period of set length (e.g. year), which included the simultaneous decisions by all firms and subsequent simultaneous transit of all players to new states according to these decisions and exogenous random processes.

In this case, discrete time is inappropriate for two major reasons. First, while there are industries where decision are made annually and simultaneously, decisions regarding drug development are made at random points in time throughout the year. Second, simultaneous transitions lead to insurmountable burden of computing the expectation over them.

Consider industry in state x; for any stage s, there are x_s drugs in that stage, and each of them can complete the trial in current period. Further, each of drugs completing the trial may (or may not) advance to the next phase. Overall, the number of possible combinations is $\left[x_5 \prod_{s=1}^{4} \frac{(x_s+1)(x_s+2)}{2}\right]$. Even for 5 drugs in each phase (entirely realistic situation, according to Table 1 below), that means almost a million combinations.

There is no opportunity to simplify the computation using independence; the changes in individual components x_s's are pair-wise dependent since a drug advancing to the next stage necessarily leaves the previous one. It turns out that with current computing technology, going through all of these realization takes prohibitively long time.

Instead, this study assumes the continuous timescale, meaning that individual trials end at random moments in the time continuum, and are instantly followed by a decision and transition to the next stage (or discontinuation). As a result, probability of two or more transitions occurring simultaneously is zero, so such events need not be considered. This leaves only the transitions of individual drugs, which permit only two possible outcomes and make the computation of expectation trivial.

Writing out expression for expected present value $V(s, x)$ requires some additional notation. Let $a_s \in \{0, 1\}$ denote decision to continue development to stage s, T_s – realized duration of this stage. Discounting of future profits and costs is parameterized by firm's cost of capital ρ; given continuous time, discount factor applied to cash flow

occurring at time t is $e^{-\rho t}$. Then the present value of a drug in stage $s = 1$ and facing industry state x_0 at $t = 0$ is given by:

$$V(1, x_0) = \max_{a_s} \mathbf{E}_{\varepsilon_s, T_s, x_t | x_0} \left\{ \begin{array}{l} e^{-\rho T_1} \{ (1 - a_2) \varepsilon_{0,1} - a_2 (R_2 - \varepsilon_{1,1}) + a_2 \times \\ \times e^{-\rho T_2} \{ (1 - a_3) \varepsilon_{0,2} - a_3 (R_3 - \varepsilon_{1,3}) + a_3 \times \\ \times e^{-\rho T_3} \{ (1 - a_4) \varepsilon_{0,3} - a_4 (R_4 - \varepsilon_{1,3}) + a_4 \times \\ \times e^{-\rho T_4} p_5 \times \\ \times \int_0^{T_5} e^{-\rho q} R (x_{q+T_1+T_2+T_3+T_4}) \, dq \} \} \} \end{array} \right\}, \quad (1)$$

and expression for value of a drug in an arbitrary stage s can be obtained from (1) by dropping first $s - 1$ lines.

Even with simplification of transition process, (1) is not tractable. Instead, this study uses Bellman optimality principle that reduces the problem to solving for one decision at a time. Note that (1) can be restated as:

$$\begin{aligned} V(1, x) &= \max_{a_2} \mathbf{E}_{\varepsilon_1, T_1, x_{T_1}} \left\{ \begin{array}{l} e^{-\rho T_1} \{ (1 - a_2) \varepsilon_{0,1} - a_2 (R_2 - \varepsilon_{1,1}) + a_2 \times \\ \times \max \mathbf{E}_{\varepsilon_s, T_s, x_t | x_{T_1}} [e^{-\rho T_2} \{ (1 - a_3) \varepsilon_{0,2} - a_3 (R_3 - \varepsilon_{1,3}) + a_3 \times \\ \times e^{-\rho T_3} \{ (1 - a_4) \varepsilon_{0,3} - a_4 (R_4 - \varepsilon_{1,3}) + a_4 \times \\ \times e^{-\rho T_4} p_5 \times \\ \times \int_0^{T_5} e^{-\rho q} R (x_{q+T_1+T_2+T_3+T_4}) \, dq \} \} \}] \end{array} \right\} \\ &= \max_{a_2} \mathbf{E}_{\varepsilon_1, T_1, x_{T_1}} \left\{ e^{-\rho T_1} \{ (1 - a_2) \varepsilon_{0,1} - a_2 (R_2 - \varepsilon_{1,1}) + a_2 V(2, x_{T_1}) \} \right. \end{aligned}$$

The next step is to consider an interpretation of continuous time as a limiting case of discrete-time model when the length of the period approaches zero. The approach is to take a short period of time Δ, write a discrete-time Bellman equation describing the change of the value over that period, transform the equation and take a limit as $\Delta \longrightarrow 0$. Since the firm's information set does not include time, firm's decision and

industry transitions are invariant of t, and the time subscript is dropped. Further details depend on the stage of the drug described by the equation ("our drug"), which is denoted as $\bar{s}$ (to distinguish it from arbitrary subscript s).

Consider a **drug in clinical trials** ($\bar{s} \in \{1, 2, 3\}$). It is easiest two write out the equation, and then explain what individual terms mean:

$$V(\bar{s}, x) = (1 - \rho\Delta) \times$$

$$\times \left\{ \begin{array}{cc} (\Delta\mu_{\bar{s}} + O(\Delta^2))\, \sigma \log \left[1 + \exp \left\{ \dfrac{V\left(\bar{s}+1, x_{-s}^{+(s+1)}\right) - R_{\bar{s}+1}}{\sigma} \right\} \right] & (A) \\ + \sum_{s=1}^{5} (x_s - 1_{\bar{s}=s}) (\Delta\mu_s + O(\Delta^2)) \left[\begin{array}{c} p(s+1, x)\, V\left(\bar{s}, x_{-s}^{+(s+1)}\right) \\ + (1 - p(s+1, x))\, V(\bar{s}, x_{-s}) \end{array} \right] & (B) \\ + (\Delta\lambda_0 + O(\Delta^2))\, V(\bar{s}, x^{+1}) & (C) \\ + \left(1 - \left[\begin{array}{c} \sum_{s=1}^{5} [x_s \Delta\mu_s + O(\Delta^2)] \\ + \Delta p_0 + O(\Delta^2) + \Delta\lambda_0 + O(\Delta^2) \end{array} \right] \right) V(\bar{s}, x) & (D) \end{array} \right\}$$

Since the drug is in the trial, it does not generate any profit, so all there is the expected future value term. The discount factor is $e^{-\rho\Delta} \approx (1 - \Delta\rho)$. Now consider the sum in the curly brackets, which is described line-by-line:

(A). This term deals with our drug finishing clinical trial during the Δ period. The probability of this event is is $\Delta\mu_{\bar{s}}$. Probability that some other drug will finish stage s is $\Delta\mu_s$. Probability that these two events will happen simultaneously is $\Delta\mu_{\bar{s}}\Delta\mu_s = \Delta^2\mu_{\bar{s}}\mu_s = O(\Delta^2)$ as the limit is taken at $\Delta \longrightarrow 0$. So one can safely assume that any expected value associated with some other drug transiting along with ours is $O(\Delta^2)$.

The $\sigma \log [...]$ term is the expected value resulting from decision to abandon the

drug ($a = 0$) or advance to next stage ($a = 1$):

$$\sigma \log \left[1 + \exp \left\{ \frac{V\left(\bar{s}+1, x_{-s}^{+(s+1)}\right) - R_{\bar{s}+1}}{\sigma} \right\} \right] =$$

$$= \mathbf{E}_{\varepsilon} \max_{a \in \{0,1\}} \left\{ (1-a)\,\varepsilon_0 + a \left[\varepsilon_1 - R_{\bar{s}+1} + V\left(\bar{s}+1, x_{-s}^{+(s+1)}\right) \right] \right\} \tag{2}$$

where $V\left(\bar{s}+1, x_{-s}^{+(s+1)}\right)$ is the value realized if the drug advances, and $x_{-s}^{+(s+1)}$ means x with x_s decreased by one, and x_{s+1} increased by one to reflect transition of our drug to the next stage. It follows from properties of EV distribution that

$$\begin{aligned} p\left(\bar{s}+1, x\right) &= \mathbf{E}_{\varepsilon^i} a \qquad (3) \\ &= \left[1 + \exp \left\{ -\frac{V\left(\bar{s}+1, x_{-s}^{+(s+1)}\right) - R_{\bar{s}+1}}{\sigma} \right\} \right]^{-1} \end{aligned}$$

(B). This term deals with other drugs completing the trials, receiving FDA approval or exiting the market. For a drug in stage s, probability of such event is $\Delta\mu_s$, probability of that for one in x_s drugs is $\Delta x_s \mu_s + O\left(\Delta^2\right)$, and expectation of more than one drug reaching the end of a stage is again $O\left(\Delta^2\right)$.

If a drug completes stage s, it advances to the next stage with probability $p\left(s+1, x\right)$, which causes the change in industry state and corresponding change in the expected value of our drug (x_{-s} means x with x_s reduced by one). To avoid separate notation for $s = 5$ (drug on the market), let $p\left(6, x\right) \equiv 0$ (i.e. it cannot transit further).

(C). This term reflects the chance that a new drug enters Phase I trials. The probability of this $\Delta\lambda_0$, plus $O\left(\Delta^2\right)$ term that incorporates simultaneous events.

(D). This term represents the value realized if none of the above events occur during the Δ period. Appropriately, the probability is one minus sum of all other probabilities, and the value realized remains at $V\left(\bar{s}, x\right)$.

Now let's transform the equation. Split the (D) term and rearrange to obtain:

$$\rho\Delta V(\bar{s},x) = (1-\rho\Delta)\times$$
$$\times\left\{\begin{array}{c}(\Delta\mu_{\bar{s}}+O(\Delta^2))\left(\sigma\log\left[1+\exp\left\{\frac{V\left(\bar{s}+1,x_{-s}^{+(s+1)}\right)-R_{\bar{s}+1}}{\sigma}\right\}\right]-V(\bar{s},x)\right)\\ +\sum_{s=1}^{5}(x_s-1_{\bar{s}=s})(\Delta\mu_s+O(\Delta^2))\left[\begin{array}{c}p(s+1,x)V\left(\bar{s},x_{-s}^{+(s+1)}\right)\\ +(1-p(s+1,x))V(\bar{s},x_{-s})\\ -V(\bar{s},x)\end{array}\right]\\ +(\Delta\lambda_0+O(\Delta^2))\left[V(\bar{s},x^{+1})-V(\bar{s},x)\right]\end{array}\right\}$$

Now note that for arbitrary constant π, $(1-\rho\Delta)(\Delta\pi+O(\Delta^2)) = \Delta\pi+O(\Delta^2)$ and take the limit of the ratio of two sides of the equation as $\Delta\longrightarrow 0$, which gives:

$$\begin{array}{c}\rho V(\bar{s},x) = \mu_{\bar{s}}\left(\sigma\log\left[1+\exp\left\{\frac{V\left(\bar{s}+1,x_{-s}^{+(s+1)}\right)-R_{\bar{s}+1}}{\sigma}\right\}\right]-V(\bar{s},x)\right)\\ +\sum_{s=1}^{5}(x_s-1_{\bar{s}=s})\mu_s\left[\begin{array}{c}p_s(s,x)V\left(\bar{s},x_{-s}^{+(s+1)}\right)\\ +(1-p_s(s,x))V(\bar{s},x_{-s})\\ -V(\bar{s},x)\end{array}\right]\\ +\lambda_0\left[V(\bar{s},x^{+1})-V(\bar{s},x)\right]\end{array} \tag{4}$$

This is the standard form of Bellman equation for continuous time model, which sets the rate of change in value implied by discount rate $(\rho V(\bar{s},x))$ equal to the expected rate of change provided by the model. The latter is a sum of products of hazard rates for each event and expected change in value as the result of that event.

The equation for a **drug under FDA review** $(\bar{s}=4)$ is constructed in a similar way, except that transition of our drug to the next stage is determined by FDA decision, which is an exogenous random event from the point of view of the firm who

only know the probability of positive decisi on $p_{\bar{s}+1}$:

$$\begin{aligned}\rho V(\bar{s},x) &= \mu_{\bar{s}}\left[p_{\bar{s}+1}V\left(\bar{s}+1,x_{-\bar{s}}^{+(\bar{s}+1)}\right)-V(\bar{s},x)\right]\\ &+\textstyle\sum_{s=1}^{5}(x_s-1_{s=\bar{s}})\,\mu_s\begin{bmatrix} p_s(s,x)\,V\left(\bar{s},x_{-s}^{+(s+1)}\right)\\ +(1-p_s(s,x))\,V(\bar{s},x_{-s})\\ -V(\bar{s},x)\end{bmatrix}\\ &\qquad +\lambda_0\left[V(\bar{s},x^{+1})-V(\bar{s},x)\right]\end{aligned} \tag{5}$$

Finally, **drug on the market** ($\bar{s}=5$) does not involve any decisions, but it can vanish from the market, and it's value is still affected by new other drugs progressing through the pipeline, entering or exiting the market:

$$\begin{aligned}\rho V(\bar{s},x) &= R_5(x)-\mu_{\bar{s}}V(\bar{s},x)\\ &+\textstyle\sum_{s=1}^{5}(x_s-1_{s=\bar{s}})\,\mu_s\begin{bmatrix} p_s(s,x)\,V\left(\bar{s},x_{-s}^{+(s+1)}\right)\\ +(1-p_s(s,x))\,V(\bar{s},x_{-s})\\ -V(\bar{s},x)\end{bmatrix}\\ &\qquad +\lambda_0\left[V(\bar{s},x^{+1})-V(\bar{s},x)\right]\end{aligned} \tag{6}$$

Taken together, equations (3), (4), (5), and (6) form the equilibrium conditions on value function $V(s,x)$ and policy function $p(s,x)$.

4 Data and Estimation approach

The dataset[11] used in this study consists of year-drug observations of development stage $\bar{s}$ along with various additional information, most important of which is classification of the drug under Anatomical-Therapeutic-Chemical system that allows

[11] Data are provided by PharmaProjects, a service of Informa UK Ltd.

to group drugs into economically meaningful markets. The dataset covers 11 years (1995-2005) and is limited to markets with active research within the broader category of Infection drugs.

The dataset does not allow to properly model the transition from pre-clinical to clinical trials. This transition involves two separate decisions – firm choosing to file the IND application, and FDA reviewing it. Review takes at most 30 days, so dataset does not even define a stage for a drug under IND review. As the result, one cannot identify drivers of firm's decision to proceed separately from FDA approval probability.

While it would be useful to have results of clinical trials, those exist only in the form of abstracts, which describe the experiments conducted, various efficiency measures and side-effect rates. There seems to be no unified approach to measuring them and no formalized data are available, so trial results are viewed as unobserved.

Observing the stage of individual drugs across the years provides an estimate μ_s's – parameters driving the duration of each stage. Similar approach gives estimate of λ_0 (the arrival rate of drugs into Phase I), since dataset starts tracking drugs from pre-clinical stage.

Further, observed changes in stage indicate the decision to continue the development of the drug (indicated by advancement to next stage) or abandon it (indicated by transit to "Discontinued" stage). For drugs transiting out of FDA stage, this directly provides an estimate of p_5 – the probability of FDA approval, which is treated as exogenous in the model. The observed transitions out of clinical trial stages become observations on continuation decision of the firm (denoted a) and serve as the basis for structural estimation of the stage costs $R = \{R_s\}_{s=2}^4$. Structural estimation also requires knowledge of industry state x, which is constructed by aggregating stage data for all drugs in given market & year.

s	$\bar{x}_s$	s.e.	$\min x_s$	$\max x_s$
1	10.86	6.18	1	22
2	14.86	7.77	3	28
3	7.86	3.67	3	15
4	3.77	3.15	0	13
5	27.87	16.01	11	58

Table 1: Summary statistics of industry state vector x.

The identification of R is possible since the dataset records decisions taken by firms that face a wide range of industry states x. This variability results from observing both different markets and different moments in time. As a confirmation, Table 1 provides summary statistics for observed industry state x.

The estimation approach is Nested Pseudo-likelihood method of Aguirregabiria and Mira (2007), which essentially combines the value iteration of Pakes and McGuire (1994) with MLE estimation. Besides the stage costs stage, the estimation process simultaneously generates a model equilibrium, as defined by $\{V(\cdot), p(\cdot)\}$ pair.

The estimation proceeds iteratively, with each iteration k starting from (a) an equilibrium "candidate" $\left\{V^k(\cdot), p^k(\cdot)\right\}$ and (b) parameter estimate $\hat{R}^k$. The iteration updates them to $(k+1)$-th iterate in two steps:

1. Pakes and McGuire (1994) update of the equilibrium candidate, which uses the equilibrium conditions (3), (4), (5), and (6). For each state $(\bar{s}, x)$, $\left\{V^{k+1}(\bar{s}, x), p^{k+1}(\bar{s}, x)\right\}$ are computed by plugging $\hat{R}^k$ and $V^k(\cdot), p^k(\cdot)$ into the equilibrium conditions and solving for $\{V(\bar{s}, x), p(\bar{s}, x)\}$.

2. MLE estimation of parameter vector $\hat{R}^{k+1}$. The likelihood of a single observation j is constructed by computing the predicted continuation probability $p^{k+1}(s^j + 1, x^j)$ and matching it to the observed action a^j. After transforma-

tions, log-likelihood function reduces to:

$$\mathcal{L}(R) = \sum_{j=1}^{N} \left[a^j \delta_j - \log\left(1 + \exp\left(\delta_j\right)\right) \right] \tag{7}$$

$$\text{where } \delta_j = \frac{V^{k+1}\left(s^j + 1, x^j\right) - R_{s^j+1}}{\sigma_{s^j}} \tag{8}$$

The new parameter vector $\hat{R}^{k+1}$ is then selected to maximize this log-likelihood.

The iterations continue until the changes in $\left\{V^k(\cdot), p^k(\cdot)\right\}$ and $\hat{R}^k$ become smaller than pre-determined tolerance level.

There is no theoretical result that guarantees either existence or uniqueness of equilibrium in this kind of model. Doraszelski and Satterthwaite (2007) prove existence of Markov perfect equilibrium in certain kinds of dynamic games, but their results are not applicable here. Besanko, Doraszelski, Kryukov, and Satterthwaite (2007) show that a dynamic game can have (economically meaningful) multiple equilibria.

Even if equilibrium exists, the algorithm presented above is not guaranteed to converge. There is a number of technical improvements (such as dampening) that help improve convergence, and indeed all cases considered in Section 5 did converge.

The potential multiplicity of equilibria is a much more serious issue; every estimation method for dynamic games assumes that if multiple equilibria exist, then same equilibrium is played out in every market. In pharmaceutical industry, however, this assumption might be at least partially justified since there are several large companies that are present in every market, so they are likely to use same strategies themselves which would force smaller firms to play same equilibrium as the best response.

A few additional notes are necessary to complete the description of model implementation and estimation.

Value function $V(\cdot)$ is represented as polynomial approximation, since discretization (computing and storing V for every possible value of $(\bar{s}, x)$ vector) is unfeasible due to the size of the state space. The polynomial approximation used in this exercise is a version of 2nd-order complete polynomial representation:

$$V(s,x) = v_0^s + \sum_{r=1}^{5} \left[v_r^s x_r + v_{r,r}^s x_r^2 \right] + \sum_{r=1}^{4} v_{r,r+1}^s x_r x_{r+1}. \tag{9}$$

Thus, the function $V(\cdot)$ is reduced to a set of coefficients $\mathcal{V} = \left\{ v_r^s, v_{r,q}^s \right\}_{r \in \{1..5\}, q \in \{r,r+1\}}^{s \in \{1..6\}}$. The Pakes and McGuire (1994) update of equilibrium in this case consists of computing V^{k+1} for a pre-determined set of states, then using OLS formula to recover the coefficients. There is no need for approximating (or even tracking) $p(\cdot)$ since (3) provides an easy way of computing it from $V(\cdot)$.

As follows from (7), it is not possible to identify R_s separately from private information variance parameter σ_s. Instead, this study follows the traditional approach of holding σ_s constant at some pre-selected level. The specific values of σ_s's are based on level of $V(s,x)$ for each stage and reflect the wide distribution of possible trial outcomes.

Finally, the dataset is compiled of markets within the same size bracket, so there is no need to specially account for it in (9).

Once an estimate of R is obtained, it is used to evaluate impact of various policies as described in Section 5 below.

5 Results

5.1 Estimates

As mentioned in Section 4 above, a number of model parameters are estimated directly from data, and then estimate of the remaining parameters and model equilibrium are produced using the Nested Pseudo-likelihood method.

Phase s	$\hat{\mu}_s$	Implied phase duration (yrs)
1	0.3929	2.55
2	0.2663	3.76
3	0.2865	3.5
4	0.3455	2.89

Table 2: Estimates of stage duration paramaters μ_s.

The estimates of μ_s – the probability that drug will complete the present stage within a year are presented in Table 2. Average annual arrival of new drugs is estimated at $\hat{\lambda}_0 = 4.05$.

Unfortunately, the PharmaProjects database does not track the sales of the drugs, so it is impossible to tell when any drug leaves the market. Instead, an assumed value of $\lambda_5 = 0.95$ is used, setting the average lifespan of a given drug equal to patent life of 20 years. In addition, a correction must be applied to the data on x_5, since in raw form they represent the number of all drugs released on the market since the records began. Since PharmaProjects started tracking drugs in late 1980's, the average age of the drugs in the sample is about 10 years, so x_5 is multiplied by $(\lambda_5)^{10}$.

The probability of FDA granting a permission to enter the market is again estimated directly from data as $\hat{p}_5 = 0.7894$.

The profit margin is set as $\pi = 0.3$, according to an industry publication; this margin excludes R&D costs, since they are already accounted for in the model. All

data come from markets placed into \$2-5 billion annual revenue bracket, so market size is set to average value: $M = 3500$ (in millions of dollars).

The discount rate ρ is set to 0.05, corresponding to long term real return on investment of 5%.

s	$\hat{R}_s$	$V(s, \mathbf{E}x)$	σ_s
1	–	22.18	–
2	13.18	30.27	10
3	100.15	112.33	25
4	383.36	458.27	100
5	–	635.37	–

Table 3: Estimate of stage costs and value function (at average industry state); standard deviation of trial results is provided for reference.

The Nested Pseudo-likelihood estimate of the model successfully converged, providing both the estimates of stage costs R_s and equilibrium value function $V(\cdot)$. Table 3 reports the estimates of stage costs and value function for average industry state[12], along with values of $\{\sigma_s\}$ that were selected to match the scale of V and R.

Stage costs are increasing from one stage to another, which is consistent with each consecutive stage of development being longer and involving more subjects than the previous one; DiMasi, Hansen, and Grabowski (2003) report similar relationship. Further, value of a drug in each subsequent stage is higher, which is reasonable as drugs more likely to reach the market. No R_s or σ_s are reported for $s = 1, 5$ since decision to enter Phase I ($s = 1$) is not included in the model due to lack of data, and the transition to the market ($s = 5$) is controlled by FDA.

A somewhat surprising finding is the relatively large cost of submitting a drug for FDA approval, since the application fee is substantially smaller than the estimate of \$383 million. However, the estimate reflects an economic cost to the firm, which in-

[12] As described in 4, $V(\cdot)$ is represented by a set of polynomial coefficients, and author feels that reporting them would be less informative.

cludes considerable effort involved in preparing the necessary application documents, and then following up with FDA officials, providing clarification on any unclear points, checking on the progress of the application, etc.

s	Observed $\bar{x}_s$	Predicted $\mathbf{E}x_s$
1	10.86	10.33
2	14.86	12.83
3	7.86	7.51
4	3.77	4.19
5	27.87	23.21

Table 4: Comparison of observed and predicted industry states.

To assess "goodness of fit", Table 4 compares the average observed industry state with the one predicted by the model. One cannot expect exact fit because model's prediction is a expectation over limiting (or ergodic) distribution[13], while observed data represent a relatively short period in life industry which cannot be reasonably expected to represent the limiting distribution.

5.2 Policy experiments

Having estimated the model parameters, this study proceeds to conduct policy experiments by mapping each policy into a change in corresponding parameter, and computing equilibrium for that new parameterization.

To make the policy interventions comparable, the experiment setup is using "equal cost" principle. The quotation marks are there since the intervening agent is doing a simplified cost computation, assuming that the number of drugs flowing through the development pipeline will remain unchanged as the result of this policy. In reality, policy intervention will (or at least should) change number of drugs flowing through

[13]See 5.2 below for details of this computation.

the system, but correcting for this requires multiple trial-and-error experiments with the model, and this study assumes that intervening agent is not sufficiently sophisticated to do that.

The specific experiments are:

- Subsidy offsetting part of stage cost R_s. The cost of this policy is naturally computed as the product of stage cost and average number of drugs that enter this stage each year. The cost of all experiments is set to match 10% decrease in cost of Phase III (R_3); corresponding decrease for Phase II (R_2) is 48%, for FDA filing (R_4) – 4%. As mentioned above, major part of R_4 is likely to be economic cost rather than actual payments by the firm, so subsidy might be harder to justify, and instead can be viewed as streamlining and facilitating the application process to reduce the economic costs of the firms.

- Subsidy towards the sales of the drug, making it accessible to those who previously could not afford it. This expands the market and hence increases profits of every drug on it. The cost of this policy is computed as the product of subsidy percentage and total market revenue (M). The amount matching the other subsidies is 2%.

  There is an additional issue related to sales subsidy. On average, Pharmaceutical firms spend 30% of their revenue on promotion. It is not reasonable to assume that this expense should apply to sales generated through subsidy, so profit margin on sales-related drugs is increased to reflect that.

In addition to subsidies, this study attempts to study effectiveness of several other policies, cost of which cannot be reliably predicted or matched to the cost of subsidy policies. Instead, this group of policy experiments aims to be internally consistent by using similar changes of model parameters:

- Shorter duration of development stages. This can be achieved through various institutional changes, such as greater sharing of information about clinical trials or streamlining the FDA review procedures. To achieve a visible effect, the assumption is that duration of each stage is reduced by 50%.

- Increased discovery research, which would result in additional drugs entering Phase I. While there are studies on productivity of research investment[14], the inability to model the transition into clinical trials prevents the proper cost computation for this policy. Instead, the experiment assumes 50% increase in number drugs entering Phase I.

The policy evaluation criteria is number of drugs entering the market per year; the flow of drugs through various stages of development is also reported to aid the understanding of mechanism by which policy works (or doesn't). This "flow" measure is preferable to "stock" of drugs on the market, since the latter is directly affected by an assumption on duration of profitable life of the drug (μ_5), which is somewhat arbitrary. Besides, the "flow" measure better matches the stated goal of increased introduction rate of new drugs.

Given a set of parameter values, an equilibrium is computed by iterating on Pakes-McGuire step described in Section 4. The estimated "baseline" equilibrium provides a convenient starting point for this computation, since best-reply dynamics of Pakes-McGuire update simulate the adjustment of an industry to a new environment. Convergence of this algorithm is again not guaranteed, but use of dampening helped ensure successful computation of all counterfactual equilibria that the experiments require.

The flow of drugs is computed as an expectation over a limiting distribution,

[14] See, for example, Henderson and Cockburn (1996).

i.e. the stable distribution of industry states that industry achieves after developing for a long period of time. While linear algebra offers a direct way to compute this distribution, it is not practical here due to large size of state space. Instead, this study simulates the development of the industry for a period of time, and takes an average over observed transitions (excluding first 20% of period, which eliminates effects of initial state). The duration of this simulation period is selected to be large enough to ensure that simulation error is well below the effect of the policy.

Policy \ Stage	Ph. I	Ph. II	Ph. III	FDA	**Market**
Baseline estimate	4.090 (0.027)	3.397 (0.026)	2.124 (0.021)	1.454 (0.017)	1.157 (0.014)
Subsidy - FDA review	+.003 (.028)	+.121 (.027)	+.154 (.022)	+.**111** (.018)	+.093 (.015)
Subsidy - Phase III	−.008 (.028)	+.129 (.027)	+.**210** (.022)	+.087 (.018)	+.070 (.015)
Subsidy - Phase II	−.011 (.028)	−.**234** (.027)	+.070 (.021)	+.035 (.017)	+.021 (.015)
Subsidy - Sales	−.007 (.028)	+.154 (.026)	+.190 (.022)	+.136 (0.017)	+.**111** (.015)
Faster FDA review	−.013 (.028)	+.224 (.027)	+.295 (.022)	+.**214** (.019)	+.170 (.016)
Faster Phase III	+.002 (.028)	+.126 (.027)	+.**112** (.022)	+.060 (.017)	+.046 (.015)
Faster Phase II	−.017 (.028)	−.**047** (.025)	−.010 (.021)	−.002 (.018)	+.001 (.014)
Increased discovery	+**2.036** (0.040)	+1.195 (.035)	+.343 (.027)	+.129 (.021)	+.107 (.018)

Table 5: Results of policy experiments: Flow of drugs through development pipeline.

Table 5 lists the results of the experiments. Top row reports the average flow of drugs through stages of development pipeline for the baseline estimate, and the following rows report change to these numbers under policy experiments; the simulation standard errors are reported in brackets.

An expected observation on this table is that all policies have either positive (or insignificant) effect on the number of drugs entering the market.

More interesting, comparing the set of policies that affect costs or durations of several consecutive development stages, one finds that policies affecting later stages are

more effective than those affecting earlier stages. There is just exception – Increased discovery. Despite affecting the earliest phase of trials, it shows higher effect than reduced duration of Phases II or III of clinical trials. However, as outlined above, the two sets of policies are not necessarily comparable.

Returning to the overall trend of interventions into later stages being more effective, it is worth investigating the reasons behind it. Note that the increase in the number of drugs flowing through the pipeline is usually the highest at the stage affected by the policy (indicated by bold font). The effect is smaller for earlier stages, and seems to be declining throughout the subsequent stages.

Under a limiting distribution, average number of drugs at a given stage remains constant, so average number of drugs entering and leaving the stage is the same[15], so any change in the flow of drugs from stage to stage is driven by the probability of advancement to the next stage $p(s, x)$. To look into these, consider the definition of this probability in (3). The only endogenous component of the expression is $V\left(\bar{s}+1, x_{-s}^{+(s+1)}\right)$ – the value that firm collects if it enters the stage.

Policy \ Stage	Ph. I	Ph. II	Ph. III	FDA	**Market**
Baseline	22.18	30.27	112.33	458.27	635.37
Subsidy - FDA review	+2.39	+2.60	+2.30	**−13.89**	−20.44
Subsidy - Phase III	+2.57	+3.01	**−5.68**	−11.15	−16.38
Subsidy - Phase II	+3.82	**−1.09**	−2.03	−3.95	−5.81
Subsidy - Sales	+3.77	+3.88	+3.02	+0.72	**−.51**
Faster FDA review	+5.03	+5.55	+5.23	**+2.08**	−25.54
Faster Phase III	+3.59	+3.07	**+1.02**	−4.81	−7.97
Faster Phase II	−0.28	**−0.73**	+0.41	+0.12	−0.19
Increased discovery	**−4.95**	−5.65	−9.66	−18.03	−26.24

Table 6: Changes to Value function as the result of policy experiments.

Table 6 presents these values for each of the experiments, evaluated at average x under limiting distribution. As before, phase affected by the policy intervention

[15] Simulation confirms this theoretical conclusion.

is indicated by bold font. With the exception of Faster Phase II, it all experiments reveal a common pattern: Values for stages prior to the one affected by policy are increased (hence increasing chances of entering the phase; values for stages subsequent to intervention have the value reduced, hence reducing chance of any given drug continuing into that phase.

The reduction for stages past the innovation are easy to explain – Table 5 shows that the flow of drugs has increased, thus necessarily increasing the average number of drugs on the market and reducing the value of a drug at any given stage (since the market size remains unchanged in all but one experiment). Same effect applies to the stages prior to policy intervention, but it is offset by the policy benefit that the firms expect to collect at a future stage, leading to an overall positive change in value.

This explains why the flow of drugs through the pipeline increases up to the point of intervention, but shrinks with every stage past the intervention. So interventions into earlier stages of development process mean that shrinking occurs over a larger number of stages, resulting in a lower effect compared to policies affecting later stages.

It is important to note that the negative effect described above is a strategic phenomenon, since it represents response of the firm to policy-induced actions of the competing firms. An attempt to evaluate effectiveness of policy intervention outside of the framework of dynamic games, e.g. using a single-agent model would have missed this effect and overstated the impact of any policy intervention.

6 Conclusion

This study has constructed a dynamic model of the drug development process, structurally estimated it and evaluated the efficiency of various policy interventions by conducting counterfactual experiments. The major conclusion is that policies ap-

plied to earlier stages of development have a smaller effect on output of new drugs. The reason for this phenomenon is that a policy-driven increase in the number of drugs necessarily decreases the value of each drug, and while policy intervention ensures firms are more willing to invest into development when they expect to benefit from policy at a future stage, they are less likely to continue development into stages subsequent to policy intervention.

I am currently working on simulating the industry development over a short interval of time, studying how long it takes for policy intervention to take its effect. The simulations above concentrate on long-term average performance of the industry, and ignore the transition from the baseline industry structure. Short-term simulations will allow for a more balanced evaluation of policies, based not just on their long-term effects, but how fast they will arrive.

Another on-going project is modifying the model to describe decision making by a multi-drug firm. Guedj and Scharfstein (2004) found that large firms with "portfolios" of drugs at every development stage behave differently from firms who have their business staked on a single drug. Proper treatment of this feature would change the model substantially, adding the firm's own drugs to the state space, altering the state transition process to keep track of individual firms with their portfolios, and possibly abandoning anonymity assumption, since firms might consider not just the number of competing drugs, but the identity of the firms that own them. On the positive side, this model will allow me to test whether the current coexistence of large and small firms is sustainable, or the industry leans towards concentration of the market in the hands of the few large firms.

A further expansion of this study would be incorporation of clinical trial outcomes into the estimate. This is a substantial undertaking, requiring a collection of clinical trial results and a method of comparing them across different markets (e.g. based on

percentiles). In return, this approach will help to distinguish between medical and economic components of drug development decisions.

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