Competition and Attrition in Drug Development

Ekaterina Khmelnitskaya
Moscow, Russia

M.S. Economics, Economic Science Institute, Chapman University, 2014
M.S. Economics, NRU Higher School of Economics (Moscow), 2011
B.S. Economics, NRU Higher School of Economics (Moscow), 2009

A Dissertation presented to the Graduate Faculty
of the University of Virginia in Candidacy for the Degree of Doctor of Philosophy

Department of Economics

University of Virginia
May, 2021

Abstract

With fewer than 10% of new drugs reaching the market, the drug development process is notorious for its high attrition rate. However, we rarely observe the reason for a drug's discontinuation. It is known that pharmaceutical firms withdraw drugs after clinical failures, such as when trial results do not demonstrate adequate safety or efficacy according to FDA standards. At the same time, surveys suggest that firms also withdraw drugs for strategic reasons, such as when competition makes it unprofitable to continue development. Disentangling these two sources of attrition is necessary in order to predict the effects a government policy would have on the number of drugs that reach consumers. In this paper, I propose an empirical framework to separately identify the two components of attrition for each disease. To this end, I build a continuous-time dynamic model of the drug development process. In the model, firms take competitors' R&D choices into account when they make exit decisions at different stages of the innovation process. To estimate the model, I use rich data on the development histories of experimental drugs, clinical trial outcomes, and disease-specific epidemiological characteristics. I find that, on average, strategic terminations account for 8.4% of all attrition, and as much as 35% for some diseases. Using these estimates in counterfactual simulations, I show that without strategic withdrawals, the rate at which new drugs reach consumers would be on average 23% higher. Large subsidies for clinical trials help realize some of that gain, with better results found for diseases that have a higher share of strategic attrition. However, the overall effect of subsidies on the rate of new drug launches is small. Alternatively, the same effect can be achieved through any minor regulatory adjustment that marginally helps lower the probability of late-stage clinical failures.

Keywords: Pharmaceutical industry, Entry, Competition, Innovation, Drug development
JEL: L13, L65, O30

Contents

Acknowledgements

I am deeply grateful to my primary advisors—Federico Ciliberto, Gaurab Aryal, and Simon Anderson. Their generous mentorship is what has made this dissertation possible, and I feel incredibly privileged and lucky to have had an opportunity to be their student.

Federico Ciliberto's faith in me and his patient guidance and support have helped me carry through with the project despite all the challenges that I didn't always think could be overcome. His involvement was absolutely formative for my professional growth; without it, I don't believe this project would have ever seen the light of the day, and my path would have looked very different.

It was due to Gaurab Aryal's enthusiastic and insightful feedback to my early ideas that I became hopeful about pursuing research in Empirical Industrial Organization—his encouragement was invaluable, it kept me thinking and trying. His encyclopedic knowledge, deep comments, and practical advice not only helped me create this dissertation but also broadened my overall perspective about how to do scientific work.

I am indebted to Simon Anderson for helping me realize, back at the beginning, in which field of economics I was most interested. I want to thank him for how incredibly exciting and stimulating it was to be first a student and then a teaching assistant in his class, for many great conversations that we have had, for all the advice he has given me, and for challenging me while also encouraging me to think deeply about underlying mechanisms of things.

I would also like to thank Denis Nekipelov for his help and all the exceptional opportunities with which he has provided me. I was lucky to be able to learn from him while being

a teaching assistant for his class. And later on, I was even more lucky to work with him as a research assistant, which led to me meeting incredible scholars from a variety of fields and contributing to fascinating research projects.

Thank you to the many other members of the UVa's Economics Department who have supported me throughout this PhD journey. I would especially like to thank Charles Holt, Eric Young, Maxim Engers, Steven Stern, John Pepper, and Amalia Miller for their advice and help. Thank you to James Harrigan and John McLaren for their guidance and for welcoming me to the Trade Research Group during my second and third year in the program. I thank Natasha Foutz for taking time to serve as my outside committee member. Patty Futrell and Sage Bradeburn were always there for us every step of the way. I would also like to thank participants of the IO research group for their valuable comments.

There are many other economists I met before starting the PhD that helped me on my path. I was especially fortunate to have worked with Leonid Polishchuk, Rinat Menyashev, Stephen Rassenti, David Porter, and Daniel Kovenock—all of whom contributed to me becoming a better researcher. I am most grateful to my friend, Kevin James. The extraordinary generosity with which he shares his time, his innumerable skills, and his vast expertise with those around him were essential to me getting to where I am now. He is also one of the best teachers I have ever had.

This dissertation relied on funding provided by a number of different organizations. I would like to thank Batten Institute Research Grant Program, Bankard Fund for Political Economy, and the UVa Quantitative Collaborative for providing financial support to my work.

One of the best parts about pursuing a PhD is getting a chance to meet and become friends with amazing people from all over the world. I send lots of love to all the members of my cohort—because of them my years in Charlottesville were filled with plenty of fun and warm memories. I thank my friends and office mates Devaki Ghose, Ia Vardishvili, Taheya Tarannum, and Emily Cook for all their help, for being part of many dry-runs and

numerous post-presentation, in-the-office and on-the-way-to-the-coffee-shop discussions. On top of that, I want to thank Ia, Taheya, and most of all Devaki for their friendship, for being here at the core of my support group and for sticking with me through thick and thin.

Thank you, Cailin Slattery, for being a great running partner, for reading through too many versions of my abstracts, and for all your help and advice that you continued giving even after graduating. A big thank you to Daniel Savelle for his support throughout the program. Sean Sullivan, thank you for being the most wonderful friend and the best activities organizer. Svetlana Pivovarova, I am so happy that we bonded here in the U.S.; sharing our experiences of going through our respective PhDs has been indispensable to me. Thank you to Jigme Norbu, Shreejaya Shrestha, Gert-Jan Duine, and (one more time) Devaki Ghose for, at different points in time, being the most amazing housemates and making Charlottesville feel like home. I send all my love and a huge thank you to my family, especially my mom Elena and my sister Polina, for their support and encouragement. I also thank my friends back in Russia, especially Asya Kalmykova and Kristina Ivasenko, who, during so many years, provided me with much-needed perspective and reminded me on multiple occasions about the whole world that exists outside of graduate school. I also thank Julia Zagachin for helping me out multiple times in very practical and very valuable ways.

Finally, thank you, Ramiro Burga, for being there in the best and in the worst of times. Thank you for being grounded and understanding and funny and so very patient with me. Thank you for believing in me and helping me believe in myself. I couldn't have done it without you.

I dedicate this dissertation to my mom, Elena Khmelnitskaya, who has been a continuing source of love and encouragement for me. It was her example of bravery, strength, resourcefulness, and determination that inspired many of the big decisions in my life, including starting a PhD.

Chapter 1

Introduction and Literature Review

The pharmaceutical industry is known for being heavily innovation-intensive, with the average R&D cost per new drug launch recently estimated at 1.4 billion USD.[1] Most of these expenditures go toward drug development, which is the process of testing newly discovered compounds in clinical trials.[2] Despite the large amounts spent, few of these compounds go on to become approved drugs: Overall, less than 10% of drug candidates make it all the way to the market. For those drugs that do reach commercialization, it takes an average of 12 years from the time they enter the development process. This timeline and high attrition characterize a complex drug development landscape, in which firms make risky long-term investment decisions while learning whether their experimental drugs demonstrate the safety and efficacy required to secure regulatory approval.

The goal of this paper is to estimate the two primary components of drug development attrition, which I term scientific and strategic. The former refers to withdrawals due to drug candidates' failing clinical trials—i.e., not demonstrating sufficient safety or efficacy after being tested on animals or human subjects. The latter describes withdrawals due to commercial considerations, such as firms deciding that further investment in development is no longer profitable. While scientific concerns constitute a major source of attrition,

[1] DiMasi et al. (2016). Estimates are in 2013 dollars.

[2] DiMasi at al. (2016) estimates that clinical trials account for about 70% of average R&D expenditures, while discovery and preclinical testing account for the remaining 30%.

survey evidence suggests that strategic considerations might account for about one-third of all terminations (Tufts CSDD Impact Reports 2013).[3] Disentangling the two attrition components is important for predicting the effects of government policies, since scientific and strategic withdrawals are shaped by different forces: One stems from the purely medicinal properties of drug candidates and the associated regulatory standards, while the other is related to competition and other economic incentives. Therefore, any policy change will have a disparate impact on the two components—and in order to adequately predict the results of the change, it will be necessary to quantify their relative importance and analyze the policy effect on each. However, no comprehensive estimates of the relative importance of the two channels have yet been reported. This paper proposes an empirical framework to identify both sources of attrition separately for each disease, and to conduct policy experiments to account for the partition.

Competition and market size are the major factors that influence expected profits, and therefore strategic attrition. Market size is affected by characteristics of the disease, such as incidence and morbidity, and determines the maximum potential revenue for an approved drug. Competition is based on the number of drugs that have already been launched or are in development for the disease. In this study, I consider only novel drugs— i.e., medicines based on new molecules that have not previously been used in approved treatments. I therefore exclude drug candidates that represent incremental improvements in existing therapies due, for example, to changes in dosage or delivery method.[4] Consequently, I consider innovation to be the process of introducing new product options to the market, as opposed to replacing existing products with better alternatives, as is the case in much of the innovation literature (recent examples include Goettler and Gordon (2011) and Igami, (2017)).[5]

[3]Tufts CSDD Impact Reports 2013 provides the split of attrition after each phase of clinical trials by reason (e.g. commercial or due to safety/efficacy). Estimating the total number of drugs dropped due to commercial considerations also requires knowing the total share of drugs terminated after each phase. For this, I use the attrition shares estimated by DiMasi et al. (2016).

[4]More details on that are available in the data section.

[5]Studies of pharmaceutical demand (for example, Crawford and Shum (2005)) show that there is a large degree of heterogeneity in patients' responses to treatment options. This suggests that a love of variety is a major property of pharmaceutical markets, as opposed to the much more homogeneous markets for

In this context, I examine how the rate of innovation, defined as the process of new drug launches, is shaped by decisions of potential entrants—who, because industry regulations make information on pharmaceutical development available to the public, are able to assess other potential entrants, as well as drugs already on the market.[6] Data on the development histories of drug candidates show that at any point in time, multiple competing experimental drugs are associated with most diseases. For example, in January 2010 there were 150 novel drugs in development for hepatitis C.[7] If several of these drug candidates end up entering the market, each would be likely to face lower profits.[8] Because information on firms' development processes is publicly available, competitors can track each others' progress. Indeed, Rao (2020) shows that firms are more likely to discontinue later-stage development after their competitors receive FDA approval. My own interviews with industry participants suggests that pharmaceutical firms closely track not only news about the latest approvals, but also about other development events, and take these into account when deciding whether to terminate their own projects.[9]

In this setting, in which some experimental drugs are discontinued for scientific reasons, and others for strategic reasons, the relationship between competition and innovation is not trivial. Increasing the number of drugs in development has two contrasting effects on the rate of new launches. On the one hand, it implies a larger probability that at least one will pass the safety and efficacy tests and enter the market. On the other hand, anticipating lower

microprocessors, as analyzed by Goettler and Gordon (2011) or for hard disc drives, as analyzed by Igami (2017).

[6]In order to ensure transparency of clinical research, regulations require that information on the development processes of pharmaceutical firms be made publicly available. For example, the Food and Drug Administration Modernization Act of 1997 established that information about clinical trials should be posted in a public registry within 21 days after the trial's start.

[7]Source: Cortellis Competitive Intelligence. Table 2.2 documents the maximum number of competing projects simultaneously in development for selected markets.

[8]For instance, when AbbVie's Viekira Pak was approved for hepatitis C in 2014, it was documented to have a negative effect on the market capitalization of Gilead and its prices of Sovaldi, the company's drug for the disease launched in 2013. For more details, see https://bit.ly/2OeTmVi and https://bit.ly/3oWL6ev

[9]For example, during a phone interview, a clinical trial manager at the University of Virginia discussed the case of a client firm that decided not to proceed with development and cited competitor's progress as the reason. During another phone interview, a manager in a pharmaceutical company confirmed that when making development decisions, they analyze and account for the competitive landscape.

expected reward, each competitor may be more likely to terminate development part way through, therefore reducing the total pool of drug candidates and, in turn, the probability that at least on will succeed. This study accounts for these trade-offs and analyzes the effect of competition on the rate at which new medicines reach consumers.

In order to study this phenomenon, I use data on drug development histories from a rich database that contains information on approximately 70,000 drug candidates that underwent development anywhere in the world since the beginning of the 1990s.[10] For each drug candidate, I observe not only the disease for which it was being developed, but also the dates of all important development milestones associated with that disease. This information includes: (i) the date the drug entered development and the dates of each transition across development stages (for example, from early to late clinical trials); (ii) whether—and, if do, when—it was discontinued; (iii) the dates on which successful drugs were submitted to the regulatory authority for the review necessary to obtain marketing approval; (iv) whether medicines submitted for regulatory review were approved; and (v) the dates on which the regulator announced its approval (or non-approval) decisions. I merge the data on development histories with the disease-level epidemiological information I use to construct a measure for market size.[11] Further, I use data on clinical trial results to parameterize probabilities of clinical success—that is, probabilities that a drug in development for a particular disease will pass safety and efficacy tests. Within the framework of this study, these probabilities are assumed to be a function of the disease-level "scientific" variables I construct from that data.[12]

I use the resulting dataset to estimate a continuous-time dynamic model adapted from Arcidiacono et al. (2016). In the model, firms arrive at the start of development endowed with a new experimental drug intended for a specific market; this represents the arrival

[10]Some records date back even earlier—to the beginning of the 1980s—but the number of such records is small. Moreover, the coverage improves after the mid-1990s.

[11]Specifically, I use a measure of disability-adjusted life years (DALYs), which estimates the total number of years lost to a particular disease. Following the medical literature, I assign monetary value to DALYs using the value of statistical life year (VSLY). More details on DALY and VSLY in the data section.

[12]Specifically, I assume that the probability of clinical success is a logistic function of the variables.

of new discoveries associated with a particular disease. Each drug must be further tested in two sets of clinical trials: small-scale (first stage) and large-scale (second stage). Each stage takes time and money, which is accounted for, respectively, by the duration and cost parameters I estimate. At the end of each stage, the firm receives a signal about the medicinal qualities of the drug (e.g., toxicity or efficacy). If the signal is bad, the firm must discontinue development. The probability of such clinical failure is both stage- and disease-specific. This reflects the differences in objectives across the two stages: Early-stage trials are mainly conducted to ensure safety, while late-stage trials are primarily conducted to detect efficacy. This also reflects differences in the biological characteristics across ailments.

After completing each stage of development, and conditional on receiving good clinical trial results, the firm must decide whether it is profitable to advance the drug to the next stage of the process. The firm makes the decision after weighing the development costs against the expected profit. Importantly, at each point in time, the firm knows the exact number of competitors at each stage of development, as well as the number of drugs currently under review by the regulator and already on the market. The company uses this knowledge to make predictions about the potential competition it will face if its drug is approved. Once the drugs have passed all stages of development—and have been positively assessed by the regulator—they enters the market, at which point firms receive the profit that is a function of the market size and the number of competing drugs available to consumers.

I solve the model using the concept of Markov perfect equilibrium, which has been standard in the dynamic games literature since Ericson and Pakes (1995). I show that the model is identified from the variation in factors that affect strategic but not scientific terminations—i.e., the market size and level of competition. Intuitively, diseases with a large market size help identify scientific attrition parameters, since these markets are so lucrative that withdrawals are predominantly due to clinical trial concerns.[13] More specifically, consider highly profitable diseases, for which differences in attrition are therefore mainly driven by differences

[13]In the limit, diseases associated with infinitely large market size will not have any strategic attrition at all.

in science. The co-variation in attrition and scientific variables then contains information about how these variables affect the probabilities of clinical failures. Meanwhile, variation in competition and attrition within markets over time helps identify strategic parameters. I estimated the model using the two-step pseudo maximum likelihood procedure, as in Aguirregabiria and Mira (2007) and Arcidiacono et al. (2016) .

The results indicate that strategic terminations account for 8.4% of attrition on average, reaching as high as 35% for some diseases. Strategic considerations are more prevalent at the early stage of clinical trials, accounting for 9.3% of discontinuations on average versus 1.2% after late-stage trials. If strategic considerations were not present, the rate of new drug launches would be 23% higher on average. I further analyze how the two sources of attrition interact in determining the rate of innovation by increasing the probability of clinical success in early- versus late-stage clinical trials. I find that in the latter case the change would lead to 50% higher response in new drug launches, with discrepancy partially explained by the differential reactions of strategic withdrawals. Finally, I find that clinical trial subsidies lead to more frequent introduction of new drugs, especially for diseases for which strategic attrition is more important. However, the overall effect is relatively small even for a subsidy that covers 90% of the late-stage cost. At the same time, a marginal one-percentage-point change in the probability of late-stage clinical success produces comparable results.

This paper is primarily related to firms' entry behavior in the pharmaceutical industry. The literature on the topic includes nonstructural studies of entry determinants for novel therapeutics—e.g., Kyle (2006), as well as Acemoglu and Linn (2004) and Dubios et al. (2015), who focus specifically on the relationship between entry and market size. Second, related literature incorporates a number of studies on generic entry—e.g., the classic study by Scott Morton (1999) and the dynamic structural models of Ching (2010) and Gallant et al. (2018). Most studies focus on explaining the observed patterns of entry, with the important exception of Rao (2020), who builds a dynamic model to examine how firm behavior before

launch is affected by competitors' actions and estimates this using R&D pipeline data.[14] However, Rao includes only late-stage development in the model, focusing exclusively on decisions regarding whether to apply for regulatory approval. In contrast, I also incorporate early-stage trials and the associated decisions regarding whether to transition between the two development stages. An important implication of having a more expansive model is that I am able to answer a larger variety of policy questions. For example, I can conduct experiments that apply not only to the regulatory stage but also to clinical stages—e.g., subsidizing the cost of late-stage trials or decreasing the time it takes to complete them.[15] Further, in contrast to Rao (2020), I explicitly model and estimate the process of scientific attrition, which allows me to separate the two sources of firm exit. Since scientific terminations impose constraints on how much an economic policy can affect the rate of innovation—for example, if they are prevalent, even large subsidies might not have a substantial effect—it is important to consider them when conducting counterfactual experiments in the industry. Without taking scientific withdrawals into account, the results of such policy experiments might be biased.[16]

This paper also contributes to the literature that analyzes sources of development attrition in the pharmaceutical industry. This literature includes studies that document the reasons behind termination cases, which are usually based on the limited number of observations obtained either directly from pharmaceutical companies or through the analysis of clinical trial outcomes (for example, Waring et al. (2015) or Hwang et al. (2016)). Recent studies also contribute to our understanding of economic contributors to the observed attrition—for example, Hermosilla (2020) shows how rushed licensing leads to future discontinuations, and Cunningham (2020) provides evidence that some acquisitions of experimental

[14] R&D pipeline data is data that on drug development histories. Another recent paper that uses pipeline data to study pharmaceutical R&D is Krieger (2020) who analyses how a particular development failure affects other firms' R&D actions.

[15] Another implication of including both stages of development into the model is that it allows me to account for dynamic interactions that arise throughout the development process with some firms getting ahead, and some firms falling behind.

[16] Another benefit of modeling and estimating scientific attrition is that I am able to study how changes in sources of that attrition affect the rate of innovation.

drugs are performed for the purpose of terminating them in order to reduce future competition.[17] I contribute to the literature by studying aggregate sources of attrition within a tractable and scalable structural model, which allows me to analyse how they would be affected by policy changes and identify the resulting innovation outcomes.

More broadly, this research adds to the large literature on how competition affects the incentives to innovate (Cohen (2010) and Gilbert (2006) survey the literature; Shapiro (2011) discusses the topic from the policy perspective). Within this broad literature, this paper is associated with two distinct strands: empirical studies of new product development in innovative industries and theoretical studies on R&D races.

Within the first strand, Goettler and Gordon (2011) studies incentives for product upgrading within a dynamic duopoly market for microprocessors. Igami (2017) focuses on decisions to introduce higher quality products by incumbents versus new entrants using the setup of the hard drive industry[18]. Kim (2014) studies innovation incentives in a dynamic duopoly in the presence of a large used goods market in the context of the aircraft manufacturing industry. Hashmi and Van Biesebroeck (2016) analyzes dynamic quality upgrading in the automobile industry. This research contributes to the literature by studying R&D decisions of pharmaceutical companies that face a variety of different market structures (where each disease is a distinct market)—as opposed to most of the other settings where the market structure is fixed. This allows me to analyze how the R&D decisions change with levels of competition—taking into account not only competitors that have already launched their products, but also those not yet on the market.

Because this study focuses on the pre-market behavior of firms and their reactions to the

[17]This project does not directly account for deals in the industry. Instead, I aggregate all the development activity associated with the same drug—which can be either parallel due to collaborative licensing arrangements or sequential due to full licensing or M&As—into one program (more detail on that in the data section). As long as killer acquisitions and discontinuations due to rushed licensing are terminations of programs (e.g. drugs), this paper will account for them. Moreover, as long as they are correlated less with scientific characteristics of diseases (e.g. clinical trial outcomes) and more with competition (for example, the acquiring firm has other drugs on the same market), they will be contributing to strategic withdrawals within the setting of this study.

[18]Notice that in such homogeneous industries new product introduction is effectively equivalent to quality upgrading.

observed R&D progress of their competitors, it is also close to the predominantly theoretical literature on multistage R&D races. Fudenberg et al. (1983) analyzes a model of a two-stage patent race where a firm can induce the other firm to drop out by advancing to the next stage of the R&D process (which happens stochastically). Grossman and Shapiro (1987) allows firms to vary their R&D efforts in order to affect the rate at which they are able to advance across stages, and Harris and Vickers (1987) extends it to allow for an arbitrary number of stages in the race. Judd (2003) introduces firms that may have multiple development projects, and Kocourek (2021) allows firms to decide whether to withhold information about progressing to the more advanced stage. This study contributes to the literature by estimating a discrete-choice version of a two-stage R&D race with many competitors: in this version firms do not continuously control the rate at which they finish trials and receive results, but they can react to changes in competition across different stages of the process by terminating their projects[19]. Two other important differences between my model and a standard model of an R&D race are that first, my model does not assume a winner-takes-it-all scenario (since multiple different drugs can be launched against the same disease); and second, in my model terminations can happen for both strategic and scientific reasons.

[19]Being able to instantly increase or decrease the intensity of R&D efforts—as in Grossman and Shapiro (1987)—does not directly apply to the context of pharmaceutical drug development, as it is not possible to speed up the progression of a clinical trial once it has begun. Even before the trial starts, companies have a limited number of tools to speed up the process, as patients have to be observed for a certain (disease-specific) amount of time to determine how the drug affected them.

Chapter 2

Industry Background and Data

2.1 Industry Background

The process of developing a new drug is tightly regulated. Before being released into the US market, a drug must first be approved by the Food and Drug Administration (FDA)—the government agency that oversees the industry. But before approval, the FDA requires proof of the drug's efficacy and safety. This makes trials conducted to investigate whether the drug has appropriate medicinal qualities crucial to drug development.

The drug development process tends to follow a certain path that consists of sequence of distinct phases. After discovery of the new compound, it is first tested on animals in so-called pre-clinical trials. If the firm wants to proceed and study the drug candidate in human participants, an Investigational New Drug (IND) application has to be filed with the FDA. If the application is approved, the firm can begin clinical research with the drug, which usually includes three phases. In Phase I, the drug is tested on a small group of healthy individuals to study toxicity of the drug and establish the safe dosage. In Phase II, the drug is tested on a small group of patients that have the targeted disease, with the primary purpose of studying efficacy of the drug. Finally, Phase III is conducted in order to confirm efficacy on a large population of patients. In what follows, I will group the *phases* of development

into two *stages* by their primary goal: stage 2 (or late-stage trials) will include phase II and phase III trials that focus more on efficacy, and stage 1 (or early-stage trials) will include earlier trials that focus more on safety.[1]

Pharmaceutical firms are not completely autonomous in deciding whether on not to promote their experimental drugs to next stages of development: throughout the whole process they are required to stay in close contact with the FDA, which retains the right to put clinical studies on hold or terminate them if it deems the information unsatisfactory.[2] Regulations in the industry also ensure that information about major development milestones is public: the Food and Drug Administration Modernization Act of 1997 established `ClinicalTrials.gov` and mandated that late-stage clinical trials should be registered there within 21 days after the trial start.[3] Information required for registration includes the phase of the trial as well as the disease for which the trial is conducted. Therefore, at each point in time pharmaceutical firms can determine how many competitors are developing drugs for the same disease, how many of them are ahead, and how many–behind.

The number of competing experimental drugs in development for the same indication can be large, reaching hundreds for some diseases (see Table 2.2). Moreover, frequently FDA approves multiple new treatments for the same disease within a relatively small time window (see Table 9.1 in Appendix 9.1 for several examples of close approvals). Therefore,

[1]There are two main reasons why I group the phases into larger categories. First reason is data limitations. FDA regulations related to early trials are not as tight as for late-stage trials—for example, firms are not required to register phase 1 trials in the public repository. Therefore, there is a concern that transition from preclinical to phase 1 is not always observed. Although observability is not a concern with respect to phases 2 and 3, sometimes firms run the two phases together (so-called phases 2/3), and in some cases (for some diseases) firms might be allowed to apply to the FDA after finishing phase 2 trials. I model this by joining the first two phases and the second two phases together. The second reason is computational—the grouping allows me to create a tractable and computationally feasible model of drug development.

[2]See the guidelines at `https://bit.ly/2PNFX9C` and the regulations at `https://bit.ly/2HjhPtM`, `https://bit.ly/2HpsJOj`, `https://bit.ly/2ThlkTF` and `https://bit.ly/3oi1N4O`. Regulations require that firms submit periodic updates. Moreover, firms are also encouraged to schedule meetings with FDA representatives after finishing each phase of clinical development to discuss the adequacy of the data to support the future application for the marketing approval of the drug (`https://bit.ly/31vVorY`).

[3]Details and interpretation of FDAMA can be found here: `https://www.ncbi.nlm.nih.gov/books/NBK338089/`. The scope of the regulation and enforcement was increased in Food and Drug Administration Amendments Act of 2007 (FDAAA). Moreover, since 2005, the International Committee of Medical Journal Editors (ICMJE) started requiring trial registration as a condition of publication.

drug development process differs from the standard concept of R&D race, according to which as soon as one firm enters the market, probability of approval of other firms drops to zero (and the winning firm holds the monopoly position). In case of drug development, multiple firms can enter the market, which alters the structure of the expected profit of firms that are still in development.

Altogether, the development process requires an average of about 10 years, with about 2 additional years for the FDA approval.[4]. At the same time, there is considerable variation in terms of the duration of each stage of the development process across diseases. For example, the average length of stage 2 is more than 7 years for Multiple Sclerosis, while it is only slightly more than 4 and a half years for Psoriasis. Moreover, drug candidates in development for the same disease can take significantly different amount of time to progress across stages (see Table 9.12 in Appendix 9.15 for estimates of stage durations for a selection of diseases).

The drug development is not only lengthy, but also expensive. Surveys of pharmaceutical firms suggest that the cost of 3 phases of clinical development can be averaging to about $340 million (DiMasi et al., 2016). Given the high cost, firms have incentives to terminate development projects with comparatively low expected profit. At the same time, termination decisions might be a result of inadequate clinical trials results that would not be able to lay the ground for the FDA approval or even trigger the FDA to shut down development. Overall, the attrition rate of potential drugs throughout the development process is high. Table 2.1 contains estimated probabilities of a compound being terminated at a particular stage of the development.[5] One can see that the churn rate, especially at the early stages, is very significant. Overall, the probability that a compound is eventually released into the market is only about 6%.[6]

[4]The author's own estimates based on the pipeline data that includes only novel experimental drugs in development by commercial companies in the U.S. Estimates of the length of clinical development are comparable to those obtained by DiMasi et al. (2016).

[5]You can find the break-down of attrition by phases of development (instead of stages) in Appendix 9.2

[6]The estimate of the overall probability of success is smaller than reported by DiMasi et al. (2016) or by Wong et al. (2019). The reason is likely to be in differences in the samples. For example, my sample

Table 2.1: Distribution of Attrition Across Development Stages

	Total Attrition	Conditional Attrition
Early-stage trials	73.9%	73.9%
Late-stage trials	19.6%	75.3%
Regulatory submission	0.64%	9.97%

Notes: This table shows shares of development projects terminated at different stages of the R&D process. *Overall* are the shares as a percent of the total. *Conditional* are the shares as a percent of the drug candidates that made it to a particular stage. Source: Cortellis Competitive Intelligence database.

Attrition varies considerably across diseases, as Table 9.3 shows. Overall, some diseases have a larger proportion of drugs that make it all the way to the FDA. Moreover, for some indications new compounds are less likely to pass early stages of development designed to make sure that the drug has all the necessary characteristics and is not associated with serious toxicity. For other indications drugs seem to be more likely to move past stage one, with later getting discontinued in stage two designed predominantly to prove efficacy. This observed variation in the scope and distribution of attrition across stages of development can result from both variation in the intensity of competition as well as characteristics of the underlying science. For some diseases drug candidates are more likely to pass toxicity tests—for example, drugs for many types of cancer tend to have significant side effects but are still allowed by the FDA to continue development due to the severity of the disease itself. At the same time, for these same diseases it can be challenging to develop a drug that actually has an effect on the progression of the disease (and in this case again cancers are notorious for having relatively low rate of efficacious treatment). For other diseases, toxicity can be a larger problem.

Finally, although the pharmaceutical industry is essentially international, US market is by far the most important source of sales for novel drugs. Data from IMS Health suggests that this market alone makes up approximately 65% of total sales of newly lunched drugs (Figure

includes pre-clinical phase and excludes all the drugs that are not based on novel molecules (e.g. all the reformulations due to, for example, change in dosage or delivery method).

9.1 in Appendix 9.3). Therefore, focusing on the drug development process associated with the US market should be a good approximation to the innovation process in the overall industry.

2.2 Data and Preliminary Evidence

The main dataset used in this project was obtained from a proprietary database called Cortellis. This database includes detailed information on more than 70,000 drug candidates that have ever been in development anywhere in the world since the beginning of 1990s.[7] In this project I use data for the period 1998-2019 for 28 disease indications.[8] The list and description of the diseases is provided in Appendix 9.10. The database aggregates information from a wide variety of sources including clinical trial registries, journal articles, patents, press releases, financial filings, presentations, conferences and FDA submissions.[9] The consistency and accuracy of the data is maintained by professional analysts.

For each drug candidate, I observe: (i) the disease for which it was being developed; (ii) the date when it entered development as well as dates of each transition across development stages; (iv) dates when it was discontinued or taken to the regulatory authorities for marketing approval; (v) whether and when medicines at the regulatory stage were approved and entered the market; (vi) if and when the drug was withdrawn from the market (usually happens due to safety concerns). Table 9.5 presents a snapshot of the data associated with development histories of several drug candidates. As the table suggests, in some cases, a firms can test the same drug candidate against multiple diseases. The data allows to track development associated with these different diseases separately. For simplicity, I

[7]Some records date back even earlier—to the beginning of 1980s—but the number of such records is small. Moreover, the coverage improves after mid-1990s.

[8]I start the panel from the year after the U.S. clinical trials registry was established. The panel ends in the third quarter of 2019 when the data was downloaded.

[9]Other than clinical trial registration rules, another set of regulations that improves reporting of development actions in the industry is associated with the The Regulation Fair Disclosure, established by the U.S. Securities and Exchange Commission in 2000. The law ensures that publicly traded firms disclose all the material information in the timely fashion.

assume that R&D decisions for different indications are independent, and use observations on the drug-disease level. Moreover, if a drug-disease was developed by several firms, either simultaneously due to collaborative licensing agreements or consequently due to mergers and acquisitions, I consider it a part of the same development project, which is my final unit of analysis.[10] Finally, I keep only projects associated with drugs based on novel molecules, and drop drugs that are based on molecules that have already been approved by the FDA. In the latter case a drug would still have to go through clinical trials if it is based on a new dosage or delivery method (for example, oral instead of injection). Appendix 9.12 provides more detail on the procedure that I implement to identify and drop these reformulations. I use data on development projects to construct competition variables—e.g. the number of other projects in early trials, late trials, at the FDA and on the market. Table 2.2 includes the corresponding summary statistics.

In order to access the market size, I use an epidemiological measure of disease burden—disability-adjusted life years (DALYs). DALYs are calculated by adding up the measure of years of life lost to disease (affected by prevalence and mortality) and the measure of years of life lost due to disability (which is affected by incidence and duration of disability associated with the disease). Therefore, the measure takes into account not only the size of the population suffering from a disease, but also the severity of the disease. I get the data on DALYs from the Global Burden of Disease, a comprehensive epidemiological study conducted by the Institute for Health Metrics and Evaluation in collaboration with the WHO and the Harvard School of Public Health.[11] The study provides measures of prevalence, incidence, mortality and DALYs across diseases and geographic areas (countries and regions). The study began in 1990 and was conducted most of the years since. I use the measure of DALYs for the US averaged across all the years for which the data is available to capture variation

[10] I consider the development project to have transitioned to the next stage as soon as at least one firm promotes that drug to the next stage. I deem a project as discontinued when it is discontinued by all the firms that have been participating in its development.

[11] For more details see `www.thelancet.com/gbd`, `www.healthdata.org/gbd`, `www.who.int/healthinfo/global_burden_disease/about/en/` and `www.hsph.harvard.edu/news/multimedia-article/global-burden-of-disease/`

in prevalence and severity across diseases.[12] Since these disease-level characteristics should shift both private and public demand for treatments associated with the disease, I use the measure as a proxy for the market size.

In order to be able to provide estimates of the structural coefficients in dollars, I monetize DALY using the value of statistical life-year (VSLY). It is derived from the value of statistical life (VSL), which in turn is evaluated based on either survey data or on studies that estimate wage differentials that workers receive for on-the-job fatality risks (Kniesner and Viscusi (2019) provide an overview of different methodologies, and also show how to derive VSLY from VSL). Following health literature that commonly uses VSLY to monetize (e.g. provide dollar value for) epidemiological measures like DALY, I multiply the disability-adjusted life years for each disease by the common VSLY value of $369000 most recently used by the FDA.[13] The resulting measure provides dollar valuation for the burden of each disease. Since VSLY is estimated using individuals' private valuations of reducing the risk of fatality, the resulting monetised DALY measure is associated with the total private willingness to pay for alleviating the disease, rather than the corresponding public value.

I use data on clinical trial outcomes to inform probabilities of clinical success for different diseases. The source of the data is again Cortellis database that organizes and analyzes information from the clinical trial registry (`clinicaltrials.com`). For the trials that report results in the registry, Cortellis shows the trial's endpoint (e.g. broadly speaking whether the trial was primarily designed to study safety or efficacy), and whether in the end it was reached (e.g. whether measures of safety or efficacy were attained).[14] The reporting of trial results in the public registry within one year of completion is required by the 2007 Food and Drug Administration Amendments Act.[15] I aggregate the data on disease level by taking

[12]The Global Burden of Disease Study began in 1990 and was conducted most of the years since. There is a large gap spanning 1995-2011 for most of the diseases.

[13]Published by the FDA in 2016: `https://bit.ly/3dToyGA`. The measure itself, however, is in 2013 dollars. That value of VSLY is also mentioned in Kniesner and Viscusi (2019).

[14]Example of an efficacy endpoint would be: statistically significant difference in survival. An example of a safety endpoint would be: no statistically significant difference in the rate of serious adverse events

[15]However, studies suggest that due to scarce enforcement there is sill under-reporting (Chen et al. 2016, Saito and Gill, 2014 and Piller, 2020), and in the data, only 39% of trials have results (moreover, only for

the share of clinical trials that have reached the safety or efficacy endpoints for a particular disease.[16] The measure provides information about how likely an early-stage (safety) trial or a late-stage (efficacy) trial to succeed—e.g., reach its stated goal—for each indication.[17]

Finally, I append the clinical trial outcome variables with data on disease toxicity. I include this information because severity of the disease might affect criteria that the FDA applies to the level of toxicity that a drug can have and still continued development (e.g., drugs for more severe diseases can be allowed to have higher toxicity levels). Disease toxicity would therefore affect the probability of clinical success in early trials.[18] To construct this variable, I use data from disease-level meta-analysis of clinical trials provided by Advera Health's Evidex, a database that collects and analyzes clinical trial results.[19] As a measure of disease toxicity I use the proportion of participants in *control* arms of trials associated with a particular disease that experienced serious adverse events (that is, life-threatening, requiring hospitalization or immediate medical intervention). For example, on average about 44% of patients in control arms of trials for myelodysplastic syndrome experience serious adverse events, while this number is only 0.92% for migraine. Table 2.2 provides the summary statistics for all the variables in the final dataset.

Tables 9.6 and 9.7 in the Appendix 9.13 provide evidence that market-level variables (DALY, clinical trial results and disease toxicity) are associated with transition outcomes.

14% of all the trials reported results would allow to judge whether or not the endpoints were reached).

[16]Specifically, I use share out of all the trials for the disease that have have enough results to judge the success of a trial. For the efficacy measure, I use results for phase II and phase III trials, e.g. the phases that correspond to stage 2 in this project. However, reporting of results for phase I trials is very low, and I cannot base the safety measure on that data. I therefore use all the trials (including phase II and phase III for which safety is usually not a primary endpoint, but the safety data would still be collected and analyzed).

[17]Although alternatively I could match the trial information on the drug level, that becomes impossible because of the many missing results. With data aggregated on disease level, there is still a concern that under-reporting might be associated with a bias towards successful trials (e.g., they would more likely be reported). However, as long as the bias is the same across disease, the measure would still capture the meaningful variation.

[18]Recall that early trials are mainly designed to analyse drugs' safety profiles. Moreover, notice that whether or not a clinical trial for a drug has reached the safety endpoint (information for which I am already including) does not automatically translate into whether or not the drug can transition to the next stage. When making that decision, FDA may account for other factors like disease toxicity, as well as how close the trial was to meeting the endpoint.

[19]The source of clinical trials information for this database is again `clinicaltrials.gov`.

Table 2.2: Descriptive statistics.

VARIABLES	# obs.	mean	s.d.	min	max
Competition variables					
# competitors in early stage	9,370	82.55	52.92	0	273
# competitors in late stage	9,370	34.96	23.84	0	152
# competitors at the FDA	9,370	0.945	1.132	0	7
# competitors on the market	9,370	9.505	6.406	0	30
Market size					
DALYs (in thousands of years)	9,370	1,039	882.3	1.940	3,384
Scientific variables					
Disease toxicity	9,370	0.143	0.088	0.009	0.465
CT efficacy	9,370	0.678	0.171	0.280	0.933
CT safety	9,370	0.666	0.139	0.259	0.890
Transitioned					
From early stage	6,676	0.217	0.412	0	1
From late stage	2,694	0.113	0.317	0	1

Notes: The numbers are based on the data for the 28 diseases, 1998-2019.

The probability of transitioning from early- to late-stage trials is higher for more severe diseases; it is also higher for diseases associated with higher proportion of trials that reach their safety endpoints. Probability of transitioning from late-stage trials to the FDA is higher for diseases that have higher proportion of trials that reach their efficacy endpoints. This suggests that disease toxicity, safety and efficacy variables are indeed associated with probabilities of clinical success. At the same time, market size is also associated with higher transition probabilities—due to strategic incentives. Table 9.8 provides reduced-form evidence of the relationship between competition and transition probabilities: the number of competitors on the market negatively affects the probability of transition both from the early and the late stages of development. Although the coefficients in front of the number of competitors in other stages are indistinguishable from zero, given that the transition probabilities from these stages are low, the effect of adding one more competitor can be small and difficult to capture. Structural assumptions about firm behavior, and what a negative effect of stage 4 competition implies for competition in other stages, will help in discerning it.[20]

[20]Another explanation is that firms do not react to their competitors in development and respond only to market entries (as if not paying attention to the pre-market information). That however would contradict anecdotal evidence from the interviews with industry participants (a clinical manager at UVA and an executive manager at a pharmaceutical company) who suggest that firms track and react to their competitors' R&D actions.

Chapter 3

Model

In this section I describe my model of the pharmaceutical R&D process. Methodologically the model is adapted and modified from Arcidiacono et al. (2016). The main factors that affect firms' decisions within the model are: the number of competing projects at each stage of development and on the market; the size of the market; the rate of arrival of new firms and the duration of the development process associated with the disease; the cost of conducting clinical trials; and finally the scientific factors, that is how likely a drug candidate is to pass the FDA requirements associated with each stage of development.

3.1 Setup

Consider an infinite horizon game in continuous time indexed by $t \in [0, \infty)$. There are multiple markets (diseases) indexed by $m = 1, ..., M$. New firms enter the development process associated with each market m at random times which occur according to a Poisson process with market-specific rate λ^e_{m1}. The unit time period is normalized to be a year, implying that all the duration parameters are measured in years and fractions of year. The process of arrival of new firms represents exogenous arrival of discoveries associated with a particular disease. At arrival, each firm is assigned a unique index i.

In order to be able to commercialize its discovery and sell it on the market, the firm has

to go through three stages: 1 (preclinical and small scale clinical trials), 2 (large-scale or pivotal clinical trials) and 3 (FDA application). When a firm arrives, it automatically enters stage 1.

Each new discovery can be one of four types: toxic and not effective, not toxic and effective, not toxic and not effective and toxic and effective. I assume that toxicity and efficacy of drug candidates are independent characteristics. I will call drug candidates that are not toxic and effective, good. New entrants do not know the type of their discovery, but they know that a new drug candidate for disease m is likely to be not toxic with probability p_{m1} and it is likely to be effective with probability p_{m2} (therefore, due to the independence assumption, a drug is likely to be good with probability $p_{m1} \times p_{m2}$). p_{m1} and p_{m2} are in turn functions of stage-specific scientific variables O_{m1} and O_{m2}: O_{m1} includes the share of clinical trials associated with disease m that reach the safety endpoint and the measure of disease m's toxicity; O_{m2} includes the share of clinical trials for disease m that reach the efficacy endpoint. I assume that the probabilities of clinical success are logistic functions of the associated variables:

$$p_{mx} = \frac{e^{\alpha_x O_{mx} + \gamma_{\tilde{m}x}}}{1 + e^{\alpha_x O_{mx} + \gamma_{\tilde{m}x}}}, \; x = 1, 2, \tag{3.1}$$

where $\gamma_{\tilde{m}x}$ is a constant term associated with stage x and therapy area $\tilde{m}$ to which disease m belongs. (see the break-down of markets by therapy areas in Table 9.4 in Appendix 9.10).

It takes time and money to finish each stage of the process. While in stage 1, the firm has to pay the flow cost c_1. Moreover, the time it takes to perform stage 1 experiments is an exponential random variable with disease-specific rate λ_{m1}—therefore, it takes on average $\frac{1}{\lambda_{m1}}$ for a firm to finish that stage. Based on the results of stage 1 both the firm and the FDA discover whether the drug candidate is toxic or not.[1] I assume FDA does not allow

[1]Notice that this assumption does not necessarily imply that FDA has to wait until the trials are finished. Think about λ_{m1} characterising average duration until arrival of the crucial information associated with the drug candidate's performance that allows to judge whether the compound is toxic or not. If the drug shows strong signs of toxicity early on, than that information would arrive before the clinical trial was initially scheduled to finish.

trials to be performed with toxic drugs. Therefore, a firm that received bad stage 1 results has to drop out from development.

If the drug candidate is not toxic, the firm has to decide whether to transition to the next stage of development or not. It makes the decision taking into account the current realizations of the state variable—which, as I describe later in more detail, is just the current number of competitors at each stage of development (and on the market)—as well the realizations of the two choice-specific shocks. The first shock ε_{i11} is a cost shock associated with initiating the second stage trials. The second shock ε_{i01} is associated with terminating development (one can think about it as a scrap value shock). Both ε's are *private information* follow the type I extreme value distribution.

If the firm decides to proceed to stage 2, it has to pay the flow cost c_2 associated with performing stage 2 experiments. The duration of stage 2 is also an exponential random variable with disease-specific rate λ_{m2}. After finishing stage 2, the firm and the FDA uncover whether the drug candidate is effective or not. I assume FDA approves drugs that are not effective with probability zero; therefore, these drugs have to be terminated.[2]

If the firm's drug candidate is effective, the firm can apply to the FDA for the marketing approval. Its decision is again based on the realizations of the state variable and the two type I extreme value shocks. If the firm decides to apply, it has to pay a flow cost c_3 associated with communicating with the FDA, providing additional information at request and so on. The amount of time it takes FDA to make a decision is common across markets and follows exponential distribution with arrival rate λ_{m3} (that is, on average it takes $\frac{1}{\lambda_{m3}}$ before the new application is approved or rejected).[3] Conditional on the drug candidate getting all the way to the FDA I assume that approval is random, and the probability of approval p_3 is

[2]Notice that sometimes firms look for signs of efficacy at the early-stage clinical trials and continue checking for toxicity at the late-stage trials. In that case one can think about the probability p_{m1} (p_{m2}) as a probability that results of stage 1 (2) provide evidence that are adequate to support the future FDA application.

[3]There is evidence that the FDA's review times are inconsistent across diseases, which might be related to differences in the difficulty of the review process, or differences in productivity of FDA divisions (see, for example, U.S. Office of the Inspector General. 2003. FDA's Review Process for New Drug Applications. `http://oig.hhs.gov/oei/reports/oei-01-01-00590.pdf` or Chorniy et al. (2020))

common across markets.

If the drug is approved, the firm automatically enters the market and receives the flow payoff $\pi_m(s_{t4}) = \theta_0 + \theta_r R_m + \theta_s ln(1 + s_{t4})$, where R_m is the size of the market, and s_{t4} is the number of other firms on the market at time t. The firm receives π_m for on average $1/\lambda_4^g$ time periods, after which generic entry takes place, which reduces the firm's per-period payoff to zero (the time till the generic entry is distributed exponentially with rate λ_4^g).[4] Finally, drugs get withdrawn from the market at rate λ_4, which usually happen because new safety concerns arise (although these events are comparatively rare). Throughout the process, firms discount future payoffs at the continuous discount rate $\rho = 0.078$, which corresponds to a yearly discount factor of 0.925.[5]

Finally, at low rates λ_{mj}^e for $j = 2, 3, 4$ new outside firms enter into later stages of development. One can think of those firms initiating development in the US after performing some part of it in Europe. I assume that US firms take those arrivals as exogenous, and only start paying attention to a competitor after it has initiated development in the US (thus indicating that it is intending to apply for approval to enter the US market).

States and decisions

Firms in development or on the market only differ by the stage in which they currently are. In other words, firm heterogeneity is reflected in the firm state $x_{it} \in \{1, 2, 3, 4\}$, where $x_{it} = 4$ represents the stage after the launch.[6] I assume that in all other ways firms are identical.

The industry state is the vector s_t that lists for each stage $x \in \{1, 2, 3, 4\}$ the number of firms at that stage in period t. Therefore, $s_t \in \mathcal{S} = \{s \in \mathbb{N}^4 \big| \sum_{x=1}^4 s(x) < \infty\}$. I assume that there is a hard cutoff in terms of the maximum number of firms in each stage.

[4]Notice that I implicitly assume that generics affect the demand only for the branded drug to which they are equivalent, and not for other branded drugs.

[5]Discount factor and the continuous time discount rate are related by the formula $\beta = e^{\rho T}$, where T is the period of time associated with the discount factor, in our case a year (e.g. $T = 1$). See Doraszelski and Judd (2012) for more detail.

[6]Moreover, since the duration of each stage follows exponential distribution, the amount of time a firm has already spent in the stage is not included in the state variables due to the memoryless property of the distribution.

That is, there exist some finite numbers N_1, N_2, N_3, N_4 such that $s_t(1) \leq N_1$, $s_t(2) \leq N_2$, $s_t(3) \leq N_3$, $s_t(4) \leq N_4$ for all t. One can think about that as due to the limit on the number of facilities in which firms can conduct clinical trials and the limit on the capacity of FDA to process applications.[7] Due to that assumption, $\mathcal{S}$ is finite and with cardinality K, where $K = N_1 \times N_2 \times N_3 \times N_4$.

Whenever a firm reaches the end of a stage, it takes an action $j \in \{0, 1\}$. Action $j = 0$ corresponds to the firm dropping out, and action $j = 1$ corresponds to the firm transitioning to the next stage. Notice that in some cases a firm *has to* take a certain action—for example due to safety or efficacy considerations at the end of stage 1 and 2; due to FDA approving or not approving the drug at the end of the review process; or due to the drug being recalled from the market. I assume that all terminations are final: once a development project has bee discontinued, it does not restart.

A firm's single-period profit/cost in each state (x_i, s) is given by the following equations: $\pi(1, s) = 0$; $\pi(2, s) = c_2$; $\pi(3, s) = c_3$; $\pi(4, s) = \theta_0 + \theta_r R_m + \theta_s ln(1 + s_4)$. The structural parameters are: the costs of clinical trials c_2 and c_3; the profit parameters θ_r and θ_s; the "scientific" parameters p_{m1} and p_{m2};the duration rates λ_m's. Figure 9.2 presents the schematic description of the model.

3.2 Equilibrium

Markov strategies. As is standard in the dynamic discrete choice literature, I focus on Markov perfect equilibrium in pure strategies. I further assume that the equilibrium is symmetric, that is all firms follow the same strategy (given the firm's state). In this model, a Markov strategy for firm i is a function δ that assigns an action from $\{0, 1\}$ to each state (x, s, ϵ_{ix}), where x is the current stage of firm i, s is the industry state and ϵ_{ix} is the vector

[7] I operationalize this by assuming that the arrival rate, λ_0 drops to zero whenever $s(1) \geq N_1$; that the probability of receiving a bad signal (for both good and bad drug) after stage 1 or 2 becomes 1 whenever $s(2) \geq N_2$ or $s(3) \geq N_3$, respectively; and the the probability of FDA approval p_3 drops to zero whenever $s(4) \geq N_4$.

of private shocks received by firm i. Given the distribution of ϵ_{ix} and a strategy $\delta(x, s, \epsilon_{ix})$, we can define the probability that a firm will choose to transition to the next stage as $\sigma_{x,x+1,s} = Pr\big(\delta(x, s, \epsilon_{ix}) = 1|x, s\big)\ \forall\ x \in \{1, 2\}, s \in \mathcal{S}$. Same way, the probability that a firm drops out is $\sigma_{x,0,s} = Pr\big(\delta(x, s, \epsilon_{ix}) = 0|x, s\big)\ \forall\ x \in \{1, 2\}, s \in \mathcal{S}$.

Let $s'(x, y, s)$ to be a continuation state that arises after player in stage x transitions to y in state s ($x = 0$ implies new entry into stage y, $y = 0$ implies exit from stage x). Further, suppose all competitors of firm i follow the same strategy δ'. Given that the cost shocks ϵ_{j1x} and the scrap value shocks ϵ_{j0x} are private information for all j, the behavior of competitors can be characterized by the set of conditional choice probabilities σ'. Then a Markov strategy is a best response for firm i if:

$$\delta(x, s, \epsilon_{ix}; \sigma') = 1 \iff \epsilon_{i1x} + V_{x+1,s'(x,x+1,s)}(\sigma') \geq \epsilon_{i0x}\ \forall\ x \in \{1, 2\}, s \in \mathcal{S}, \tag{3.2}$$

where $V_{x+1,s'(x,x+1,s)}(\sigma')$ is the expected present value of firm i being in state $(x + 1, s')$ and behaving optimally in all points in the future given that its competitors behave according to σ'. In what follows define the these value functions formally.

Value Functions. Let $\tilde{\sigma}'$ be the conditional transition probability that takes into account the scientific probabilities of termination. That is, $\tilde{\sigma}'_{12s} = p_1\sigma'_{12s}$ and $\tilde{\sigma}'_{10s} = p_1\sigma'_{i10s} + (1 - p_1)$; and similarly for stage 2. Finally, for convenience denote $p_3^4 = p_3$ and $p_3^0 = 1 - p_3$. Following Blevins (2014), for the small time increments h I can express the present discounted value

of *being* in stage 2 (and behaving optimally in the future) as following:

$$V_{2,s}(\sigma') = \frac{1}{1+\rho h}\Bigg[c_2 + \overbrace{\sum_{x=1}^{4}\lambda_x^e h V_{2,s'(0,x,s)}(\sigma')}^{\mathbf{1}} + \overbrace{s(1)\lambda_1 h \sum_{y\in\{0,2\}}\tilde{\sigma}'_{1ys}V_{2,s'(1,y,s)}(\sigma')}^{\mathbf{2}} + \\ \overbrace{+\big(s(2)-1\big)\lambda_2 h \sum_{y\in\{0,3\}}\tilde{\sigma}'_{2ys}V_{2,s'(2,y,s)}(\sigma')}^{\mathbf{3}} + \overbrace{s(3)\lambda_3 h \sum_{y\in\{0,4\}}p_3^y V_{2,s'(3,y,s)}(\sigma')}^{\mathbf{4}} + \\ \overbrace{+ s(4)\lambda_4 h V_{2,s'(4,0,s)}(\sigma')}^{\mathbf{5}} + \overbrace{\lambda_2 h p_2 Emax_j\{\epsilon_{i02}, \epsilon_{i12} + V_{3,s'(2,3,s)}(\sigma')\}}^{\mathbf{6}} + \\ \overbrace{+\lambda_2 h(1-p_2)E(\epsilon_{i02})}^{\mathbf{7}} + \overbrace{\Big(1-\sum_{x=1}^{4}\lambda_x^e h - \sum_{x=1}^{4}s(x)\lambda_x h\Big)V_{2,s}(\sigma') + o(h)}^{\mathbf{8}}\Bigg], \tag{3.3}$$

where $s(x)\lambda_x h$ can be interpreted as the probability that one of the firms that is currently in stage x will get an opportunity to move to the next stage (or drop out) at the next time increment h. The following will explain the intuition behind each of the 8 parts of the equation:

1. Expected value for the case if a new firm arrives at stage x (according to an exogenous arrival rate λ_x^e).

2. Expected value for the case if one of the competing firms in stage 1 will get a chance to move forward (or drop out).

3. Expected value for the case if one of the competing firms in stage 2 will get a chance to move forward (or drop out). Notice that I subtract 1 because firm i is also in stage 2, and $s(2)$ is the total number of firms in stage 2.

4. Expected value for the case if one of the competing firms at the regulatory stage will get/will be declined a market approval.

5. Expected value for the case if one of the competing firms on the market will exit.

6. Expected value for the case if firm i will get a chance to move forward/drop out.

7. Expected value for the case if the results of firm i's clinical trials are unsatisfactory.

8. Expected value for the case if no changes happen in the next instance of time.

Rearranging and letting $h \to 0$, we can obtain the following expression:

$$\begin{aligned} V_{2,s}(\sigma') = \frac{1}{\sum_{x=1}^{4} \lambda_x^e + \sum_{x=1}^{4} s(x)\lambda_x + \rho} \Bigg[\sum_{x=1}^{4} \lambda_x^e V_{2,s'(0,x,s)}(\sigma') + \\ + s(1)\lambda_1 \sum_{y \in \{0,2\}} \tilde{\sigma}'_{1ys} V_{2,s'(1,y,s)}(\sigma') + \big(s(2)-1\big)\lambda_2 \sum_{y \in \{0,3\}} \tilde{\sigma}'_{2ys} V_{2,s'(2,y,s)}(\sigma') + \\ + s(3)\lambda_3 \sum_{y \in \{0,4\}} p_3^y V_{2,s'(3,y,s)}(\sigma') + s(4)\lambda_4 V_{2,s'(4,0,s)}(\sigma') + \\ + \lambda_2 p_2 Emax_j\{\epsilon_{i02}, \epsilon_{i12} + V_{2,s'(1,2,s)}(\sigma')\} + \lambda_2(1-p_2)E(\epsilon_{i02}) \Bigg] \end{aligned} \tag{3.4}$$

In the same way we can derive the value functions for the three other stages, see Appendix 9.5 for details.

Linear representation of the value functions. For the further analysis, it will be useful to express the Bellman equations in the matrix form, as a a linear function of transition probabilities. To simplify the notation, I will use $V_x^{'}$ instead of $V_x(\sigma')$. In Appendix 9.6 I show that the value functions associated with each stage x can be represented in the following way:

$$V_4^{'} = {\Omega_4^{'}}^{-1}\big[\theta_0 + \theta_r R + \theta_s ln(1+S_4)\big] \tag{3.5}$$

$$V_3^{'} = {\Omega_3^{'}}^{-1}\Big[C_3 + \lambda_3 p_3^0 \boldsymbol{\gamma} + \lambda_3 p_3^4 L_{3,4} V_4^{'}\Big], \tag{3.6}$$

$$V_2^{'} = {\Omega_2^{'}}^{-1}\Big[C_2 + \lambda_2 \boldsymbol{\gamma} + \lambda_2 p_2 L_{2,3} E\big(p_2, \tilde{\sigma}_{2,3}\big)\Big], \tag{3.7}$$

$$V_1^{'} = {\Omega_1^{'}}^{-1}\Big[\lambda_1 \boldsymbol{\gamma} + \lambda_1 p_1 L_{1,2} E\big(p_1, \tilde{\sigma}_{1,2}\big)\Big], \tag{3.8}$$

where $\Omega_x^{'}$ is a $K \times K$ matrix that collects the rates of exogenous state transitions (entry of new firms, FDA approval and exit from stage 4) and state transitions due to actions of competitors

that behave according to σ'. S_4 is the $K \times 1$ vector that denotes the number of firms in stage 4 associated with each state s. C_x is a $K \times 1$ vector of flow cost associated with the stage x. $L_{x,x+1}$ is a $K \times K$ matrix that denotes industry states that follow after a firm transitions from stage x to stage $x+1$; and $\boldsymbol{\gamma}$ is a $K \times 1$ vector of Euler's constants. That is, each element (l, l') of the matrix indexes the states (s, s') such that s' arises if a firm transitions from stage x to stage $x+1$, and the original state was s. $\tilde{\sigma}_{x,x+1}$ is a $K \times 1$ vector of probabilities $\tilde{\sigma}_{x,x+1,s}$ that a firm transitions from stage x to stage $x+1$ (that includes the probability of being terminated endogenously by the FDA) when the industry state is s associated with the firm's strategy σ. Finally, $E\big(p_x, \tilde{\sigma}_{x,x+1}\big)$ is a $K \times 1$ vector, where each element is a function $ln\Big(\frac{p_x}{p_x - \tilde{\sigma}_{x,x+1,s}}\Big)$.

Definition. A stationary policy policy rule δ is a *Markov perfect equilibrium* if:

1. $\delta(x, s, \epsilon_{ix})$ is a best response for all i, $x \in 1, 2$, s and ϵ_{ix}
2. For all firms, the conditional choice probabilities σ are consistent with the best response probabilities implied by $\delta(x, s, \epsilon_{ix})$ for all $x \in \{1, 2\}$ and s.

Equilibrium Existence. Define a mapping Ψ: $[0,1]^{K \times 2} \longrightarrow [0,1]^{K \times 2}$ by expressing the best response probabilities using the linear representation of the value functions from above and the best response mapping (3.2):

$$\Psi_{x,s}(\sigma) = \int \{V_{x+1,s'(x,x+1,s)}(\sigma) \geq \epsilon_{i0x} - \epsilon_{i1x}\} f(\epsilon_{ix}) d\epsilon_{ix}$$

Notice that since ϵ_{ix} are distributed i.i.d. across all firms, the mapping Ψ is the same for all i. Further, notice that after plugging (3.5) into (3.6), we can express both V_3 and V_2 as a K-dimensional function of only structural parameters and conditional choice probabilities. That implies that the mapping Ψ is a continuous mapping from a compact set onto itself. By the Brouwer's fixed point theorem, it has a fixed point. The fixed point probabilities imply Markov strategies that constitute a Markov perfect equilibrium.[8]

[8]Notice that the mapping may have more that one fixed point, which implies that there may be more than one equilibrium.

Chapter 4

Identification

The model is characterized by two sets of model primitives. First set of model primitives is related to the per-period flow payoffs and the coefficients associated with disease-level probabilities of getting good clinical trial results ("scientific" probabilities) or being approved by the FDA: $(c_2, c_3, \theta_0, \theta_r, \theta_s, \alpha_{m1}, \alpha_{m2}, \gamma_{\tilde{m}1}, \gamma_{\tilde{m}2}, p_3)$. The second set of model primitives is related to the market-level arrival rates of new firms and average duration of each stage of development: $(\lambda^e_{m1}, ..., \lambda^e_{m4}, \lambda^g_4, \lambda_{m1}, \lambda_{m2}, \lambda_{m3}, \lambda_4)$. In what follows I prove that given that the market size (R_m), arrival and transition times as well as all the drop out and transition events are observed, all the underlying structural parameters of the model are identified.

Identification of arrival rates. Assuming that we observe the exact times of arrival of new firms into each stage of the development process, and given the assumption that these arrivals are characterized by the exogenous Poisson process, we can identify the arrival rates λ^e_{mj} for each stage j and market m. The rates can be identified either as the average number of arrivals into each stage that happen within a given interval of time, or as the average duration between the two subsequent arrivals.

In the same way, assuming that we observe exact timing of arrival of generic competitors, we can identify the rate λ^g_4. Given that the timing of entry of generic analogs depends on many factors—for example, for how long the company is able to extend the patent life of the original approved drug, or alternatively the policies in place that are intended to improve generic penetration—approximating

generic arrival by a random Poisson process seems appropriate. At the moment, however, I am not using the data on generic entry, and instead assume that novel therapeutics get on average 20 years on the market (the standard patent protection duration) before generic entry, that is $\lambda_4^g = 1/20$.[1]

Identification of stage durations. Recall that the model assumes that as soon as the firm finishes a particular stage of development, it can either transition to the next stage or drop out.[2] Given that we observe all the transitions and drop-outs, the average duration of a particular stage j associated with a particular market m (λ_{mj}) can be identified by the average time between when a firm enters the stage and when it transitions or drops out of the stage.

Identification of the approval probability. Given that conditional on the drug reaching the FDA stage, the regulatory decision is random with constant exogenous probability of approval p_3, that probability can be identified simply as a share of firms that transition from the FDA stage to the market.

Identification of the remaining parameters. I will prove identification of the remaining parameters in multiple steps. First, following most of the literature on dynamic discrete choice models (e.g. Bajari et al. (2007), Aguirregabiria and Mira (2007), Aguirregabiria and Mira (2010) and Arcidiacono et al. (2016)), I assume that a single Markov perfect equilibrium is played in each market m, in each state s, and that all the firms expect the same equilibrium to be played at all times.[3] Given this assumption, the observed shares of firms that transition to the next stage in each state s, market m identify the conditional transition probabilities associated with that particular equilibrium.[4]

[1] While patents are usually obtained sometime before firms start clinical trials and therefore can expire earlier that 20 years after the drug enters the market, the expiration does not automatically imply generic entry, which in many cases happen much later. For example, dementia medication Namenda did not face any generic competition for 24 years since its approval (Feldman (2018)).

[2] If the firm is in stage 4, it can only droop out.

[3] This assumption is required because although I proved the existence of a Market prefect equilibrium in the model, I did not prove its uniqueness.

[4] Implicitly I assume that it is possible to identify CTPs for all the states. Alternatively, one can assume that it would be possible to identify the CTPs only for the subset of states that are included in the recurrent class associated with the equilibrium behavior on a particular market (see Erickson and Pakes (1995) for more information on the concept of a recurrent class). The further identification proof would proceed in the same way under both assumptions.

Second, after plugging the linear representation of V_4 (equation 3.5) into V_3 (equation 3.6), I can express the probability of transition from stage 2 to stage 3 for a particular state s in the following way:

$$\tilde{\sigma}_{m23s} = p_{m2}\frac{e^{V_{m,3,s'(2,3,s)}}}{1+e^{V_{m,3,s'(2,3,s)}}} = p_{m2}\frac{e^{w_{m,3,s}c_3+x_{m,3,s}\theta_0+y_{m,3,s}\theta_r+z_{m,3,s}\theta_s+u_{m,3,s}}}{1+e^{w_{m,3,s}c_3+x_{m,3,s}\theta_r+y_{m,3,s}\theta_s+z_{m,3,s}\theta_s+u_{m,3,s}}}, \tag{4.1}$$

where the particular logistic form is due to the assumption on the distribution of the scrap value shocks and the cost shocks. Here $(c_3, \theta_0, \theta_r, \theta_s)$ are unknown structural parameters, p_{m2} is a known function of unknown parameters α_2, $\gamma_{\tilde{m}2}$ and known scientific variables; $(w_{m,3,s}, x_{m,3,s}, y_{m,3,s}, z_{m,3,s}, u_{m,3,s})$ are known real numbers that depend on the market size R_m, the number of firms in each stage in state s as well as the states in some sense adjacent to it, equilibrium transition probabilities, arrival rates, stage durations, and the approval probability of the FDA (notice that all those quantities are either observed directly or already identified).[5]

Denote $W_{ms} = (w_{m,3,s}, x_{m,3,s}, y_{m,3,s}, z_{m,3,s}, u_{m,3,s})$, $W_m = (w_{m,3}, x_{m,3}, y_{m,3}, z_{m,3}, u_{m,3})$ for a given market m and $W = (w_3, x_3, y_3, z_3, u_3)$ for all the markets. Denote β_0 the vector of true values of parameters $(c_3, \theta_0, \theta_r, \theta_s)$. Define $F_{ms}(\beta)$ in the following way:

$$F_{ms}(\beta) = F(W_{ms}\beta) = \frac{e^{w_{m,3,s}c_3+x_{m,3,s}\theta_0+y_{m,3,s}\theta_r+z_{m,3,s}\theta_s+u_{m,3,s}}}{1+e^{w_{m,3,s}c_3+x_{m,3,s}\theta_0+y_{m,3,s}\theta_r+z_{m,3,s}\theta_s+u_{m,3,s}}} \tag{4.2}$$

Denote $F_m(\beta)$ the vector of $F_{ms}(\beta)$ associated with all states related to a particular market m. Denote $F(\beta)$ the vector of $F_m(\beta)$ associated with all the markets.

Assume $|W(\beta - \beta_0)| > 0$ for all $\beta \neq \beta_0$ (notice that the assumption implies that W has at least 4 linear independent rows). Since $F(.)$ is strictly monotone, this implies that $F(\beta) \neq F(\beta_0)$ for all $\beta \neq \beta_0$. If scientific terminations did not happen this assumption would directly imply identification of $(c_3, \theta_0, \theta_r, \theta_s)$. Identification in the model with scientific terminations still requires the assumption to hold (below I provide intuition for why it does in this setting), but additional requirements have to be satisfied to separately identify parameters inside p_{m2}. In order to separate p_{m2}, I propose two approaches. The first approach relies on the functional form of the probability

[5]These dependencies are hidden within the matrices Ω_4^{-1} and Ω_3^{-1}. For more details about how these matrices are constructed, see Appendix 9.6.

of receiving a good stage 2 signal: I assume that it is a logistic function of the linear index of scientific variables a therapy area-specific constant terms (see Equation 3.1). The second approach relies on the functional form of strategic transitions (also a logistic function as equation 4.1 shows). I present both of these identification approaches below.

Separating science, approach 1. For the first approach, notice that the probability of transitioning to the next stage after having received a good signal increases in the market size: intuitively, firms are more likely to invest in further development if the associated disease is very profitable.[6] Then as long as R_m (market size) is not strongly correlated with O_{m2} (scientific variables associated with stage 2), scientific parameters α_2 and $\gamma_{\tilde{m}2}$ can be identified from overall transition probabilities $\tilde{\sigma}$ associated with large markets ($R_m \to +\infty$) within a particular therapy area. For these markets, the probability of strategic transitions becomes equal to one, and the observed transition shares identify p_{m2}, e.g. $p_{m2} = \tilde{\sigma}_{m23}$, or:

$$\alpha_2 O_{m2} + \gamma_{\tilde{m}2} = ln\Big(\frac{\tilde{\sigma}_{m23}}{1-\tilde{\sigma}_{m23}}\Big) \tag{4.3}$$

Provided that there are at least $dim(O_{m2}) + 1$ of these markets (with different values of O_{m2}, the number of clinical trials reaching efficacy endpoint) for at least one therapy area, parameters α_2 are identified (as they are constant across therapy areas). Then at least one additional large market is required for each therapy area to identify constants $\gamma_{\tilde{m}2}$.

Separating science, approach 2. Within this approach I show that given the functional form of $F(.)$, for any β such that $F_m(\beta) \neq F_m(\beta_0)$ there is no $p_{m2,\beta}$ such that $p_{m2,\beta}F_m(\beta) = p_{m2,\beta_0}F_m(\beta_0)$, where p_{m2,β_0} is the true value of the parameter p_{m2}. To prove that statement, suppose without loss of generality that $F_{ms}(\beta) > F_{ms}(\beta_0)$ for some state s. Pick $p_{m2,\beta}$ such that $p_{m2,\beta}F_{ms}(\beta) = p_{m2,\beta_0}F_{ms}(\beta_0)$. There is only one such value of $p_{m2,\beta}$, moreover, $p_{m2,\beta} < p_{m2,\beta_0}$. Pick the state s' such that $F_{ms}(\beta) - F_{ms'}(\beta) < F_{ms}(\beta_0) - F_{ms'}(\beta_0)$. Then $p_{m2,\beta}F_{ms}(\beta) - p_{m2,\beta}F_{ms'}(\beta) < p_{m2,\beta_0}F_{ms}(\beta_0) - p_{m2,\beta_0}F_{ms'}(\beta_0)$. Given that $p_{m2,\beta}F_{ms}(\beta) = p_{m2,\beta_0}F_{ms}(\beta_0)$, we get: $-p_{m2,\beta}F_{ms'}(\beta) < -p_{m2,\beta_0}F_{ms'}(\beta_0)$, or $p_{m2,\beta}F_{ms'}(\beta) > p_{m2,\beta_0}F_{ms'}(\beta_0)$. Therefore, as long as for

[6] To see that, notice that each row of V_4 positively depends on R_m, and each row of V_3 positively depends on V_4 (see Appendix 9.6).

each guess β there exists such state s', parameters $(c_3, \theta_0, \theta_r, \theta_s)$ as well as p_{m2} are identified (within this approach the probability of scientific success is identified nonparametrically).[7] In Appendix 9.7 I show that if W has at least four linear independent rows, it is possible to limit the number of guesses for $p_{m2,\beta}$ to three. Then one can proceed with the logic provided in the proof above to eliminate the two guesses that do not coincide with p_{m2,β_0}.

Identification of stage 1 parameters. Finally, notice that after plugging in the linear representation of V_3 (Equation 3.6) into V_2 (Equation 3.7), we can express the probability of transition from stage 2 to stage 3 given state s in the following way (again omitting subscript m):

$$\tilde{\sigma}_{m12s} = p_{m1} \frac{e^{V_{m,2,s'(1,2,s)}}}{1 + e^{V_{m,2,s'(1,2,s)}}} = p_{m1} \frac{e^{x_{m,2,s}c_2 + y_{m,2,s}g(p_{m,2}) + z_{m,2,s}}}{1 + e^{x_{m,2,s}c_2 + y_{m,2,s}g(p_{m,2}) + z_{m,2,s}}}, \tag{4.4}$$

where $g(p_{m2}) = p_{m2} ln\Big(\frac{p_{m2}}{p_{m2} - \tilde{\sigma}_{m,23s'}}\Big)$ (see Appendix 9.6 for details). Given that p_{m2} is already identified, the only remaining unknown structural parameters are c_2 and parameters inside p_{m1}: $(\alpha_1, \gamma_{\tilde{m}1})$. These parameters can be identified using the same logic as presented above. Finally, I normalize the cost of early-stage trials c_1 to zero.[8]

Discussion. Once arrival rates, stage durations and the approval probability are identified, the only difference between the standard dynamic discrete choice model and this model are the "scientific" probabilities p_1 and p_2. Because development projects can be terminated due to poor clinical trial results, and because that event is independent from the current state s, the observed probability that a firm transitions from, for example, stage 2 to stage 3 given s is not just equal to the conditional choice probability (CCP) like in the standard model. Instead, it equals to the CCP times the probability of exogenous termination. If exogenous termination did not happen, and CCPs were observed directly, the standard assumption $|W(\beta - \beta_0)| > 0$ would suffice for identification. In this setting, the intuition for identification of the cost and profit parameters are the same. The coefficient θ_s is identified due to variation in competition across states s; the coefficient θ_r is identified separately from c_3 due to variation in the market size across markets; the

[7] Notice in the data I observe hundreds of states for most markets.

[8] I do not estimate c_1, and the normalization does not play a role in estimation of other structural parameters. The normalization only makes a difference for the values of the value function at stage 1.

coefficient θ_0 is identified separately from c_3 due to variation in the FDA review duration across markets; c_2 is identified separately from c_3 due to the restrictions that model puts on how firms react to changes in the cost of clinical trials for different stage across different levels of competition.[9]

Parameters p_1 and p_2 are identified due to: (i) variation in market size across diseases that only affects strategic but not scientific attrition (ii) the nonlinearity of the distribution function $F(.)$ and variation in competition within the same market that also only affects strategic but not scientific attrition. With respect to the second approach, the importance of the non-linearity assumption has been discussed in the previous literature that has provided identification for similar models, although not in the context of a dynamic discrete choice setting. Particularly, Hausman et al. (1998) provides identification for an analog of Equation 4.1, assuming continuous support for the observed covariates in W. The paper shows that theoretically particular functional form of the distribution $F(.)$ is not required for identification, as long as $F(.)$ is nonlinear, strictly monotone and known.

[9]Intuitively, when the firm decides whether or not to enter stage 2, the expected value associated with later entering/not entering stage 3 changes in a known way depending on the current state s, which puts restrictions on possible values for c_2.

Chapter 5

Estimation

The estimation of the model proceeds in two steps. In the first step I estimate: (i) exogenous discovery rate for each market; (ii) average duration of each stage of development for each market; (iii) probability of the FDA approval conditional on applying for the regulatory review; (iv) conditional transition probabilities (CTPs) as a function of observed states. In the second step I use the methods developed in Arcidiacono et al. (2016) to estimate the cost, the profit and the scientific parameters of the model. I discuss both steps of the estimation procedure in detail in the following subsections.

5.1 Step 1. Estimation of λ-s and transition probabilities

I estimate the entry rates (λ^e-s) from the average amount of time between two subsequent entries into a particular stage for a particular market. I estimate the stage duration rates (λ-s) from the average amount of time between the start of the stage and the time when the drug either transitions to the next stage or is terminated. In both cases I adjust for censoring of the data - the details on that are in Appendix 9.8. I estimate the FDA approval probability as the share of drugs that reached the market out of all the drugs that were submitted for the FDA review. Appendix 9.15 provides results for the entry and duration parameters. Most of the diseases that I study are

characterized by frequent entry of new discoveries (on average, a new discovery enters early clinical trials every 1.2 months). Drugs need to spend on average 6 years in early stage trials and 7 years in late stage trials before reaching the FDA, and there is sizeable variation in stage duration across diseases.

I estimate the conditional transition probability (CTP) of a drug transitioning to the next stage of development as a function of the total number of development projects at each stage, conditional on the drug's own stage and the disease for which it is being developed. It would be ideal to estimate the CTPs as the shares of drugs that transitioned at each state (where a particular state is characterised by the disease m, the stage of development x and the level of competition s). However, it is impossible given the size of the state space and the number of data points that I observe. Instead, I estimate the transition probabilities as a flexible parametric function of the level of competition s and market-level variables. I use the following specification for the probability that at the end of stage $x = 1, 2$ the drug transitions to the next stage $y = 2, 3$ given $s = \big(s(1), s(2), s(3), s(4)\big)$, the number of firms in each stage of development, for market m:

$$\tilde{\sigma}_{xysm} = \frac{e^{f(s,\beta_{xm})+\gamma_m}}{1 + e^{f(s,\beta_{xm})+\gamma_m}}, \tag{5.1}$$

where $f(s, \beta_{xm})$ is a second order polynomial in the number of firms in each stage and disease characteristics (e.g. market size and scientific variables). To improve prediction, I also include market-level fixed effects γ_m.[1] Results of the estimation are presented in Appendix 9.16.

5.2 Step 2. Estimation of structural parameters

In what follows I omit the market subscript m to simplify the notation. Using equations 4.4 and 4.1, we can express the value of being in the next stage $y = 2, 3$ of development as a function of the probability of transition from the earlier stage $x = 1, 2$ at state s:

$$V_{y,s'(x,y,s)} = ln\Big(\frac{\tilde{\sigma}_{xys}}{p_x - \tilde{\sigma}_{xys}}\Big) \tag{5.2}$$

[1] It is known that fixed effects introduce bias into the estimates of the *coefficients*. However, that is not a concern in this case, since I am only interested in predicting the *transition probabilities*.

Similarly, we can derive the value as a function of the CTP for every state *adjacent* to s, that is a state that is connected to state s by one or more state changes (transitions, entries or terminations). One example of the adjacent state is the state $s'(0,1,s)$, e.g. the state that is reached when a new firm enters stage 1 in state s. The value of being in stage 2 at state $s'(0,1,s)$ can be expressed as following:

$$V_{2,s'(0,1,s)} = ln\Big(\frac{\tilde{\sigma}_{12s''(2,1,s')}}{p_x - \tilde{\sigma}_{12s''(2,1,s')}}\Big) \tag{5.3}$$

Here the CTP is associated with the state s'' that has one less drug in stage 2 and one more drug in stage 1 comparative to s'. Although the state s'' cannot be reached from the state s' (the transition from stage 2 to stage 1 is impossible), the reverse is possible: state s' can be reached from the state s''. Moreover, the probability of this transition will be the function of $V_{2,s'''(1,2,s'')} = V_{2,s'''(1,2,s''(2,1,s'))} = V_{2,s'}$. Inverting that function, we can express $V_{2,s'}$ as a function of $\tilde{\sigma}_{12s''(2,1,s')}$ as in (5.3).

Following the same procedure for all the states *adjacent* to state s, we can replace all the values of the value function on the right-hand side of (3.4) with the corresponding functions of the CTPs.

$$V_{2,s}(\theta,\tilde{\sigma},\lambda) = \frac{1}{\sum_{x=1}^{3}\lambda_x^e + \sum_{x=1}^{3} s(x)\lambda_x + \rho}\Bigg[c_2 + \lambda_2\gamma + \overbrace{\sum_{y=1}^{3}\lambda_y^e\Big[ln\Big(\frac{\tilde{\sigma}_{12s''(2,1,s'(0,y,s))}}{p_1 - \tilde{\sigma}_{12s''(2,1,s'(0,y,s))}}\Big)\Big]}^{\textbf{1. new firm}} +$$

$$+\overbrace{s(1)\lambda_1\sum_{y\in\{0,2\}}\tilde{\sigma}_{1ys'}\Big[ln\Big(\frac{\tilde{\sigma}_{12s''(2,1,s'(1,y,s))}}{p_1 - \tilde{\sigma}_{12s''(2,1,s'(1,y,s))}}\Big)\Big]}^{\textbf{2. firm in 1 moves}} + \overbrace{\big(s(2)-1\big)\lambda_2\sum_{y\in\{0,3\}}\tilde{\sigma}_{2ys'}\Big[ln\Big(\frac{\tilde{\sigma}_{12s''(2,1,s'(2,y,s))}}{p_1 - \tilde{\sigma}_{12s''(2,1,s'(2,y,s))}}\Big)\Big]}^{\textbf{3. firm in 2 moves}}$$

$$+\overbrace{s(3)\lambda_3\sum_{y\in\{0,4\}}p_3^y\Big[ln\Big(\frac{\tilde{\sigma}_{12s''(2,1,s'(3,y,s))}}{p_1 - \tilde{\sigma}_{12s''(2,1,s'(3,y,s))}}\Big)\Big]}^{\textbf{firm in 3 moves}} + \overbrace{s(4)\lambda_4\Big[ln\Big(\frac{\tilde{\sigma}_{12s''(2,1,s'(4,0,s))}}{p_1 - \tilde{\sigma}_{12s''(2,1,s'(4,0,s))}}\Big)\Big]}^{\textbf{4. firm in 4 drops out}} + \overbrace{\lambda_2 p_2 ln\Big(\frac{p_2}{p_2 - \tilde{\sigma}_{23s}}\Big)}^{\textbf{5. firm i gets good signal}}\Bigg] \tag{5.4}$$

Similarly we can do the same for the expression of $V_{3,\boldsymbol{s}}$, details on that are in Appendix 9.17. Equation (5.4) allows us to express the value of V_2 at any state s as a function of transition probabilities $\tilde{\sigma}$, entry and duration rates λ and structural parameters θ. We then can plug the

resulting value of V_2 into the structural probability of a drug transitioning to stage 2 and into state s is:

$$\tilde{\sigma}_{12s_0}(\theta, \tilde{\sigma}, \lambda) = p_1 \frac{e^{V_{2,s'(1,2,s_0)}(\theta,\tilde{\sigma},\lambda)}}{1 + e^{V_{2,s'(1,2,s_0)}(\theta,\tilde{\sigma},\lambda)}}, \tag{5.5}$$

where s_0 is the state associated with the firm transitioning/terminating development at the end of stage 1 in the data. Omitting the subscript for the stage into which the drug is transitioning (since it can only be stage 2), the corresponding likelihood is given by:

$$l_{1s_0}(\theta, \tilde{\sigma}, \lambda) = \frac{\mathbb{1}\{d_{12s_0} = 0\} + \mathbb{1}\{d_{12s_0} = 1\} \times p_1 e^{V_{2,s'(1,2,s_0)}(\theta,\tilde{\sigma},\lambda)}}{1 + e^{V_{2,s'(1,2,s_0)}(\theta,\tilde{\sigma},\lambda)}}, \tag{5.6}$$

Since the cost shocks ϵ_{11} and outside value shocks ϵ_{01} are i.i.d., then conditional on the observed state the transition decisions are independent, which implies that we can aggregate the likelihood across all the states associated with stage 1 decisions observed in the data in the following way:

$$l_1(\theta, \tilde{\sigma}, \lambda) = \prod_{s_0 \in S_1} l_{1s_0}(\theta, \tilde{\sigma}, \lambda), \tag{5.7}$$

where S_1 is the set of all the states observed in the data that are associated with stage 1 decisions. Similarly, we can express transition probabilities and likelihoods for the observed states associated with decisions at the end of stage 2. Plugging in the estimates of the transition probabilities $\hat{\tilde{\sigma}}$ and duration and entry rates $\hat{\lambda}$ from step 1, we can formulate the pseudo log-likelihood function:

$$L(\theta, \hat{\tilde{\sigma}}, \hat{\lambda}) = \sum_{s_0 \in S_1} ln(l_{1s_0}(\theta, \hat{\tilde{\sigma}}, \hat{\lambda})) + \sum_{s_0 \in S_2} ln(l_{2s_0}(\theta, \hat{\tilde{\sigma}}, \hat{\lambda})), \tag{5.8}$$

which we maximize to obtain the pseudo maximum likelihood estimator of the structural parameters:

$$\hat{\theta} = \arg\max_{\theta \in \Theta} L(\theta, \hat{\tilde{\sigma}}, \hat{\lambda}) \tag{5.9}$$

The parameter estimates are consistent if $T \to \infty$, where T is the length of the panel, or $M_{\tilde{m}} \to \infty \; \forall \; \tilde{m}$, where $M_{\tilde{m}}$ is the number of markets within therapy area $\tilde{m}$, or both. Arcidiacono

et al. (2016) shows consistency under $M \to \infty$, where M is the total number of markets. In this case, however, this requirement has to hold for markets within each therapy area. The latter is necessary in order to resolve the incidental parameters problem associated with the therapy area fixed effects inside the p_1 and p_2 functions (see Neyman and Scott (1948) and Heckman (1981)). The problem should also not be prominent in the sample, since even the smallest number of observations per therapy area is still more than a hundred (see Table 9.9 in Appendix 9.14).

Chapter 6

Results

The structural parameter estimates are presented in Table 6.1. The estimate of the stage 2 clinical trials cost c_2 suggests that a year of late stage clinical trials costs almost \$50 million.[1] Taking into account stage 2 duration averaged across diseases, the overall average cost of stage 2 trials is close to \$266 million.[2] These estimates are comparable to the estimates obtained through surveys of pharmaceutical firms.[3] The average total cost of stage 3 (e.g. regulatory review stage) is approximately \$95 million (although c_3 is not precisely estimated).[4] Since within the model framework I cannot separate the cost of the FDA and the expected cost associated with the drug launch, the estimate implicitly includes both. The average yearly monopoly profit is approximately \$4.3 billion per year, ranging from \$1.9 billion for Hepatitis C to \$10 billion for Chronic obstructive pulmonary disease (COPD) (see Figure 9.4 in Appendix 9.18). The coefficient estimate for the competition

[1]Notice that the interpretation of the cost and profit parameters in dollars is conditional on assuming the unit scale parameter of the distribution of the ϵ-s. In order to aggregate the estimates of flow costs to costs per year (and given that the unit of time in the model is set to be a year) we need to integrate over a unit time period taking the discount factor into account: $\int_0^1 c_2 e^{-\rho t} dt = c_2 \frac{1}{\rho}\left(1 - e^{-\rho}\right)$.

[2]The average duration of stage 2 trials across all the indications that I use is 6.9 years. Aggregating the flow cost across this time period gives $\int_0^{6.9} c_2 e^{-\rho t} dt = c_2 \frac{1}{\rho}\left(1 - e^{-\rho \times 6.9}\right) \approx 0.266$

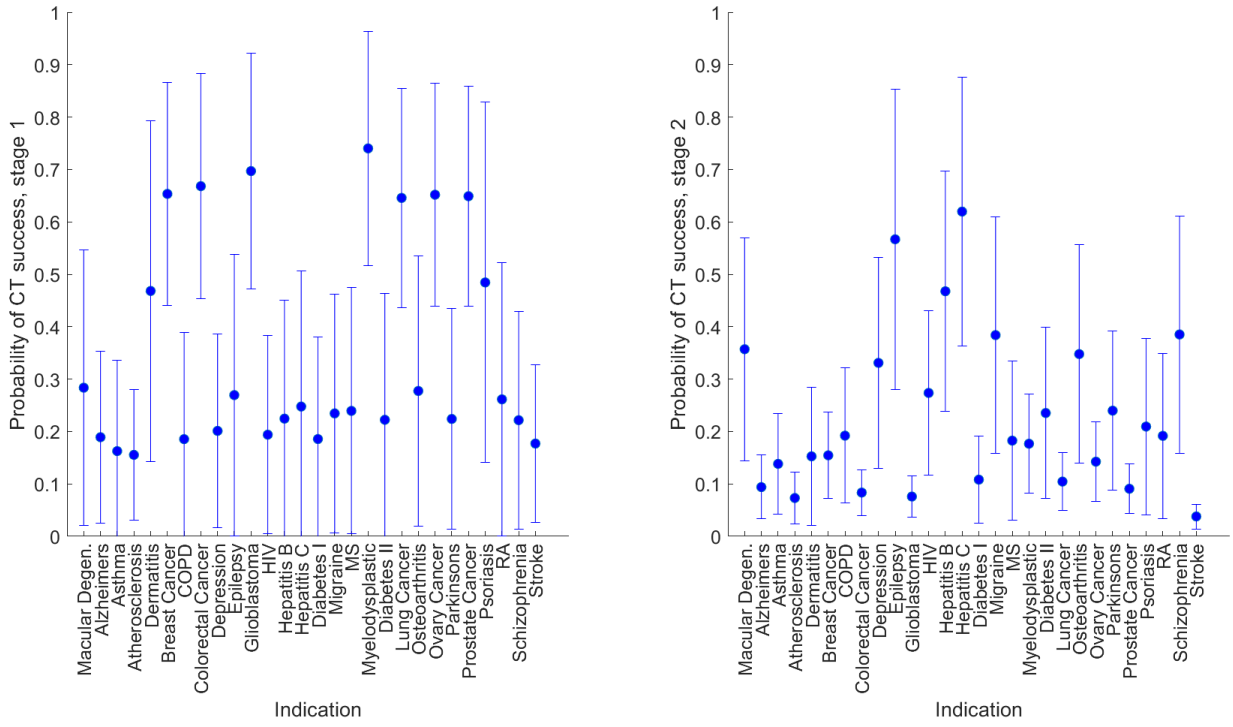
[3]DiMasi et al. (2016) provides estimates of the cost of clinical trials using information provided by pharmaceutical firm. Based on these estimates, the costs that the firms expect to pay when entering the late-stage trials is around \$206 million. Although the two estimates are not directly comparable: estimates in DiMasi et al. (2016) are based on a selected sample of pharmaceutical firms, and estimates provided in this paper are based on a selected sample of diseases - the fact that they have the same order of magnitude is reassuring.

[4]Increasing the number of diseases included in the sample should help in improving the precision of the estimate of c_3 .

effect θ_s implies that the entry of the first competitor decreases the profit by \$250 million per year. After accounting for the number of drugs that were launched on the market, the estimates of the average yearly profits are provided in Figure 9.4: they range from \$7.7 hundred million for Hepatitis B to about \$9.4 billion for COPD, with the average of \$3.5 billion.[5]

The estimates of the parameters associated with the scientific variables (e.g. disease toxicity, and the proportion of clinical trials that reached the safety/efficacy endpoints) have the expected sign. The associated disease-level estimates of the clinical trial success probabilities p_1 and p_2 are provided in Table 9.14 along with Figure 6.1. Notice that all of the p_1 and p_2 are significantly below one.Moreover, the figure shows heterogeneity across diseases: for example, the probability of succeeding in early stage clinical trials is higher for cancer drugs in the sample, likely because the associated diseases are relatively more severe.

Figure 6.1: Estimates of the probabilities of clinical trials success by indications for 28 diseases.



As a validation check, I solve the model at the parameter estimates and then use the it to

[5]These numbers are large, but within the range of the observed pharmaceutical sales data. Yearly sales of blockbuster drugs (usually defined as drugs that generate annual sales of at least \$1 billion) can go as high as \$20 billion. Since my dataset includes only novel therapeutics (and not reformulations, biosimilars of generics), these drugs are more likely to reach the blockbuster status.

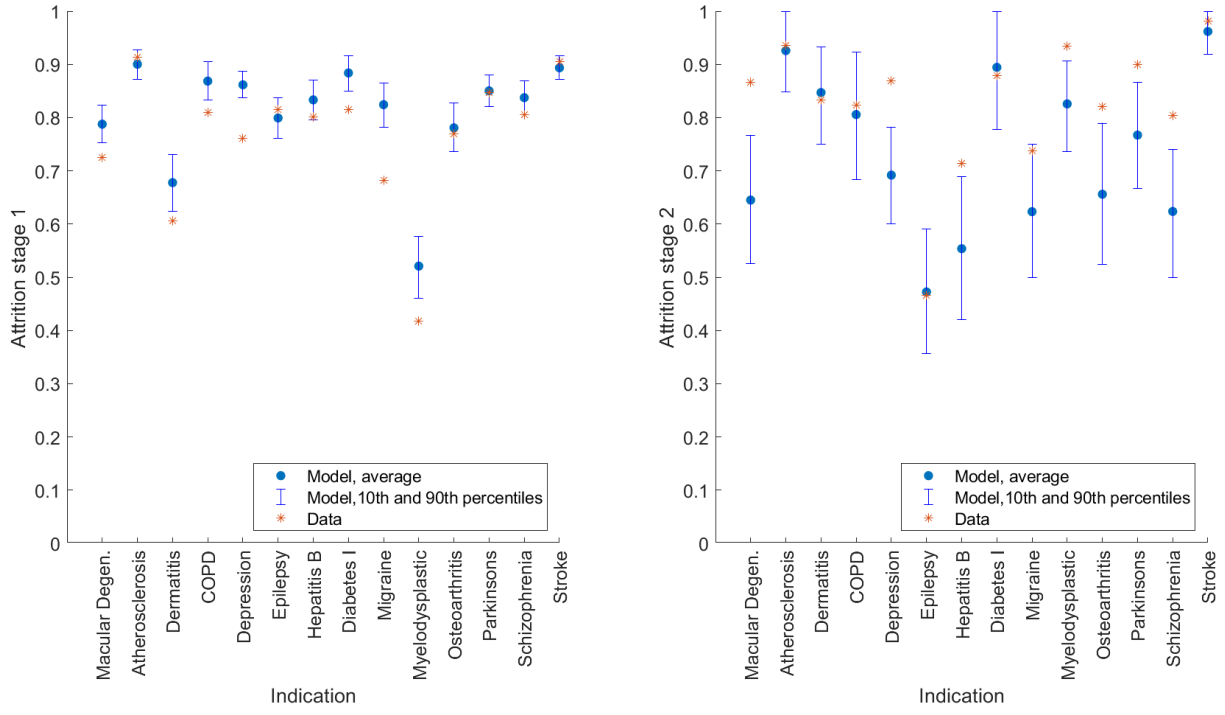
Table 6.1: Estimates of structural parameters.

Parameter	Coeff.	S.E.
Cost stage 2 (c_2)	-0.050***	0.016
Cost stage 3 (c_3)	-0.055	0.051
Profit, constant (θ_0)	2.401***	0.188
Profit, market size (θ_r)	0.007***	0.002
Profit, competition (θ_s)	-0.635***	0.152
p_1 parameters:		
Cancer f.e. stage 1	0.000	0.000
Other f.e. stage 1	-1.770***	0.285
Dermatologic f.e. stage 1	-1.027***	0.263
Endocrine f.e. stage 1	-2.383***	0.226
Immune f.e. stage 1	-1.923***	0.277
Infection f.e. stage 1	-2.175***	0.248
Neurology f.e. stage 1	-1.933***	0.236
Respiratory f.e. stage 1	-2.388***	0.257
Disease toxicity stage 1	1.100*	0.568
CT safety stage 1	1.679**	0.656
Constant stage 1	-0.540**	0.267
p_2 parameters:		
Cancer f.e. stage 2	0.000	0.000
Other f.e. stage 2	0.540	0.478
Dermatologic f.e. stage 2	-1.198***	0.288
Endocrine f.e. stage 2	-1.151***	0.269
Immune f.e. stage 2	-0.189	0.373
Infection f.e. stage 2	0.373	0.453
Neurology f.e. stage 2	0.751*	0.432
Respiratory f.e. stage 2	-0.827***	0.292
CT efficacy stage 2	6.730***	0.421
Constant stage 2	-5.822***	0.237

Notes: Estimates of cost and profit parameters are in billions of dollars. Standard errors are computed using 200 bootstrap samples.

forward simulate 1000 paths for 14 diseases in my dataset.[6] For every particular disease, I start each path from the state $\boldsymbol{s}$ that was first observed in the data at the beginning of the panel. The results of the simulations that compare the attrition shares predicted by the model and those observed in the data are presented in Figure 6.2. Although the model tends to overestimate the share of terminations for early stage trials and underestimate them for the late stage trials, overall it seems to replicate the data reasonably well. The worse fit for the second stage can be due to two reasons: the estimates of c_3 are too low (recall that this estimate is very imprecise); the value for the parameter λ_g^e is too high (recall that I assume that on average novel therapeutics get 20 years on the market before generic entry). Including more diseases in the sample and appending the data on actual generic entry should remedy both issues and improve the fit.

Figure 6.2: Model fit based on 1000 simulated paths for 14 diseases.



The model allows me to separate overall attrition into scientific and strategic, as within the simulations I know the reason for each particular termination. Table 6.2 reports the corresponding shares. Overall, strategic attrition is responsible for about 8.4% of all terminations.[7] However,

[6] I solve the model using the value function iteration method. Since there is heterogeneity in disease-level parameters, I solve the model disease-by-disease. Because this process is computationally costly, at the moment I use only 14 diseases.

[7] The number is obtained not by averaging the shares provided in the table across diseases, but rather

there is large heterogeneity in the importance of strategy: it is responsible for only 5.5% of all terminations for the COPD, but for almost 35% for myelodyplastic syndrome. Moreover, the probability of strategic terminations is much higher after the early stage trials: 9.3% versus 1.2%.[8] The average shares again hide considerable variation across diseases: for stage 1, the share of strategic attrition goes from 6.1 for COPD to 49.9 for myelodyplastic syndrome; for stage 2, it goes from almost 0 for Stroke to 8.4 for Epilepsy. Significant strategic attrition is more likely for disease that have higher probability of clinical trials success. One reason for that is purely mechanical - a drug is less likely to fail clinical trials and be dropped for scientific reasons. At the same time, for those diseases the overall probability of being dropped as well as the probability of being dropped conditional on clinical trials success (especially for stage 2) tends to be higher, which suggests substitutability between the two sources of attrition. Indeed, for a drug that has passed stage 2 clinical trials, it is better to have done that for a disease for which it is difficult to do—as these barriers to entry will protect the drug from follow-on competition. I explore this in more detail in my first counterfactual.

In order to analyze how strategic attrition contributes to the rate of new drug launches, I run the simulations after shutting down the strategic channel—that is, I set the probability that a drug is terminated after stage 1 (stage 2) to be always exactly p_1 (p_2). I conceptualize this exercise as trying to analyze what would be the rate of new drug launches, if the government was purchasing all the discoveries from private companies and then committing to develop them into drugs (unless their medicinal properties were bad). I simulate 1000 paths both with and without strategic attrition starting in this case from the zero state (e.g. state where the number of firms in each stage is zero). I simulate each path 30 years forward, but only use the last 20 years—in order to allow the process to get away from the low-probability state with small number of competitors in development stages. I calculate the average time between subsequent launches for each of the regimes (e.g. original, clinical success in late increased by 10 p.p., and clinical success in early increased by 10 p.p.) and plot it on the graph presented in Figure 6.3. On average, the duration

by taking the overall (without separation by disease) attrition shares and averaging them across the 1000 simulations.

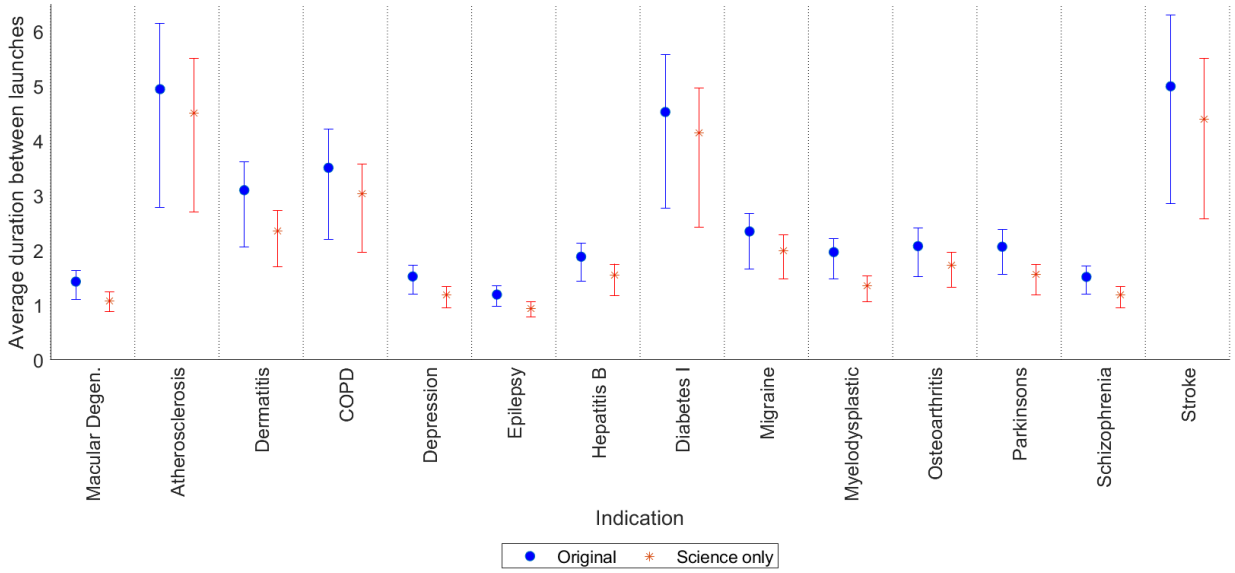
[8] In this case the numbers are also obtained not by averaging the shares provided in the table across diseases, but rather by taking the overall (without separation by disease) attrition shares and averaging them across the 1000 simulations.

Table 6.2: Average share of strategic attrition, in percent

Indication	Both Strategy/ Dropped	Stage 1 Strategy/ Dropped	Stage 1 Strategy/ Finished	Stage 1 Strategy/ Passed CT	Stage 2 Strategy/ Dropped	Stage 2 Strategy/ Finished	Stage 2 Strategy/ Passed CT
Atherosclerosis	5.58	6.12	5.51	35.65	0.01	0.01	0.04
COPD	5.45	6.12	5.32	28.76	0.12	0.09	0.41
Depression	6.78	7.17	6.18	30.85	3.16	2.16	6.32
Dermatitis	16.99	21.53	14.59	31.12	0.02	0.02	0.07
Diabetes I	7.24	7.87	6.96	37.53	0.01	0.01	0.04
Epilepsy	8.63	8.65	6.91	25.55	8.39	3.88	6.70
Hepatitis B	6.59	6.88	5.73	25.50	3.81	2.04	4.15
Macular Degen.	8.12	8.98	7.07	24.95	0.52	0.31	0.79
Migraine	6.28	6.96	5.74	24.57	1.41	0.84	2.07
Myelodysplastic	34.82	49.94	26.03	35.20	0.05	0.04	0.14
Osteoarthritis	6.56	7.44	5.80	20.88	0.50	0.30	0.74
Parkinsons	8.06	8.77	7.46	33.29	0.60	0.45	1.72
Schizophrenia	6.43	6.88	5.76	26.09	1.74	1.05	2.53
Stroke	7.03	7.86	7.02	39.73	0.00	0.00	0.00

between subsequent drug launches would be 18.73% lower if strategic terminations were not present (that corresponds to 23% increase in the launch rate). Table 9.15 in Appendix 9.20 presents the change for each disease.

Figure 6.3: Average duration between subsequent launches (in years) with and without strategic attrition.



Notes: Results are based on 1000 simulated paths for 14 diseases.

Chapter 7

Counterfactual Experiments

7.1 Effect of an increase in the probability of clinical success

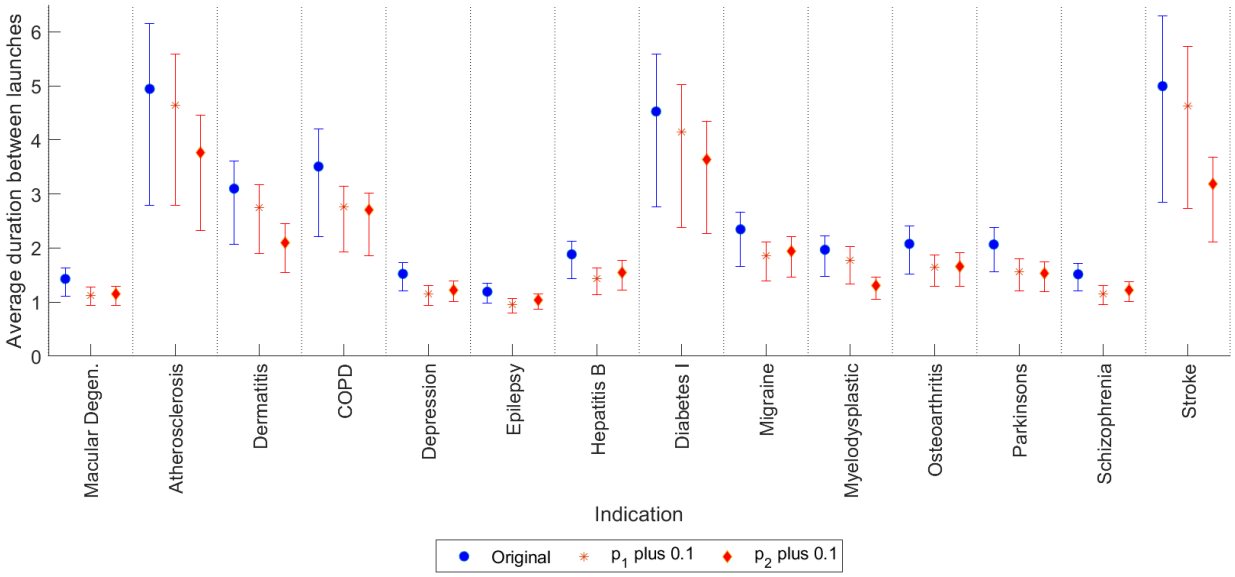
My first counterfactual explores how the scientific and strategic attrition interact in determining the rate of new drug introduction in a comparative static exercise. In order to do that, I increase the probability of clinical trial success in stage 1 or stage 2 (e.g. p_1 or p_2) by 10 percentage points uniformly across diseases, and analyze how strategic withdrawals and the rate of new launches changes in simulations.[1] Notice that from the point of view of an individual firm the change has two effects: first, it improves its chances of success and therefore increases the expected profit; second, it improves the chances of success of its competitors and therefore decreases the expected profit. Moreover, for a firm that has already passed all the clinical trials and is making a strategic decision of whether or not to apply for the regulatory approval, only the second (negative) effect will remain: for this firm higher scientific probabilities mean that it should expect higher follow-on competition. The model allows me to quantify all these effects, and the resulting changes in the rate of new drug launches.

For this exercise, I simulate 1000 paths for both the original values of parameters and the values

[1]Here I use a relatively large change in the scientific probabilities in order to ensure that the effects are pronounced and easy to compare.

after the policy change, in each case starting from the zero state (e.g. state where the number of firms in each stage is zero). I simulate each path 30 years forward, but use only the last 20 years—in order to allow the process to get away from the low-probability states with small number of competitors in development stages. I calculate the average time between subsequent launches for each of the regimes (e.g. original, clinical success in late increased by 10 p.p., and clinical success in early increased by 10 p.p.) and plot it on the graph presented in Figure 7.1.

Figure 7.1: Average duration between subsequent drug launches as a result or 10 percentage points change in p_1 or p_2.



On average, increase in the probability of early stage clinical success by 10 percentage points decreases the time between subsequent drug launched by 17% (corresponding to approximately 20% increase in the rate of new drug introduction, which is the inverse of average duration). The same increase in the probability of late stage clinical success decreases the duration by 23% (30% increase in the launch rate). Part of this discrepancy is simply mechanical—for some diseases, like atherosclerosis and stroke, p_2 is much lower than p_1, and increasing the former would results in a larger number of transitions even if science was the only source of attrition.[2] Indeed, if I repeated the same exercise, but completely shut down the strategic channel (both at the original values of

[2]Without the strategic interactions, the average share of drugs that reach the market is, roughly speaking, $p_1p_2p_3$. Increasing p_1 by 0.1 results in the new share being $p_1p_2p_3+0.1p_2p_3$, while increasing p_2 by 0.1 results in the new share of $p_1p_2p_3 + 0.1p_1p_3$. If p_1 is larger than p_2, then the increase would be larger in the latter case.

parameters and after implementing changes to p_1 or p_2), then the duration between launches would decrease on average by 22% and 25% respectively (corresponds to 28% and 33% increase in the launch rate).[3] When strategy is accounted for, the size of the effect in both cases is smaller, but the gap between the results of the two policies is twice as large.

In order to see how strategic behavior contributes to the outcome, I repeat the exercises (e.g. increase p_1 or p_2 by 10 p.p.) without allowing firms to adjust their behavior. That is, I keep the probabilities of strategic terminations at the equilibrium level established before the change. The results are presented in Appendix 9.22. The graph shows that without strategic adjustments of transition probabilities increasing p_1 would have resulted in slightly higher rate of innovation, while the opposite would be the case when p_2 is increased (for many of the diseases the difference is not detectable). The intuition behind this dynamic is that increasing p_1 increases strategic attrition both after stage 1 and stage 2 (as for those firms higher p_1 means lower barriers to entry and thus potentially higher follow on competition). On the other hand, increasing p_2 only increases strategic attrition after stage 2, while encouraging more firms to initiate late-stage clinical trials (as for them the positive effect of having a higher probability to pass that stage in the end outweighs the negative effect of higher potential competition).

The other way to see that pattern is to analyze the change in strategic attrition before and after the policy change presented in Appendix 9.24. As a results of increase in p_1, the average proportion of strategic terminations conditional on clinical success increases on average by 1.7 percentage points for stage 1, and by 1.2 percentage points for stage 2. At the same time, a 10 percentage points increase in p_2 leads to 1.1 percentage points increase in strategic terminations after stage 2, and 3 percentage points decrease—after stage 1. In the latter case the effect of the policy is strongest for Stroke that had the lowest p_2 before the change, and the weakest for epilepsy that had the largest p_2. Part of that gap is explained by the difference in response of strategic attrition after the fist stage (largest for stroke and smallest for epilepsy), and the difference in the increase in strategic terminations after the second stage (small for stroke, large for epilepsy). After the p_1 change the pattern of the effect is different—it is the smallest for diseases that have low p_2 like atherosclerosis, stroke and diabetes. The effect is large for diseases that have relatively small

[3]See the corresponding graph in Appendix 9.21.

p_1 and relatively large p_2, although there is also a stronger dampening effect due to increase in strategic withdrawals.

Notice that the change in CCPs averaged across the states along the paths simulated after the change is smaller than change in average shares of strategic terminations. The reason for that is because the proportion of strategic attrition is due to on average more launches happening after the changes, which discourages development by firms that have not reached the market yet.

7.2 Effect of a clinical trial subsidy

My first policy counterfactual studies how a decrease in the cost of clinical trials affect the rate of new drug launches. One example of such policy is direct clinical trial subsidies from the government—for example, recently the U.S. government has provided more than $10 billion in direct subsidies to multiple companies working on COVID vaccines[4]. Notice that subsidizing late-stage development can only affect the strategic incentives of firms, but it does not affect the probabilities of clinical success directly. Therefore, from the perspective of increasing the rate of new drug introduction, the only leverage that this policy change has is to decrease strategic attrition after the first stage by providing incentives for more firms to attempt the late stage development, as it is now cheaper to do. The goal of this counterfactual is to access how effective such policy would be in increasing the rate at which new drugs reach consumers.

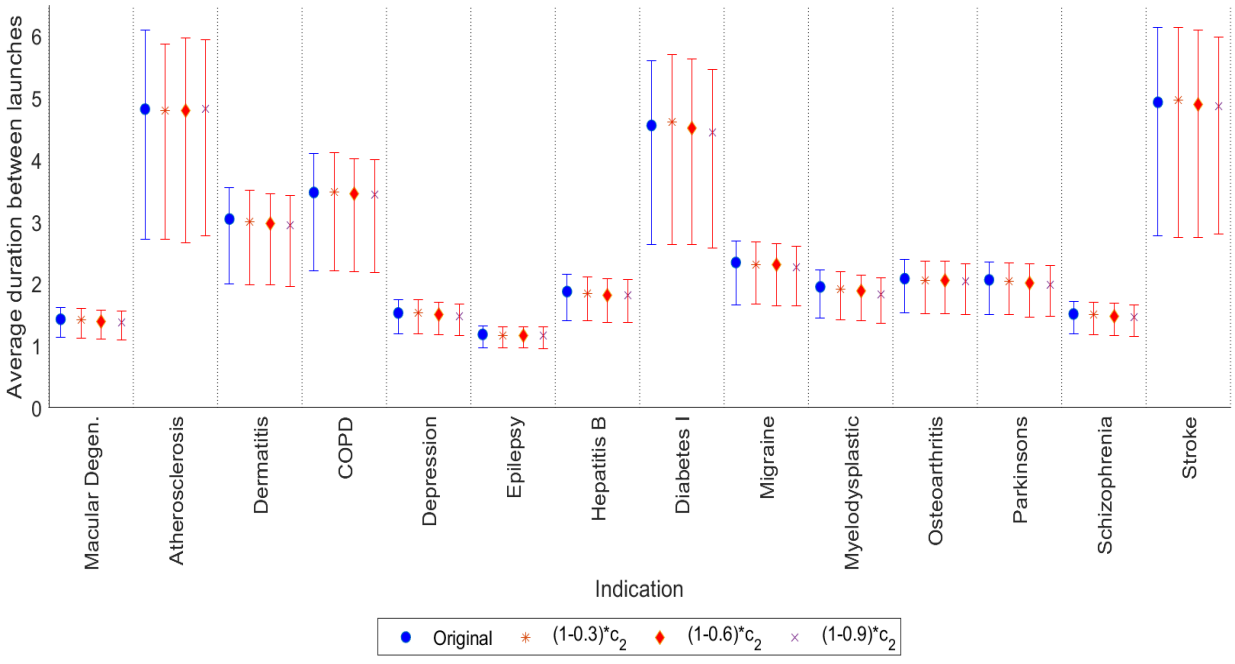
In order to study the effect of clinical trials subsidies, I decrease the yearly cost of late stage clinical development by 30%, 60% and 90% (which corresponds to approximately $15, $30 and $45 million per year)—e.g. I study the effect of a small, medium and large clinical subsidy that is applied to the cost of late clinical development of *all* firms that enter stage two trials. For each change, I simulate 5000 paths starting from the zero state (e.g. state where the number of firms in each stage is zero).[5] Like for the first policy experiment, I simulate each path 30 years forward, but discard the first 10 years. Figure 7.2 and Table 9.19 in the Appendix 9.25 presents the results in terms of the

[4]Several of the COVID-related subsidy deals include commitments by firms to provide a certain number of doses to the government if their vaccines are approved. This kind of market commitments are not part of the counterfactual experiment, but can potentially be explored in the future.

[5]Notice that for this counterfactual I simulate more paths than for the previous policy experiment, because the size of the effect is much smaller.

average time between subsequent drug launches. As the table shows, even large subsidies that cover 90% of yearly clinical trial cost decrease the duration between subsequent launches by on average only 2.8% (corresponds to 2.9% increase in the rate of new launches). The largest decrease of 6.3% (6.7% increase in the launch rate) is associated with myelodysplastic syndrome, for which strategic attrition after stage 1 was much more prominent than for other diseases (see Table 6.2). Overall, because strategic attrition is relatively less important than scientific, the effect of the subsidy that can only move the latter is small. While Table 9.20 in the Appendix 9.26 shows that the proportion of strategic withdrawals after stage 1 success drops on average by 3.6 percentage points (which is comparable to the change after large increase in p_2 by 10 percentage points), these additional drugs are still likely to fail stage 2 clinical trials (plus a small increase in strategic probability due to follow-on competition).

Figure 7.2: Average duration between subsequent drug launches after 30%, 60% and 90% decrease in c_2.



7.3 Change in the FDA regulations

My second policy counterfactual studies how a small adjustment in regulations related to late-stage clinical trials would affect the rate of new drug introductions. Notice that the probability of clinical success after stage 2 is determined not only by science, but also by the FDA's view on whether the amount and the type of evidence obtained as well as the strength of this evidence are enough to demonstrate adequate efficacy of new drugs.[6] In order to study the effect of a change in FDA's regulations, I marginally increase the probability of late stage success by 1 percentage point. This small change can plausibly be interpreted as a result of regulatory adjustments that would not lead to a significant change in quality of drugs that arrive on the market (e.g. in the model all the parameters of the profit function and the probability of drug withdrawal from the market remain the same). Moreover, the change is applied to success in efficacy trials as opposed to early stage safety trials, which would be less likely as the main goal of the FDA is to prevent unsafe drugs from reaching consumers. Besides, leveraging the knowledge obtained from the comparative static exercise, I expect an increase in p_2 to have a larger effect on the rate of new drug launches. Overall, I am agnostic about a particular policy that would lead to the analyzed change in p_2, as the main goal of this counterfactual is to study the sensitivity of pharmaceutical innovation to the FDA regulations in a general way. However, in practice such policy could be related to, for example, decrease in regulatory uncertainty or larger unification between the FDA's efficacy standards and those of its European counterpart.[7]

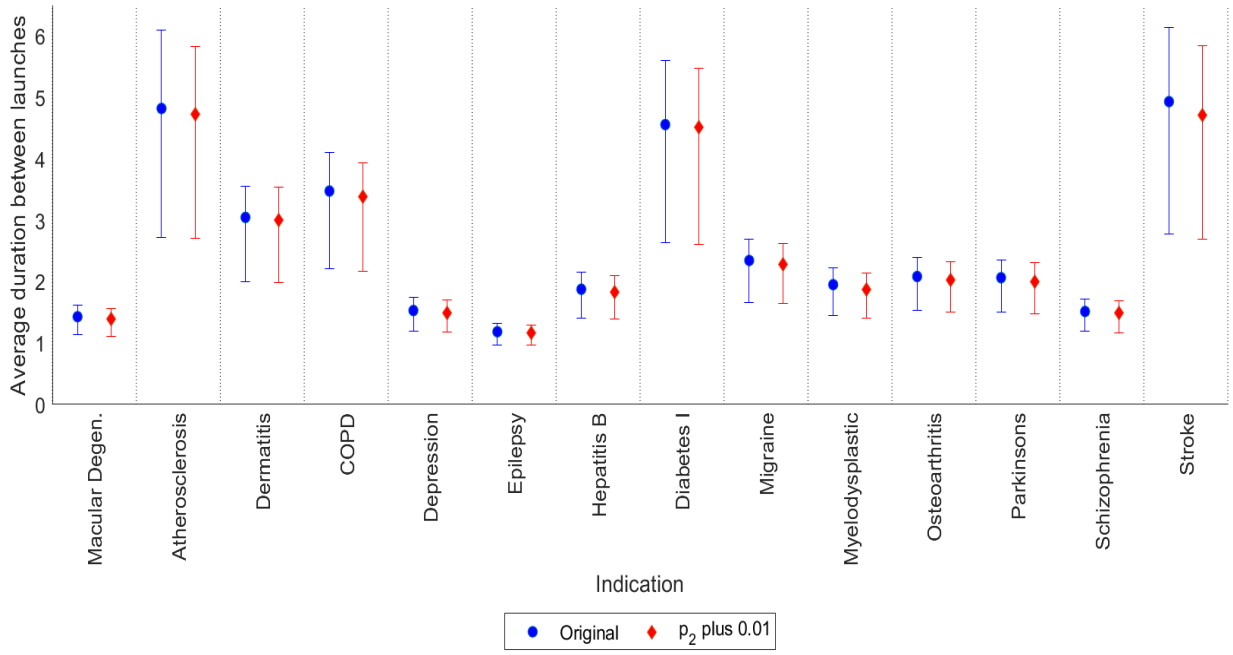
Figure 7.3 and Table present the results: the average drop in duration between launches across all the diseases is 2.5% (corresponds to 2.6% increase in the rate of new drug introductions). The effect is comparable to the 2.8% change that would be induced by a large clinical trial subsidy that would cover 90% of the late stage cost. Therefore, one can conclude that overall an effort directed towards decreasing regulatory barriers at the end of stage 2 might be more suitable in terms of

[6]For example, Sacks et al. (2014) shows that FDA frequently responds negatively to applications for new drug approvals not because it deems the results of trials inadequate, but because it regards the type and amount of information submitted unsatisfactory.

[7]For example, Kashoki et al. (2020) shows that FDA tends to be more stringent than the European Medicines Agency (EMA) in both its initial and final approval response to new drug applications, primarily due to differences in conclusions about efficacy. Isakov et al. (2019) show that for some severe disease FDA's decision thresholds might be too conservative.

increasing the rate at which new drugs reach consumers than policies directed towards reducing the clinical trial cost. At the same time, the pattern of change across diseases is different depending on disease characteristics, and clinical cost subsidies are more effective for diseases like diabetes, dermatitis and schizophrenia, while the opposite is true for diseases like atherosclerosis, stroke and COPD.

Figure 7.3: Average duration between subsequent drug launches after 1 p.p. change in p_2.



Chapter 8

Conclusion

High development attrition is perhaps one of the most prominent characteristics of the pharmaceutical industry. It affects the rate at which new drugs reach consumers, and is the major contributor to the overall cost of R&D. This together with the fact that R&D cost is often quoted as a justification for high drug prices in the U.S. makes development attrition an important topic of interest. That being said, the sources of attrition are yet to be comprehensively accessed. It is known that firms withdraw drug candidates primarily due to either clinical failures or commercial considerations. However, since generally we do not observe reasons behind firms' discontinuation decision, to determine the relative importance of the two attrition channels we need to rely on a model.

This paper proposes a framework that allows us to identify the importance of each attrition component separately for each disease. For that, I build a structural dynamic discrete choice model of pharmaceutical firms' R&D behavior and estimate it using a rich dataset on development histories of the population of experimental drugs. My estimates suggest that on average commercial terminations account for 8.4% of all attrition, but there is considerable heterogeneity across diseases, with the share of commercial terminations getting as high as 35% for some of them. Separately quantifying the two sources of attrition is crucial to predict the effects of government policies. Specifically, I demonstrate that the effect of clinical trial subsidies is heterogeneous across diseases, partially due to differences in the relative importance of the two attrition channels. Moreover, as a result of separating scientific and strategic attrition, this paper is able to study new forms of regulatory interventions. Particularly, I analyze how a marginal decrease in the probability of late

stage clinical failures affects the rate of innovation, and how that effect compares to the effect of a policy that decreases the cost of clinical trials.

There are at least two possible avenues for future research. One is to endogenize the rates of discovery. Currently, while I do allow for heterogeneity in the rates of entry into development across diseases, they are assumed to be exogenous, and therefore do not respond to changes introduced in counterfactual experiments. Adding this channel of adjustment will allow me to access the full effects of government policies. Implementing this modification is challenging as it requires setting up a model for drug discovery and determining potential entrants into R&D for a particular disease. One possibility is to consider large firms deciding in which diseases to invest. However, in that case, their choices across diseases will be interlinked. Since these firms usually simultaneously develop several drugs against different conditions, they in fact manage portfolios of experimental treatments, implying that their operations with assets in the portfolio are not independent. In fact, the problem that each firm faces is similar to a multi-arm bandit problem, with payoffs depending on competitors' decisions. Allowing for these interactions poses multiple challenges, including the need to incorporate the model of portfolio management, solve it given the large state space and estimate it allowing for the appropriate correlation structure.

Another avenue of research is to incorporate learning and technological spillovers in the innovation process. Recent research suggests that firms learn about the feasibility of the mechanism of action behind their experimental treatments from successes/failures of other drugs that rely on the same scientific process (Krieger (2020)). Modeling inter-firm learning is challenging, but solving and estimating the model poses additional computational obstacles. For one, it requires keeping track of every firms' updating process, which implies the need to handle potentially a very large state space. This is exacerbated by the fact that drug development is characterised by many alternative technologies with constant churning of the ineffective ones and introduction of new ones.

Chapter 9

Appendices

9.1 Examples of Close Approvals

Therapeutic Use	Year	Trade Name	Company
Hypertension	2002	Inspra (eplerenone)	Pharmacia Corp. (now Pfizer Inc.)
Hypertension	2002	Benicar (olmesartan medoxomil)	Sankyo Co Ltd (now Daiichi Sankyo Co Ltd)
Rheumathoid Arthritis	2009	Cimzia (certolizumab pegol)	UCB SA
Rheumathoid Arthritis	2009	Simponi (golimumab)	Janssen Biotech Inc (subsidiary of Johnson & Johnson)
HIV	1996	Crixivan (indinavir)	Merck & Co Inc
HIV	1996	Norvir (ritonavir)	Abbott Laboratories
Hepatitis C	2014	Exvira (dasabuvir)/Viekira Pak	AbbVie Inc
Hepatitis C	2013	Sovaldi (sofosbuvir)	Gilead Sciences Inc

Table 9.1: Selected examples of drugs approved by FDA for the same indication in the same year or two consecutive years. Source: Cortellis Competitive Intellignece database.

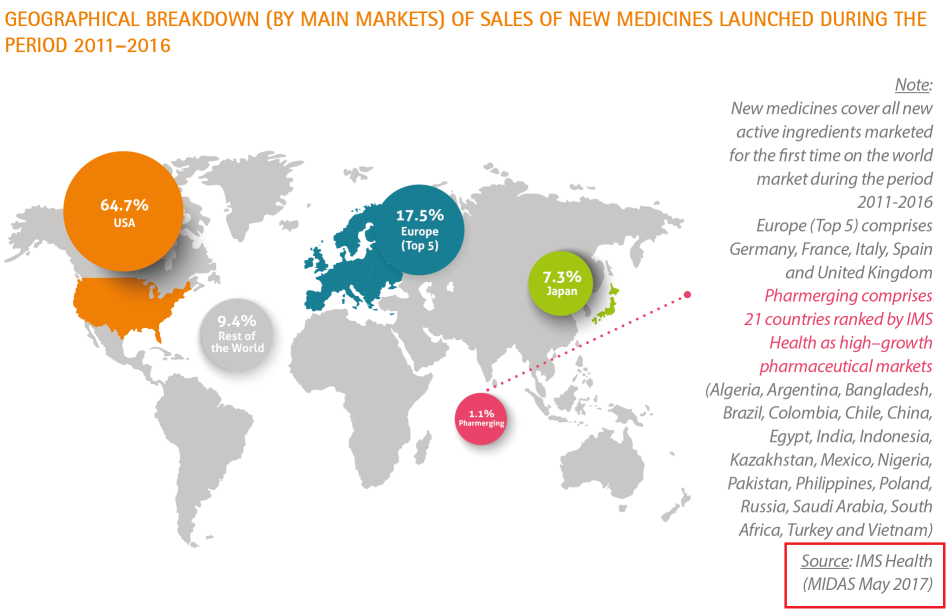
9.2 Transition Matrix by Phase

	Total Attrition	Conditional Attrition
Preclinical	62.9%	62.9%
Phase I	11.0%	29.7%
Phase II	16.0%	61.7%
Phase III	3.5%	35.4%
Regulatory submission	0.64%	9.97%

Table 9.2: Share of development project terminated at a particular stage of the R&D process. *Overall* are the shares as a percent of the total. *Conditional* are the shares as a percent of the drug candidates that made it to a particular stage. Source: Cortellis Competitive Intelligence database. In cases when the earlier phase is ot recorded, but later I observe the drug entering a later phase, I assume that the earlier phase was successfully completed (mostly applies to phase 1).

9.3 Sales by Country

Figure 9.1: Sales of novel medicines by country, IMS Healt.



9.4 The Model

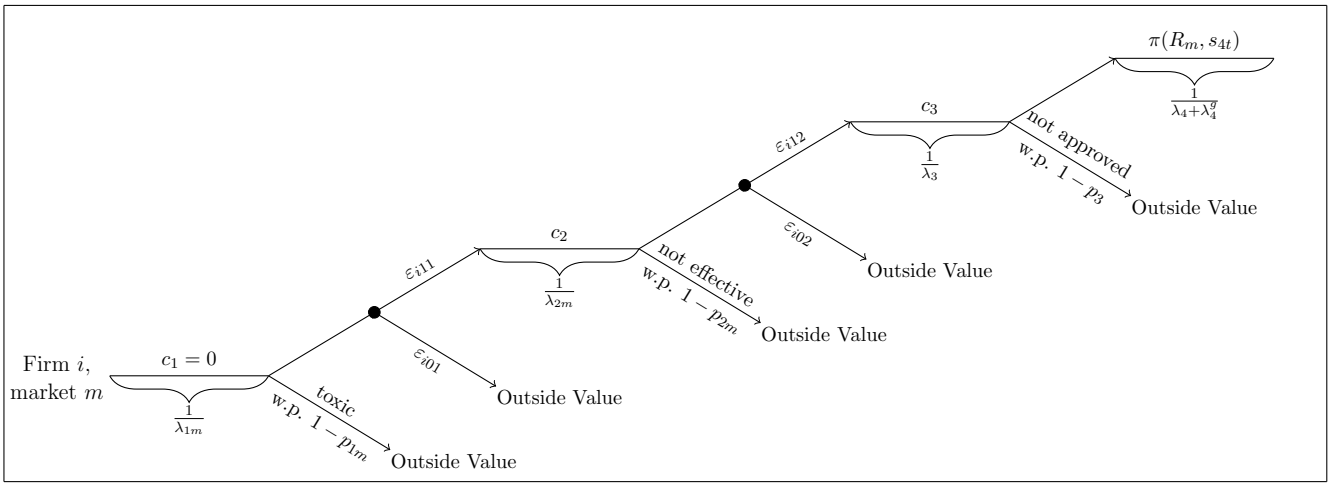


Figure 9.2: Schematic description of the model. Decision points are marked bold.

9.5 Value Functions

Value associated with being in stage 2:

$$
\begin{aligned}
V_{1,s}(\sigma') = \frac{1}{\sum_{x=1}^{4} \lambda_x^e + \sum_{x=1}^{4} s(x)\lambda_x + \rho} \Bigg[& \sum_{x=1}^{4} \lambda_x^e V_{1,s'(0,x,s)}(\sigma') + \\
& + \big(s(1) - 1\big)\lambda_1 \sum_{y \in \{0,2\}} \tilde{\sigma}'_{1ys} V_{1,s'(1,y,s)}(\sigma') + s(2)\lambda_2 \sum_{y \in \{0,3\}} \tilde{\sigma}'_{2ys} V_{1,s'(2,y,s)}(\sigma') + \\
& + s(3)\lambda_3 \sum_{y \in \{0,4\}} p_3^y V_{1,s'(3,y,s)}(\sigma') + s(4)\lambda_4 V_{1,s'(4,0,s)}(\sigma') + \\
& + \lambda_1 p_1 Emax_j\{\epsilon_{i01}, \epsilon_{i11} + V_{2,s'(1,2,s)}(\sigma')\} + \lambda_1(1 - p_1)E(\epsilon_{i01}) \Bigg]
\end{aligned}
\tag{9.1}
$$

Value associated with being in stage 3:

$$
\begin{aligned}
V_{3,s}(\sigma') = \frac{1}{\sum_{x=1}^{4}\lambda_x^e + \sum_{x=1}^{4} s(x)\lambda_x + \rho}\Bigg[& c_3 + \sum_{x=1}^{4}\lambda_x^e V_{3,s'(0,x,s)}(\sigma') + \\
& + s(1)\lambda_1 \sum_{y\in\{0,2\}} \tilde{\sigma}'_{1ys} V_{3,s'(1,y,s)}(\sigma') + s(2)\lambda_2 \sum_{y\in\{0,3\}} \tilde{\sigma}'_{2ys} V_{3,s'(2,y,s)}(\sigma') + \\
& + \big(s(3)-1\big)\lambda_3 \sum_{y\in\{0,4\}} p_3^y V_{3,s'(3,y,s)}(\sigma') + s(4)\lambda_4 V_{3,s'(4,0,s)}(\sigma') + \\
& + \lambda_3 p_3^4 V_{4,s'(3,4,s)}(\sigma') + \lambda_1 p_3^0 E(\epsilon_{i03})\Bigg]
\end{aligned}
\tag{9.2}
$$

Value associated with being in stage 4:

$$
\begin{aligned}
V_{4,s}(\sigma') = \frac{1}{\sum_{x=1}^{4}\lambda_x^e + \sum_{x=1}^{4} s(x)\lambda_x + \lambda_4^g + \rho}\Bigg[& \theta_0 + \theta_r R + \theta_s ln\big(1+s(4)\big) + \\
& \sum_{x=1}^{4}\lambda_x^e V_{4,s'(0,x,s)}(\sigma') + s(1)\lambda_1 \sum_{y\in\{0,2\}} \tilde{\sigma}'_{1ys} V_{4,s'(1,y,s)}(\sigma') + \\
& + s(2)\lambda_2 \sum_{y\in\{0,3\}} \tilde{\sigma}'_{2ys} V_{4,s'(2,y,s)}(\sigma') + s(3)\lambda_3 \sum_{y\in\{0,4\}} p_3^y V_{4,s'(3,y,s)}(\sigma') + \\
& \big(s(4)-1\big)\lambda_4 V_{4,s'(4,0,s)}(\sigma')\Bigg]
\end{aligned}
\tag{9.3}
$$

Notice that at rate $\lambda_4 + \lambda_4^g$ the firm at stage 4 receives the payoff of zero.

9.6 Linear Representation

Let $V_4^{'}$ be a $K \times 1$ vector of that contains the value of the value function for a firm at stage 4 for each industry state vector s given that other firms follow the strategy σ' (it will be zero for industry states in which there are a total of zero firms in stage 4). Further, let S be a $K \times 4$ matrix that collects all the industry states: the (k, x) element of the matrix is the total number of firms at stage $x \in 1, 2, 3, 4$ in state k. Let S_x be the x-th column of that matrix, and e be a $K \times 1$ column vector of ones, and let $\mathbb{1}_4$ be equal to 1 if the stage equals to 4, and zero otherwise. Let $D_x = e(\sum_{x=1}^{4}\lambda_x^e + \mathbb{1}_4\lambda_4^g) + \sum_{x=1}^{4}\lambda_x S_x$ and $\tilde{D}_x = diag(D_x)$.

Let $\Sigma_x^{'}$ be a $K \times K$ transition matrix that collects the probabilities of transition of firms at

stage x: element (k, k') of the matrix is the probability of that a firm at stage $x \in 1, 2$ given the industry state k will induce transition to the industry state k'.[1] Finally, let Q_4 be the $K \times K$ exogenous state transition matrix: the (k, k') element of the matrix denotes the rates of exogenous state transition from state k to state k' (that is, transition due to exogenous entry of new firms, exogenous regulatory approval decisions or exogenous exit of firms from the market).[2]

Then based on equation (9.3) we can write down the following matrix-form representation for the value function of the firm at stage 4:

$$\tilde{D}_4 V_4^{'} = \theta_0 + \theta_r R + \theta_s ln(1 + S_4) + \Big[Q_4 + \sum_{x=1}^{2} diag(\lambda_x S_x)\Sigma_x^{'}\Big] V_4^{'},$$

which represents a system of linear equation. Given that the matrix $\Big[\tilde{D}_4 - Q_4 - \sum_{x=1}^{2} diag(\lambda_x S_x)\Sigma_x^{'}\Big]$ is inevitable, we can solve for $V_4^{'}$:

$$V_4^{'} = \Big[\tilde{D}_4 - Q_4 - \sum_{x=1}^{2} diag(\lambda_x S_x)\Sigma_x^{'}\Big]^{-1} \Big[\theta_r ln(R) + \theta_s ln(1 + S_4)\Big] \tag{9.4}$$

By denoting $\tilde{D}_4 - Q_4 - \sum_{x=1}^{2} diag(\lambda_x S_x)\Sigma_x^{'} = \Omega_4^{'}$, we will get our final expression:

$$V_4^{'} = {\Omega_4^{'}}^{-1} \Big[\theta_r ln(R) + \theta_s ln(1 + S_4)\Big]$$

[1] One can construct the matrix in the following way. Let $L_{x,x+1}$ be a $K \times K$ location matrix that denotes the industry state that will result in firm at stage $x \in 1, 2$ deciding to transition to the next stage—the element (k, k') is the industry state induced by a firms at stage x transitioning to the next stage given that the industry state is k. Let $\Sigma_{x,x+1}^{'} = diag(\tilde{\sigma}_{x,x+1,1}^{'}, ..., \tilde{\sigma}_{x,x+1,K}^{'})$ be the diagonal matrix containing the probabilities that the firm at stage $x \in 1, 2$ given the industry state k transitions to the next stage (notice that it includes the probability of being exogenously terminated by the FDA). Same way construct $L_{x,0}$ and $\Sigma_{x,0}^{'}$—similar matrices associated with firms dropping out. Then $\Sigma_x^{'} = \Sigma_{x,x+1}^{'} L_{x,x+1} + \Sigma_{x,0}^{'} L_{x,0}$

[2] One can construct the matrix in the following way. Let $L_{0,x}$ be a $K \times K$ location matrix that denotes the industry state that will be induced if a new firm entered stage x given that the industry state is k. Let $L_{3,4}$ be a $K \times K$ location matrix that denotes the industry state that will be induced if a firm at stage 3 has gotten a regulatory approval given that the industry state is k (same way, $L_{3,0}$ will be the matrix that will denote the state if the firm in 3 was not approved). Further, let $L_{4,0}$ be a $K \times K$ location matrix that denotes the industry state that will be induced if a firm on the market exits given that the industry state is k. Let $diag(v)$ denote a diagonal matrix with the elements of vector v on the main diagonal. Let e_4 be a $K \times 1$ vector where the k-th element is equal to 1 if the number of firms in stage 4 in the k-th state is greater than zero; otherwise, the k-th element of e_4 is zero. Then $Q_4 = \sum_{x=1}^{4} \lambda_x^e L_{0,x} + diag(\lambda_3 p_3^4 S_3) L_{3,4} + diag(\lambda_3 p_3^0 S_3) L_{3,0} + diag(\lambda_4 (S_4 - e_4)) L_{4,0}$.

In the same way we can write down the matrix representation for $V_3^{'}$:

$$V_3^{'} = \Big[\tilde{D}_3 - Q_3 - \sum_{x=1}^{2} diag(\lambda_x S_x)\Sigma_x^{'}\Big]^{-1}\Big[C_3 + \lambda_3 p_3^0 \boldsymbol{\gamma} + \lambda_3 p_3^4 L_{3,4} V_4^{'}\Big], \tag{9.5}$$

where $\boldsymbol{\gamma}$ is the vector of the unconditional expectations of the scrap value shocks. Since the scrap value shock is distributed according to the Type I extreme value distribution, its expected value in every state equals to the Euler's constant.[3] By denoting $\tilde{D}_3 - Q_3 - \sum_{x=1}^{2} diag(\lambda_x S_x)\Sigma_x^{'} = \Omega_3^{'}$, we will get our final expression:

$$V_3^{'} = \Omega_3^{'-1}\Big[C_3 + \lambda_3 p_3^0 \boldsymbol{\gamma} + \lambda_3 p_3^4 L_{3,4} V_4^{'}\Big],$$

Following the same strategy, we can write down the value function associated with the stage 2:

$$V_2^{'} = \Big[\tilde{D}_2 - Q_2 - \sum_{x=1}^{2} diag(\lambda_x \tilde{S}_x)\Sigma_x^{'}\Big]^{-1}\Big[C_2 + \lambda_2(1-p_2)\boldsymbol{\gamma} + \lambda_2 p_2 L_{2,3} E_{max}(V_3^{'})\Big], \tag{9.6}$$

where $\tilde{S}_x = S_x$ if $x = 1$, 3 and 4, but $\tilde{S}_2 = S_2 - e_2$.[4] $E_{max}(V_3^{'})$ is a $K \times 1$ vector, for which the k-th element equals to $Emax\{\epsilon_{i02}, \epsilon_{i12} + V_{3,s'(2,3,s)}(\sigma')\}$, where s is the k-th state. The assumption that both ϵ_{i02} and ϵ_{i12} are distributed i.i.d according to the Type I extreme value distribution, allows us to write this expectation in the following form:

$$Emax\{\epsilon_{i02}, \epsilon_{i12} + V_{3,s'(2,3,s)}^{'}\} = ln\Big(1 + e^{V_{3,s'(2,3,s)}^{'}}\Big) + \gamma \tag{9.7}$$

We further can use the idea originating in Hotz and Miller (1993) that the conditional transition probabilities (CTPs) can be inverted, which allows to express the expectation above in terms of these CTPs. Notice that if given that a firm behaves optimally, its decisions correspond to the best response strategy described in (3.2). Then the probability that a firm transitions from stage 2 to

[3] $Q_3 = \sum_{x=1}^{4} \lambda_x^e L_{0,x} + diag(\lambda_3 p_3^4(S_3 - e))L_{3,4} + diag(\lambda_3 p_3^0(S_3 - e_3))L_{3,0} + diag(\lambda_4)L_{4,0}$. e_3 is a $K \times 1$ vector where the k-th element is equal to 1 if the number of firms in stage 3 in the k-th state is greater than zero; otherwise, the k-th element of e_3 is zero.

[4] Recall that e_2 is a $K \times 1$ vector where the k-th element is equal to 1 if the number of firms in stage 2 in the k-th state is greater than zero; otherwise, the k-th element of e_2 is zero.

stage 3 (conditional on the state s) is determined by:

$$\tilde{\sigma}_{23s} = p_2 Pr(\epsilon_{i12} + V^{'}_{3,s'(2,3,s)} \geq \epsilon_{i02}) \tag{9.8}$$

Since both ϵ_{i12} and ϵ_{i02} are i.i.d., and follow Type I extreme value distribution, (9.8) can be re-written in the following way:

$$\tilde{\sigma}_{23s} = p_2 \frac{e^{V^{'}_{3,s'(2,3,s)}}}{1 + e^{V^{'}_{3,s'(2,3,s)}}} \tag{9.9}$$

Inverting the function in (9.9), we get:

$$V^{'}_{3,s'(2,3,s)} = ln\Big(\frac{\tilde{\sigma}_{23s}}{p_2 - \tilde{\sigma}_{23s}}\Big) \tag{9.10}$$

Plugging (9.10) into (9.7), we get:

$$Emax\{\epsilon_{i02}, \epsilon_{i12} + V^{'}_{3,s'(2,3,s)}\} = ln\left(\frac{p_2}{p_2 - \tilde{\sigma}_{23s}}\right) + \gamma \tag{9.11}$$

Stacking the expressions derived according to (9.11) for each state to form $E\big(p_2, \tilde{\sigma}_{2,3}\big) + \boldsymbol{\gamma}$ and plugging it into (9.6), we get the final expression:

$$V^{'}_2 = \Omega^{'-1}_2 \Big[C_2 + \lambda_2 \boldsymbol{\gamma} + \lambda_2 p_2 L_{2,3} E\big(p_2, \tilde{\sigma}_{2,3}\big)\Big],$$

Similarly we can get an expression for the value function associated with stage 1.

9.7 Identification

To simplify the notation, in what follows I will suppress the stage-related indices. Notice that for some state s_1 I can rewrite (4.1) in the following way:

$$w_{s_1} c_3 + x_{s_1}\theta_0 + y_{s_1}\theta_r + z_{s_1}\theta_s + u_{s_1} + log(p - \sigma_{s_1}) = log(\sigma_{s_1}) \tag{9.12}$$

It might not be possible to separate c_3,θ_0 and θ_r using only variation in levels of competition

within one market (that is, without using variation in market size R_m and FDA duration λ_{3m} across markets). That implies, however, that I can solve for a linear combination of those parameters $c_3 + \frac{x_{s_1}}{w_{s_1}}\theta_0 + \frac{y_{s_1}}{w_{s_1}}\theta_r$, which I will denote $\tilde{\theta}_r$.

I use one more equation associated with the same market m and other state s_2 to solve for θ_s and $\tilde{\theta}_r$.

$$\begin{pmatrix} \tilde{\theta}_r \\ \theta_s \end{pmatrix} = \begin{pmatrix} w_{s_1} & z_{s_1} \\ w_{s_2} & z_{s_2} \end{pmatrix}^{-1} \begin{pmatrix} log(\sigma_{s_1}) - log(p - \sigma_{s_1}) - u_{s_1} \\ log(\sigma_{s_2}) - log(p - \sigma_{s_2}) - u_{s_2} \end{pmatrix} \tag{9.13}$$

Using (9.13) and the third equation I get:

$$A_1 + B_1 log(p - \sigma_{s_1}) + C_1 log(p - \sigma_{s_2}) + log(p - \sigma_{s_3}) = 0, \tag{9.14}$$

where (A_1, B_1, C_1) are real numbers. Notice that Equation (9.14) has at most 3 roots. To prove that, notice that we can write the first derivative of the the function on the left-hand side of the Equation (9.14) with respect to p in the following way:

$$\frac{B_1}{p - \sigma_{s_1}} + \frac{C_1}{p - \sigma_{s_2}} + \frac{1}{p - \sigma_{s_3}}, \tag{9.15}$$

which can be re-written as:

$$\frac{B_1(p - \sigma_{s_2})(p - \sigma_{s_3}) + C_1(p - \sigma_{s_1})(p - \sigma_{s_3}) + (p - \sigma_{s_1})(p - \sigma_{s_2})}{(p - \sigma_{s_1})(p - \sigma_{s_2})(p - \sigma_{s_3})},$$

Notice that it has to be that $p > \sigma_{s_1}$, $p > \sigma_{s_2}$, $p > \sigma_{s_3}$, $p > \sigma_{s_4}$, therefore the denominator is positive. The numerator is a quadratic equation in p, and thus has at most 2 roots. Therefore, the original function changes from increasing to decreasing (or vice versa) at most two times. At each interval where the its increasing/decreasing it can intersect the zero at most once. This implies that Equation (9.14) has at most 3 roots. Denote them $\{p^1, p^2, p^3\}$. Using (9.13), derive the associated $\{(\tilde{\theta}_r^l, \theta_s^l), l = 1, ..., 3\}$. Exclude the ones that do not coincide with the true p, $\tilde{\theta}_r$, θ_s using the method described in the main text. Notice that once the true $\tilde{\theta}_r$ is identified for multiple markets, one can use variation in R_m and λ_{m3} across markets to separately identify θ_0, θ_r and c_3.

9.8 Estimation of duration parameters

To estimate the duration parameters I construct a maximum likelihood function under the assumption that observed duration draws are independently and identically distributed according to an exponential distribution with the rate $\lambda > 0$ that I estimate. The density function for the exponential distribution is $f(x;\lambda) = \lambda exp(\lambda x)$ and the tail function (e.g. the probability that the duration is longer than x) $G(x;\lambda) = 1 - F(x;\lambda) = exp(\lambda x)$. Suppose I observe duration draws $x_1, \ldots, x_n$, and the first k observations are fully observed, while the rest of the observation are censored, e.g. we only know that $x_j > t_j$ for some known positive constants t_j. Using the density function and the tail function, we can construct the likelihood function $L(\lambda) = \prod_{i=1}^{k} f(x_i;\lambda) \prod_{i=k+1}^{n} G(t_j;\lambda)$. Then the log-likelihood function is $l(\lambda) = klog\lambda - \lambda(x_1 + ... + x_r + t_{k+1} + ... + t_n) = klog\lambda - \lambda T$, where $T = x_1 + ... + x_k + t_{k+1} + ... + t_n$ (sum of observations and censoring times). The maximum likelihood estimator of λ is $\hat{\lambda} = k/T$, and the asymptotic variance is k/T^2. The average duration can be obtained as the mean of the exponential, which equals to $1/\lambda$, and the variance of the mean duration $k/T^2 \times (-1/\hat{\lambda})^2$ can be obtained using the delta method.

9.9 Attrition by disease

Table 9.3: Termination shares by disease

Indication	Conditional attrition stage 1	stage 2
Macular Degen	0.72	0.87
Alzheimers	0.85	0.98
Asthma	0.86	0.95
Atherosclerosis	0.91	0.94
Dermatitis	0.61	0.83
Breast tumor	0.76	0.92
COPD	0.81	0.82
Colorectal tumor	0.67	0.92
Depression	0.76	0.87
Epilepsy	0.82	0.47
Glioblastoma	0.55	0.95
HIV	0.86	0.85
Hepatitis B	0.80	0.71
Hepatitis C	0.80	0.88
Diabetes I	0.82	0.88
Migraine	0.68	0.74
MS	0.85	0.77
Myelodysplastic	0.42	0.93
Diabetes II	0.79	0.87
Lung cancer	0.39	0.88
Osteoarthritis	0.77	0.82
Ovary tumor	0.71	0.96
Parkinsons	0.85	0.90
Prostate tumor	0.76	0.94
Psoriasis	0.69	0.83
RA	0.79	0.88
Schizophrenia	0.81	0.80
Stroke	0.91	0.98

9.10 Diseases by Therapy Area

The diseases in the sample are indications characterised by a large amount of development activity and are widespread or severe enough to have the disease-specific epidemiological information on

Table 9.4: Break Down of Diseases by Therapy Area

Therapy area	Indication
Other	Macular Degen.
Neurology/Psychiatric	Alzheimers
Respiratory	Asthma
Other	Atherosclerosis
Dermatologic	Dermatitis
Cancer	Breast Tumor
Respiratory	COPD
Cancer	Colorectal Tumor
Neurology/Psychiatric	Depression
Neurology/Psychiatric	Epilepsy
Cancer	Glioblastoma
Infection	HIV
Infection	Hepatitis B
Infection	Hepatitis C
Endocrine/Metabolic	Diabetes I
Neurology/Psychiatric	Migraine
Immune	MS
Cancer	Myelodysplastic
Endocrine/Metabolic	Diabetes II
Cancer	Lung Cancer
Other	Osteoarthritis
Cancer	Ovary Tumor
Neurology/Psychiatric	Parkinsons
Cancer	Prostate Tumor
Dermatologic	Psoriasis
Immune	RA
Neurology/Psychiatric	Schizophrenia
Neurology/Psychiatric	Stroke

prevalence, incidence and DALY collected within the Global Burden of Disease project (alternatively, the information is collected at a more aggregate level).

9.11 Data Snapshot

Table 9.5: Snapshot of the Cortellis pipeline data.

		Entry				
Drug	**Market**	**Small scale**	**Large scale**	**FDA**	**Approval**	**Exit**
AC-0025	Rheumatoid arthritis	10/29 2013	-	-	-	09/24 2015
Ivacaftor	Cystic fibrosis	7/31 2003	4/30 2007	19/11 2011	1/31 2012	-
albinterferon alfa-2b	Hepatitis C	10/19 2000	10/28 2003	11/25 2009	-	10/5 2010

9.12 Dropping Reformulations

For large molecules (biologics), Cortellis provides information on whether the drug is a biosimilar or not; I use that information to drop all the biosimilars. Cortellis does not provide information on whether the small molecule drug is novel or not. In order to detemine that, I use the Chemical Abstracts Service (CAS) numbers that Cortellis provides for the drugs in its database. CAS number is a unique identifier assigned to every chemical substance described in the scientific literature. If a drug in development has the same CAS number as a drug that has been approved, it means that it's based on exactly the same small chemical substance. I use the following criterion to identify reformulations: a drug is a reformulation if it started development or was in development after a drug with the same CAS had been launched in the US. Finally, I also drop all the diagnostic agents (since they are not treatments, but are intended to diagnose the disease) and combination therapies (since they are likely to include a drug that has already been approved).

9.13 Preliminary Evidence

Table 9.6: Linear probability model of transition from early and late-stage clinical trials. All the independent variables are standardized.

	(1)	(2)
VARIABLES	Transition from early	Transition from late
DALYs	0.03648***	0.01878***
	(0.00629)	(0.00709)
Disease toxicity	0.03749***	
	(0.00790)	
CT safety	0.07963***	
	(0.00886)	
CT efficacy		0.07134***
		(0.01152)
Constant	0.33243***	0.12228***
	(0.01303)	(0.01175)
Observations	6,676	2,694
R-squared	0.03499	0.02672
Therapy Area FE	YES	YES

*** p<0.01, ** p<0.05, * p<0.1.

Table 9.7: Linear model of disease-level shares of drugs transitioned from early and late-stage clinical trials. All the independent variables are standardized.

VARIABLES	(1) Share transitioned early	(2) Share transitioned late
DALYs	0.03958*	0.00381
	(0.01990)	(0.02087)
Disease toxicity	0.05488**	
	(0.02542)	
CT safety	0.07424***	
	(0.02355)	
CT efficacy		0.08171***
		(0.02487)
Constant	0.38078***	0.13915***
	(0.04282)	(0.03801)
Observations	28	28
R-squared	0.72684	0.52030
Therapy Area FE	YES	YES

*** p<0.01, ** p<0.05, * p<0.1.

Figure 9.3: Scatter plot based on the linear models in Table 9.7.

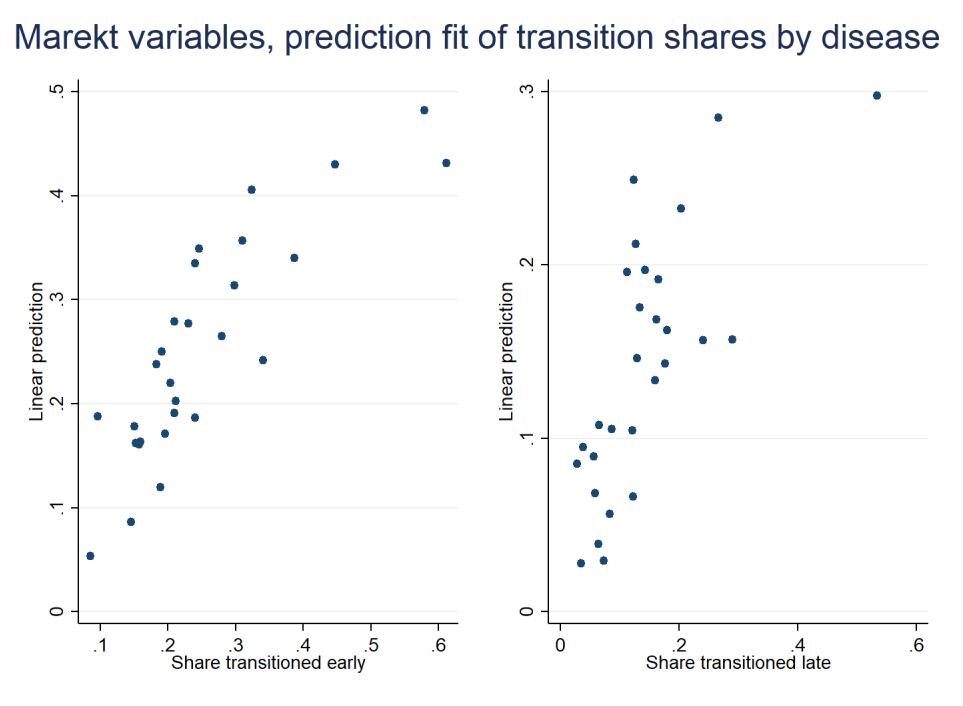


Table 9.8: Linear probability model of transition from early and late-stage clinical trials. All the independent variables are standardized.

	(1)	(2)
VARIABLES	Transition from early	Transition from late
# competitors in 4	-0.04748***	-0.03477***
	(0.01106)	(0.01290)
# competitors in 3	-0.00352	0.00142
	(0.00567)	(0.00693)
# competitors in 2	0.01649	-0.00963
	(0.01426)	(0.01659)
# competitors in 1	0.01592	0.01555
	(0.01328)	(0.01568)
Constant	0.24824***	0.09253*
	(0.03270)	(0.04848)
Observations	6,676	2,694
R-squared	0.05428	0.05464
Indication FE	YES	YES

*** p<0.01, ** p<0.05, * p<0.1.

9.14 Number of observations per therapy area

Table 9.9: Number of observations per therapy area in the sample.

Therapy area	Stage of clinical trials		
	Early	Late	Total
	No.	No.	No.
Cancer	1,571	1,191	2,762
Dermatologic	259	140	399
Endocrine/Metabolic	575	195	770
Immune	631	210	841
Infection	1,040	255	1,295
Neurology/Psychiatric	1,677	430	2,107
Other	435	115	550
Respiratory	488	158	646
Total	6,676	2,694	9,370

9.15 Estimates of duration parameters

Table 9.10: Average duration of a stage, years.

	stage 1 val.	stage 1 st.err.	stage 2 val.	stage 2 st.err.	stage 3 val.	stage 3 st.err.
Macular degen.	6.73	.53	7.31	1.11	1.6	.65
Alzheimers	7.12	.34	6.15	.63	1.32	.93
Asthma	5.56	.32	5.4	.57	1.57	.64
Atherosclerosis	5.73	.51	5.81	1.14	.93	.65
Atopic dermatitis	5.04	.66	6.79	1.39	2	1.15
Breast tumor	7.35	.45	8.22	.62	.81	.2
COPD	5.41	.52	5.75	.81	1.46	.46
Colorectal tumor	6.01	.44	7.41	.5	.96	.23
Depression	4.79	.33	5.06	.56	2.78	.84
Epilepsy	6.4	.63	6.65	1.28	1.72	.43
Glioblastoma	7.21	.83	12.42	1.99	3.55	2.51
HIV	7.16	.33	7.48	.77	1.25	.29
Hepatitis B	7.25	.74	6.08	1.17	3.85	1.07
Hepatitis C	5.67	.34	6.39	.72	1.04	.33
Diabetes I	6.45	.62	8.05	1.45	2.95	1.32
Migraine	4.35	.53	5.85	.99	2.54	.9
MS	6.48	.46	7.83	1.19	1.77	.56
Myelodysplastic	5.14	.69	9.52	1.44	1.13	.65
Diabetes II	5.34	.26	5.4	.44	1.59	.33
Lung cancer	5.17	.44	7.97	.58	1.16	.25
Osteoarthritis	4.92	.55	5.28	.87	2.67	.94
Ovary	6.56	.57	9.49	.9	3.27	1.63
tumor	8.23	.59	7.81	1.32	2.31	.94
Parkinsons	6.34	.28	7.65	.44	1.92	.41
Prostate tumor	4.33	.34	5.05	.5	1.54	.4
Psoriasis	5.16	.29	4.62	.39	2.42	.56
RA	5.06	.39	6.24	.91	1.68	.56
Schizophrenia	6.52	.48	5.53	.81	.16	.16

Table 9.11: Average duration between subsequent entries into a stage, years.

	stage 1 val.	stage 1 st.err.	stage 2 val.	stage 2 st.err.
Macular degen.	.08	.00008	.56	.006577
Alzheimers	.03	7.000e-06	.33	.001817
Asthma	.06	.000034	.32	.001963
Atherosclerosis	.13	.00026	1.25	.05261
Atopic dermatitis	.21	.001109	.53	.008533
Breast tumor	.04	.000013	.1	.000089
COPD	.14	.00036	.43	.004594
Colorectal tumor	.05	.000035	.07	.000048
Depression	.08	.000097	.36	.002808
Epilepsy	.13	.000263	.96	.026613
Glioblastoma	.12	.000219	.27	.000918
HIV	.03	8.000e-06	.41	.002279
Hepatitis B	.14	.000263	1.19	.044824
Hepatitis C	.06	.000043	.51	.004682
Diabetes I	.13	.000249	.72	.011629
Migraine	.25	.001731	.79	.017895
MS	.07	.000058	.65	.00811
Myelodysplastic	.18	.000861	.37	.002223
Diabetes II	.04	.000014	.22	.000704
Lung cancer	.07	.000088	.08	.000057
Osteoarthritis	.19	.000829	.63	.012328
Ovary	.08	.000083	.12	.000136
tumor	.06	.000033	.8	.013908
Parkinsons	.03	5.000e-06	.07	.000033
Prostate tumor	.1	.000199	.26	.001348
Psoriasis	.05	.000029	.25	.001154
RA	.1	.000151	.62	.008979
Schizophrenia	.09	.000091	.61	.010001

Table 9.12: Durations that are common across diseases, years.

stage 4 duration val.	stage 4 duration st.err.	stage 3 entry val.	stage 3 entry st.err.
170.64	41.39	9.09	1.69

9.16 Step 1 estimation results

	(1)		(2)	
	transitioned		transitioned	
	b	se	b	se
transitioned				
# in 1	-.0135266	.0195806	.0289245	.0517635
# in 2	-.0497407	.0418682	-.060113	.094272
# in 3	-.6759824	.3096467	-1.281774	.680325
# in 4	.1664209	.1134451	.2683254	.2394859
# in 1 squared	-4.66e-06	.0000246	.0000527	.0000633
# in 2 squared	.0001123	.0001378	.0007081	.0002951
# in 3 squared	-.0335227	.0222432	-.0017909	.0443353
# in 4 squared	.0014837	.0020676	.0161457	.0043634
# in 1 times # in 2	.0003078	.0000814	.0001397	.0001838
# in 1 times # in 3	-.0005903	.00099	-.0000589	.002061
# in 1 times # in 4	-.000628	.0003942	-.0030907	.000891
# in 1 times # DALYs	-.000016	7.70e-06	.0000127	.0000174
# in 1 times disease toxicity	.0302755	.034801	.1134999	.0848348
# in 1 times CT safety	.0049875	.0653335	-.4615849	.1859599
# in 1 times CT efficacy	.0086823	.0511242	.4106534	.1432965
# in 2 times # in 3	.0021523	.0019809	.0006519	.0039901
# in 2 times # in 4	-.001067	.0007818	-.0016616	.0015459
# in 2 times # DALYs	2.41e-06	.000013	.0000123	.0000226
# in 2 times disease toxicity	.0164847	.0620319	-.2876043	.1344391
# in 2 times CT safety	.1828428	.1882764	-.1444338	.4467133
# in 2 times CT efficacy	-.1607859	.1546569	.1975903	.3692551
# in 3 times # in 4	-.0083972	.0087999	-.0019744	.0183148
# in 3 times # DALYs	5.42e-06	.0001107	.0002184	.0002306

# in 3 times disease toxicity	.4507876	.5669547	-.818985	1.071307
# in 3 times CT safety	2.195068	1.320009	4.299093	3.003434
# in 3 times CT efficacy	-1.038481	1.054376	-2.494952	2.407861
# in 4 times # DALYs	.0000655	.0000452	-.0000453	.0000875
# in 4 times disease toxicity	-.0162831	.1751784	-.7018014	.3497491
# in 4 times CT safety	.3859959	.5380888	-1.908936	.9944184
# in 4 times CT efficacy	-.5603939	.4668638	1.380859	.8598656
Constant	-.8156047	.3097113	.1630745	.6913054
Age related macular degeneration	0	.	0	.
Alzheimers disease	.1425951	.5095761	-.3495824	1.601786
Asthma	.1229551	.413693	-2.550238	.9846327
Atherosclerosis	-.7637034	.8707146	-8.10329	2.675057
Atopic dermatitis	.5442701	.3713189	-1.30639	.8222398
Breast tumor	.4408959	.4544955	-1.209357	1.058154
Chronic obstructive pulmonary disease	-.0412426	.6391441	-2.20496	1.234607
Colorectal tumor	.4652879	.5199804	1.709055	.9985189
Depression	.3315723	.6548146	-2.253712	1.33696
Epilepsy	-.7777682	.467583	1.366972	.8925013
Glioblastoma	.1796452	.5970878	1.114652	1.221115
HIV infection	1.624081	.6374788	-2.612305	1.631735
Hepatitis B virus infection	-1.257588	.604919	1.618863	.9518246
Hepatitis C virus infection	-.2053222	.3261889	-1.018661	.7765121
Insulin dependent diabetes	-.2444464	.3636123	-1.635641	.8313732
Migraine	.3273657	.5266158	-1.457881	1.003353
Multiple sclerosis	-.4304991	.3700931	-.4019021	.822225
Myelodysplastic syndrome	1.186395	.54673	.604178	1.092901
Non-insulin dependent diabetes	1.193515	.6668938	-1.596397	1.41992
Non-small-cell lung cancer	1.44799	.9147711	.5382848	1.173245

Osteoarthritis	-.5607265	.3724558	-.4758024	.767978
Ovary tumor	.3292287	.4330092	-2.007496	1.088063
Parkinsons disease	-.6998769	.3408036	1.044623	.7960683
Prostate tumor	.2431731	.5224994	-.5553975	1.232649
Psoriasis	.8416113	.3581025	-1.513773	.7844319
Rheumatoid arthritis	.5006133	.4313698	-1.691164	.9845043
Schizophrenia	-.1165093	.3821931	-.8999356	.8263373
Stroke	-.2567891	.547066	1.394826	1.588259
Observations	6676		2694	

9.17 Step 2 Estimation

In Equation 9.17 (see Appendix 9.5), I can replace all the V_3-s on the right-hand side of the equation by the functions of transition probabilities into stage 3 from the appropriate adjacent states and p_2-s. However, that is not possible to do directly for V_4, since firms do not make decisions whether or not to enter the market after being approved by the FDA. Instead I use the Bellman equation for $V_{4,s'(4,0,s)}$:

$$\begin{aligned} V_{4,s'} = \frac{1}{\sum_{x=1}^{4}\lambda_x^e + \sum_{x=1}^{4} s'(x)\lambda_x + \lambda_4^g + \rho}\Bigg[\theta_0 + \theta_r R + \theta_s ln\big(1+s'(4)\big) + \\ \sum_{x=1}^{4}\lambda_x^e V_{4,s''(0,x,s')} + s'(1)\lambda_1 \sum_{y\in\{0,2\}} \tilde{\sigma}'_{1ys'} V_{4,s''(1,y,s')} + \\ + s'(2)\lambda_2 \sum_{y\in\{0,3\}} \tilde{\sigma}'_{2ys'} V_{4,s''(2,y,s')} + s'(3)\lambda_3 \sum_{y\in\{0,4\}} p_3^y V_{4,s''(3,y,s')} + \\ \big(s(4)-1\big)\lambda_4 V_{4,s''(4,0,s')}\Bigg] \end{aligned} \tag{9.16}$$

Then I can use the Bellman equations for V_3-s associated with appropriate states to express all the V_4-s on the right-hand side of equation 9.16. For example, to express $V_{4,s''(0,x,s')}$, I can use the Bellman equation for the state $s''' = s'''(4,3,s'')$:

$$\begin{aligned} V_{3,s'''} = \frac{1}{\sum_{x=1}^{4}\lambda_x^e + \sum_{x=1}^{4} s'''(x)\lambda_x + \rho}\Bigg[c_3 + \sum_{x=1}^{4}\lambda_x^e V_{3,s''''(0,x,s''')} + \\ + s'''(1)\lambda_1 \sum_{y\in\{0,2\}} \tilde{\sigma}'_{1ys'''} V_{3,s''''(1,y,s''')} + s'''(2)\lambda_2 \sum_{y\in\{0,3\}} \tilde{\sigma}'_{2ys'''} V_{3,s''''(2,y,s''')} + \\ + \big(s'''(3)-1\big)\lambda_3 \sum_{y\in\{0,4\}} p_3^y V_{3,s''''(3,y,s''')} + s(4)\lambda_4 V_{3,s''''(4,0,s''')} + \\ + \lambda_3 p_3^4 V_{4,s''} + \lambda_1 p_3^0 E(\epsilon_{i03})\Bigg], \end{aligned} \tag{9.17}$$

where all the V_3-s both on the left- and the right-hand side can be expressed as functions of appropriate transition probabilities and p_2-s. That allows me to express the only V_4 in the equation through them.

9.18 Profits

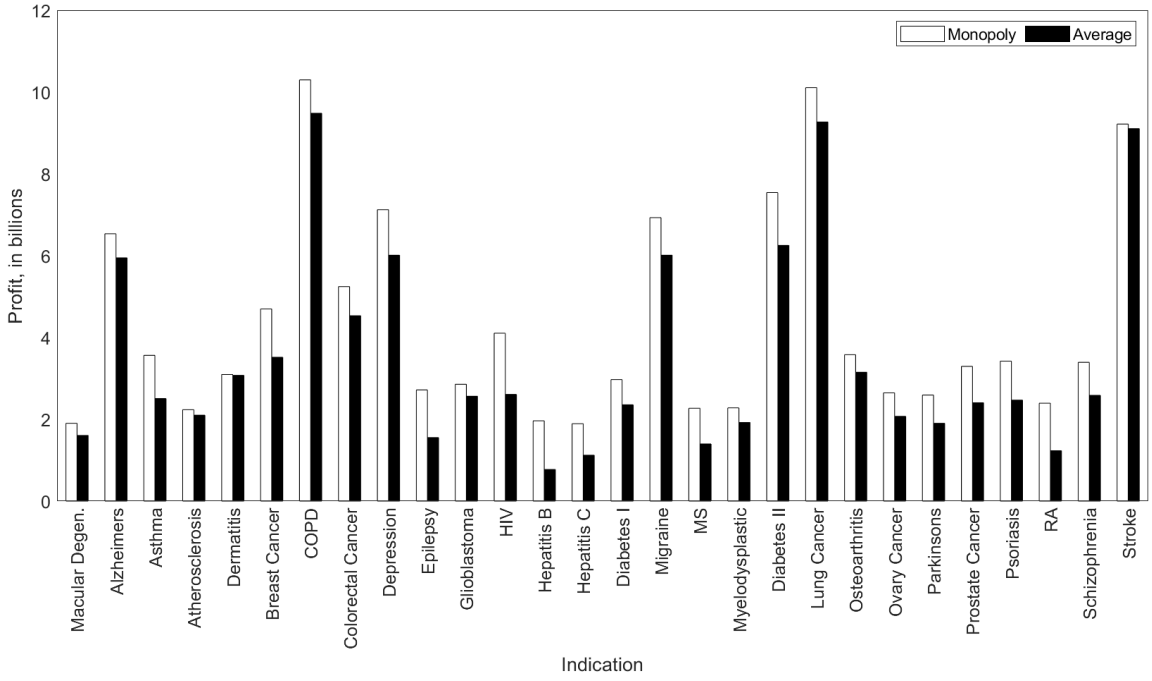


Figure 9.4: Monopoly yearly profit and average yearly profit by disease.

9.19 Scientific Probabilities

Table 9.14: Estimates of the probabilities of clinical trial success

Indication	p_1	S.E. p_1	p_2	S.E. p_2
Macular Degen	0.28	0.13	0.36	0.11
Alzheimers	0.19	0.08	0.09	0.03
Asthma	0.16	0.09	0.14	0.05
Atherosclerosis	0.16	0.06	0.07	0.03
Dermatitis	0.47	0.17	0.15	0.07
Breast Cancer	0.65	0.11	0.15	0.04
COPD	0.19	0.10	0.19	0.07
Colorectal Cancer	0.67	0.11	0.08	0.02
Depression	0.20	0.09	0.33	0.10
Epilepsy	0.27	0.14	0.57	0.15
Glioblastoma	0.70	0.11	0.08	0.02
HIV	0.19	0.10	0.27	0.08
Hepatitis B	0.22	0.12	0.47	0.12
Hepatitis C	0.25	0.13	0.62	0.13
Diabetes I	0.19	0.10	0.11	0.04
Migraine	0.23	0.12	0.38	0.12
MS	0.24	0.12	0.18	0.08
Myelodysplastic	0.74	0.11	0.18	0.05
Diabetes II	0.22	0.12	0.24	0.08
Lung Cancer	0.65	0.11	0.10	0.03
Osteoarthritis	0.28	0.13	0.35	0.11
Ovary Cancer	0.65	0.11	0.14	0.04
Parkinsons	0.22	0.11	0.24	0.08
Prostate Cancer	0.65	0.11	0.09	0.02
Psoriasis	0.48	0.18	0.21	0.09
RA	0.26	0.13	0.19	0.08
Schizophrenia	0.22	0.11	0.39	0.12
Stroke	0.18	0.08	0.04	0.01

9.20 Duration between launches with and without the strategic component

Table 9.15: Difference in average duration between subsequent drug launches with and without strategic attrition

Indication	Change in duration, years	Change in duration, std.	% change in duration
Macular Degen	-0.35	0.02	-24.47
Atherosclerosis	-0.43	0.14	-8.72
Dermatitis	-0.74	0.07	-23.87
COPD	-0.48	0.09	-13.66
Depression	-0.34	0.02	-22.36
Epilepsy	-0.25	0.01	-21.16
Hepatitis B	-0.33	0.03	-17.75
Diabetes I	-0.39	0.13	-8.52
Migraine	-0.36	0.05	-15.25
Myelodysplastic	-0.62	0.03	-31.50
Osteoarthritis	-0.35	0.03	-16.61
Parkinsons	-0.51	0.03	-24.47
Schizophrenia	-0.33	0.02	-21.76
Stroke	-0.60	0.14	-12.09

9.21 With and without the strategic attrition

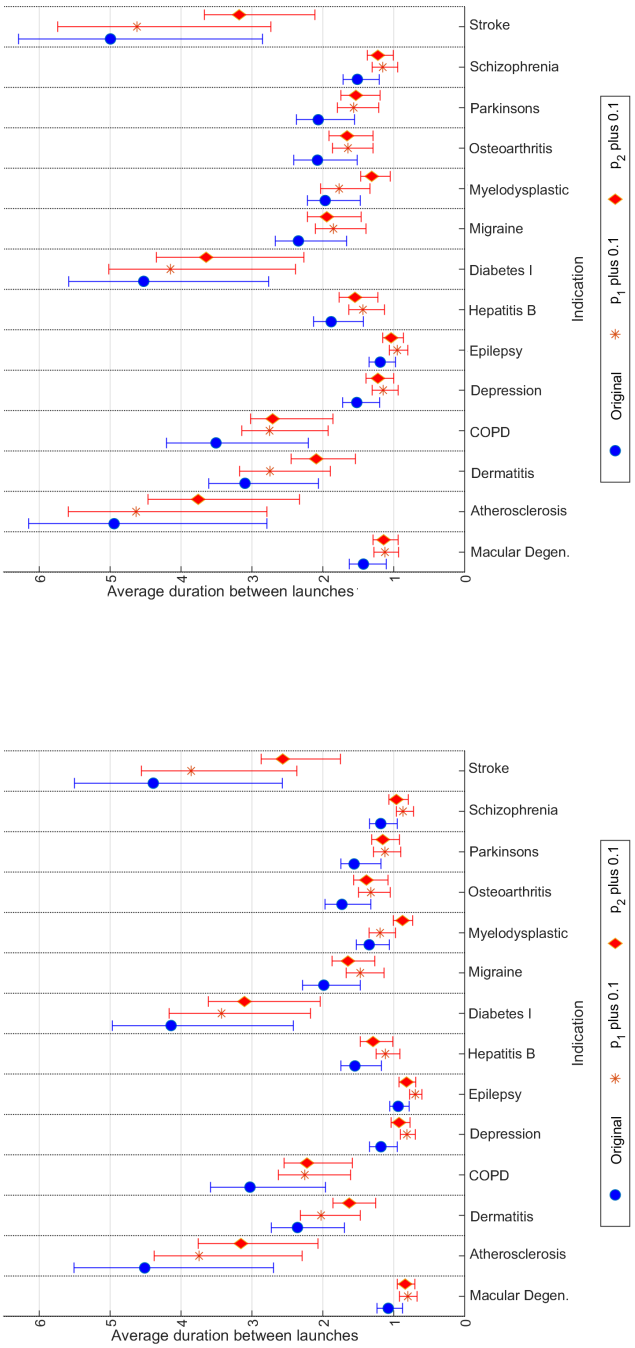


Figure 9.5: The left (right) graph is for the case without (with) strategic attrition.

9.22 With and without strategic probability adjustment

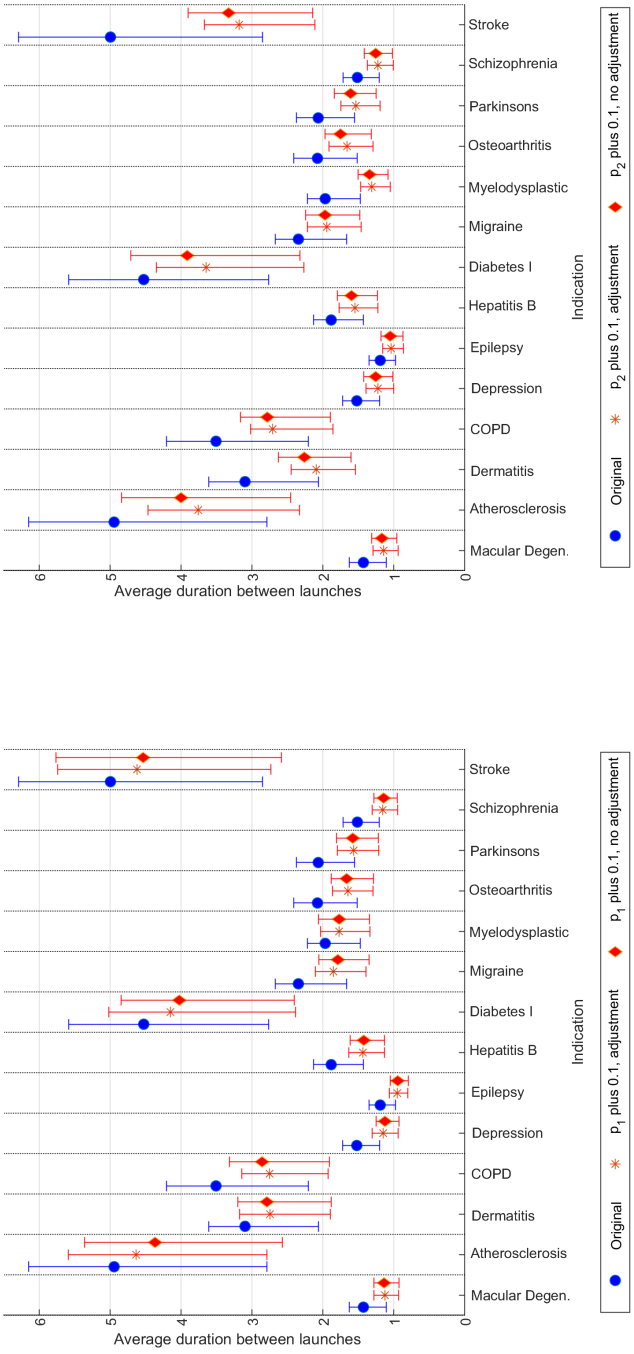


Figure 9.6: The left graph is for changes in p_1; the right graph is for changes in p_2.

9.23 Change in average duration due to change in p-s

Table 9.16: Difference in average duration between subsequent drug launches after change in p_1 or p_2

Indication	Stage 1 Change in duration, years	Stage 1 Change in duration, std.	Stage 1 % change in duration	Stage 2 Change in duration, years	Stage 2 Change in duration, std.	Stage 2 % change in duration
Macular Degen	-0.30	0.02	-21.03	-0.28	0.02	-19.80
Atherosclerosis	-0.31	0.14	-6.21	-1.18	0.13	-23.92
Dermatitis	-0.35	0.07	-11.40	-1.00	0.06	-32.38
COPD	-0.75	0.08	-21.43	-0.80	0.08	-22.69
Depression	-0.37	0.02	-24.34	-0.29	0.02	-19.35
Epilepsy	-0.24	0.01	-19.96	-0.16	0.01	-13.08
Hepatitis B	-0.44	0.03	-23.61	-0.34	0.03	-17.93
Diabetes I	-0.38	0.12	-8.32	-0.88	0.11	-19.50
Migraine	-0.50	0.05	-21.11	-0.40	0.05	-16.95
Myelodysplastic	-0.20	0.03	-9.91	-0.66	0.03	-33.40
Osteoarthritis	-0.43	0.03	-20.63	-0.42	0.03	-20.01
Parkinsons	-0.50	0.03	-24.19	-0.53	0.03	-25.52
Schizophrenia	-0.36	0.02	-23.63	-0.29	0.02	-19.11
Stroke	-0.37	0.14	-7.50	-1.81	0.12	-36.30

9.24 Change in p-s, strategic adjustments

Table 9.17: Adjustments after change in p_1. The second (fifth) column provides the difference (in percentage points) in average strategic attrition conditional on clinical trial success after stage 1 (stage 2). The third (seventh) column provides the different (in percentage points) in the equilibrium conditional choice probabilities (σ-s) averaged across all the states that appear along the simulation paths after the policy change.

	Stage 1				Stage 2			
Indication	strategy/ success	strategy/ success std.	CCPs change	CCPs change std.	strategy/ success	strategy/ success std.	CCPs change	CCPs change std.
Macular Degen	2.62	0.22	0.45	0.21	2.07	0.21	0.16	0.06
Atherosclerosis	0.50	0.34	0.14	0.03	0.04	0.04	0.00	0.00
Dermatitis	0.37	0.27	0.15	0.04	0.09	0.12	0.02	0.01
COPD	0.89	0.32	0.36	0.07	0.11	0.09	0.03	0.03
Depression	2.33	0.23	0.53	0.17	3.40	0.25	0.45	0.18
Epilepsy	3.28	0.25	0.76	0.22	3.25	0.24	0.47	0.21
Hepatitis B	3.22	0.29	0.69	0.17	2.19	0.24	0.35	0.16
Diabetes I	0.83	0.35	0.16	0.03	0.16	0.11	0.01	0.01
Migraine	2.68	0.31	0.49	0.11	0.50	0.18	0.12	0.07
Myelodysplastic	0.47	0.20	0.11	0.04	0.08	0.15	0.03	0.02
Osteoarthritis	1.55	0.29	0.42	0.12	0.88	0.19	0.12	0.05
Parkinsons	1.98	0.22	0.47	0.17	1.17	0.17	0.15	0.07
Schizophrenia	2.56	0.25	0.61	0.22	2.41	0.21	0.29	0.12
Stroke	0.06	0.26	0.07	0.01	0.00	0.00	0.00	0.00

Table 9.18: Adjustments after change in p_2. The second (fifth) column provides the difference (in percentage points) in average strategic attrition conditional on clinical trial success after stage 1 (stage 2). The third (seventh) column provides the different (in percentage points) in the equilibrium conditional choice probabilities (σ-s) averaged across all the states that appear along the simulation paths after the policy change.

	Stage 1				Stage 2			
Indication	strategy/ success	strategy/ success std.	CCPs change	CCPs change std.	strategy/ success	strategy/ success std.	CCPs change	CCPs change std.
Macular Degen	-0.87	0.24	-2.51	0.31	2.10	0.21	0.49	0.18
Atherosclerosis	-8.73	0.38	-8.94	0.98	0.09	0.05	0.04	0.04
Dermatitis	-3.72	0.27	-4.87	0.65	0.81	0.13	0.28	0.17
COPD	-4.49	0.34	-5.00	0.46	0.27	0.11	0.16	0.12
Depression	-0.95	0.24	-2.21	0.30	2.58	0.25	1.04	0.45
Epilepsy	-0.28	0.26	-1.61	0.19	1.53	0.24	0.70	0.35
Hepatitis B	-0.61	0.30	-2.22	0.22	1.58	0.24	0.53	0.27
Diabetes I	-5.69	0.37	-6.51	0.77	0.15	0.10	0.10	0.08
Migraine	-1.40	0.34	-2.94	0.18	0.56	0.19	0.29	0.17
Myelodysplastic	-1.69	0.20	-3.13	0.58	1.70	0.17	0.59	0.29
Osteoarthritis	-2.17	0.30	-3.10	0.20	0.75	0.19	0.36	0.17
Parkinsons	-1.83	0.24	-3.30	0.50	1.53	0.18	0.47	0.24
Schizophrenia	-1.24	0.26	-2.40	0.23	1.50	0.20	0.59	0.29
Stroke	-9.04	0.29	-9.40	1.25	0.26	0.08	0.08	0.08

9.25 Change in average duration after clinical trial subsidies

Table 9.19: Change in average duration between subsequent drug launches after clinical trial subsidies.

	30% change in c_2			60% change in c_2			90% change in c_2		
Indication	abs. dif.	abs. dif. std.	% dif.	abs. dif.	abs. dif. std.	% dif.	abs. dif.	abs. dif. std.	% dif.
Macular Degen	-0.02	0.01	-1.07	-0.04	0.01	-2.69	-0.05	0.01	-3.61
Atherosclerosis	-0.02	0.06	-0.43	-0.02	0.06	-0.45	0.00	0.06	0.04
Dermatitis	-0.05	0.03	-1.65	-0.07	0.03	-2.43	-0.10	0.03	-3.17
COPD	0.00	0.04	0.14	-0.02	0.04	-0.58	-0.03	0.04	-0.88
Depression	0.00	0.01	0.16	-0.03	0.01	-1.81	-0.05	0.01	-3.16
Epilepsy	-0.02	0.01	-1.49	-0.02	0.01	-1.84	-0.02	0.01	-2.07
Hepatitis B	-0.03	0.01	-1.53	-0.05	0.01	-2.92	-0.06	0.01	-3.34
Diabetes I	0.06	0.06	1.36	-0.05	0.06	-1.08	-0.11	0.06	-2.45
Migraine	-0.03	0.02	-1.34	-0.03	0.02	-1.37	-0.08	0.02	-3.54
Myelodysplastic	-0.03	0.02	-1.79	-0.06	0.02	-3.19	-0.12	0.02	-6.34
Osteoarthritis	-0.03	0.02	-1.46	-0.02	0.02	-1.19	-0.05	0.02	-2.36
Parkinsons	-0.02	0.02	-1.06	-0.06	0.02	-2.77	-0.07	0.02	-3.56
Schizophrenia	-0.02	0.01	-1.05	-0.04	0.01	-2.36	-0.05	0.01	-3.29
Stroke	0.03	0.07	0.69	-0.03	0.06	-0.66	-0.07	0.06	-1.35

9.26 Strategic adjustments after clinical trial subsidies

Table 9.20: Change in strategic attrition for the 90% subsidy. The second (fifth) column provides the difference (in percentage points) in average strategic attrition conditional on clinical trial success after stage 1 (stage 2). The third (seventh) column provides the different (in percentage points) in the equilibrium conditional choice probabilities (σ-s) averaged across all the states that appear along the simulation paths after the policy change.

	Stage 1				Stage 2			
Indication	strategy/ success	strategy/ success std.	CCPs change	CCPs change std.	strategy/ success	strategy/ success std.	CCPs change	CCPs change std.
Macular Degen	-3.68	0.11	-4.04	0.38	0.25	0.09	0.03	0.01
Atherosclerosis	-3.87	0.17	-3.98	0.07	0.04	0.03	0.00	0.00
Dermatitis	-4.17	0.12	-4.23	0.15	-0.04	0.06	0.01	0.00
COPD	-3.35	0.15	-3.38	0.19	0.04	0.05	0.00	0.00
Depression	-2.93	0.11	-3.12	0.25	0.22	0.11	0.04	0.02
Epilepsy	-2.92	0.12	-3.24	0.54	0.44	0.10	0.06	0.04
Hepatitis B	-2.72	0.13	-3.04	0.42	0.30	0.10	0.03	0.02
Diabetes I	-5.05	0.16	-4.99	0.09	0.10	0.05	0.00	0.00
Migraine	-2.71	0.15	-2.84	0.36	-0.13	0.08	0.01	0.01
Myelodysplastic	-5.15	0.09	-5.51	0.18	0.20	0.06	0.02	0.01
Osteoarthritis	-2.81	0.13	-2.81	0.31	0.20	0.08	0.01	0.01
Parkinsons	-4.31	0.11	-4.49	0.25	0.11	0.07	0.02	0.01
Schizophrenia	-3.14	0.12	-3.37	0.38	0.10	0.09	0.03	0.02
Stroke	-4.08	0.13	-4.04	0.03	0.00	0.02	0.00	0.00

9.27 Average rate change after the FDA regulation change

Table 9.21: Change in average duration between subsequent drug launches after change in p_2

Indication	Change in duration, years	Change in duration, std.	% change in duration
Macular Degen	-0.04	0.01	-2.69
Atherosclerosis	-0.10	0.06	-2.03
Dermatitis	-0.05	0.03	-1.56
COPD	-0.09	0.04	-2.72
Depression	-0.03	0.01	-2.15
Epilepsy	-0.02	0.01	-2.03
Hepatitis B	-0.04	0.01	-2.19
Diabetes I	-0.04	0.06	-0.90
Migraine	-0.06	0.02	-2.48
Myelodysplastic	-0.08	0.02	-4.23
Osteoarthritis	-0.06	0.02	-3.02
Parkinsons	-0.06	0.02	-2.92
Schizophrenia	-0.03	0.01	-1.70
Stroke	-0.23	0.06	-4.58

Bibliography

Acemoglu, D., and J. Linn. "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry". *The Quarterly Journal of Economics* 119, no. 3 (2004): 1049–1090.

Aguirregabiria, Victor, and Pedro Mira. "Dynamic discrete choice structural models: A survey". *Journal of Econometrics* 156, no. 1 (2010): 38–67.

— . "Sequential Estimation of Dynamic Discrete Games". *Econometrica* 75, no. 1 (2007): 1–53.

Arcidiacono, Peter, et al. "Estimation of Dynamic Discrete Choice Models in Continuous Time with an Application to Retail Competition". *The Review of Economic Studies* 83, no. 3 (2016): 889–931.

Bajari, Patrick, C. Lanier Benkard, and Jonathan Levin. "Estimating Dynamic Models of Imperfect Competition". *Econometrica* 75, no. 5 (2007): 1331–1370.

Blevins, Jason R. "Identification and Estimation of Continuous Time Dynamic Discrete Choice Games" (2018).

Chen, Ruijun, et al. "Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers". *BMJ* 352 (2016).

Ching, Andrew T. "A dynamic oligopoly structural model for the prescription drug market after patent expiration". *International Economic Review* 51, no. 4 (2010): 1175–1207.

Chorniy, Anna, et al. "Regulatory review time and pharmaceutical research and development". *Health Economics* (2020).

Cohen, Wesley M. "Chapter 4 – Fifty Years of Empirical Studies of Innovative Activity and Performance". In *Handbook of the Economics of Innovation*, 1:129–213. 2010.

Crawford, Gregory S., and Matthew Shum. "Uncertainty and learning in pharmaceutical demand". *Econometrica* 73, no. 4 (2005): 1137–1173.

Cunningham, Colleen, Florian Ederer, and Song Ma. "Killer Acquisitions". *Journal of Political Economy, forthcoming* (2020).

DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen. "Innovation in the pharmaceutical industry: New estimates of R&D costs". *Journal of Health Economics* 47 (2016): 20–33.

Doraszelski, Ulrich, and Kenneth L. Judd. "Avoiding the curse of dimensionality in dynamic stochastic games". *Quantitative Economics* 3, no. 1 (2012): 53–93.

Dubois, Pierre, et al. "Market size and pharmaceutical innovation". *The RAND Journal of Economics* 46, no. 4 (2015): 844–871.

Ericson, Richard, and Ariel Pakes. "Markov-Perfect Industry Dynamics: A Framework for Empirical Work". *The Review of Economic Studies* 62, no. 1 (1995): 53–82.

Feldman, Robin. "May your drug price be evergreen". *Journal of Law and the Biosciences* 5, no. 3 (2018): 590–647.

Fudenberg, Drew, et al. "Preemption, leapfrogging and competition in patent races". *European Economic Review* 22, no. 1 (1983): 3–31.

Gallant, A. Ronald, Han Hong, and Ahmed Khwaja. "The dynamic spillovers of entry: An application to the generic drug industry". *Management Science* 64, no. 3 (2018): 1189–1211.

Gilbert, Richard. *Looking for Mr. Schumpeter: Where Are We in the Competition-Innovation Debate?* Tech. rep. 2006.

Goettler, Ronald L, and Brett R Gordon. "Does AMD Spur Intel to Innovate More?" *Journal of Political Economy* 119, no. 6 (2011): 1141–1200.

Grossman, Gene M, and Carl Shapiro. "Dynamic R&D Competition". *The Economic Journal* 97, no. 386 (1987): 372–387.

Harris, Christopher, and John Vickers. "Racing with Uncertainty". *The Review of Economic Studies* 54, no. 1 (1987): 1–21.

Hashmi, Aamir Rafique, and Johannes Van Biesebroeck. "The Relationship between Market Structure and Innovation in Industry Equilibrium: A Case Study of the Global Automobile Industry". *Review of Economics and Statistics* 98, no. 1 (2016): 192–208.

Hausman, J.A., Jason Abrevaya, and F.M. Scott-Morton. "Misclassification of the dependent variable in a discrete-response setting". *Journal of Econometrics* 87, no. 2 (1998): 239–269.

Heckman, James. "The Incidental Parameters Problem and the Problem of Initial Conditions in Estimating a Discrete Time-Discrete Data Stochastic Process". In *Manski, C.F., McFadden, D. (Eds.), Structural Analysis of Discrete Data with Econometric Applications. MIT Press, Cambridge, MA.* 1981.

Hermosilla, Manuel. "Rushed Innovation: Evidence from Drug Licensing". *Management Science* (2020): 1–22.

Hotz, V Joseph, and Robert A Miller. "Conditional Choice Probabilities and the Estimation of Dynamic Models". *The Review of Economic Studies* 60, no. 3 (1993): 497–529.

Hwang, Thomas J., et al. "Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results". *JAMA Internal Medicine* 176, no. 12 (2016): 1826–1833.

Igami, Mitsuru. "Estimating the Innovator's Dilemma: Structural Analysis of Creative Destruction in the Hard Disk Drive Industry, 1981–1998". *Journal of Political Economy* 125, no. 3 (2017): 798–847.

Isakov, Leah, Andrew W. Lo, and Vahid Montazerhodjat. "Is the FDA too conservative or too aggressive?: A Bayesian decision analysis of clinical trial design". *Journal of Econometrics* 211, no. 1 (2019): 117–136.

Judd, Kenneth L. "Closed-loop equilibrium in a multi-stage innovation race". *Economic Theory* 21 (2003): 673–695.

Kashoki, Mwango, et al. "A Comparison of EMA and FDA Decisions for New Drug Marketing Applications 2014–2016: Concordance, Discordance, and Why". *Clinical Pharmacology & Therapeutics* 107, no. 1 (2020): 195–202.

Kim, Myongjin. "Strategic Responses to Used Goods Markets: Airbus and Boeing" (2014).

Kniesner, Thomas J., and W. Kip Viscusi. "The Value of a Statistical Life". *SSRN Electronic Journal* (2019).

Kocourek, Pavel. "Revealing Private Information in a Patent Race *" (2021).

Krieger, Joshua L. "Trials and Terminations: Learning from Competitors' R&D Failures". *Management Science (forthcoming)* (2020).

Kyle, Margaret K. "The role of firm characteristics in pharmaceutical product launches". *The RAND Journal of Economics* 37, no. 3 (2006): 602–618.

Neyman, J., and Elizabeth L. Scott. "Consistent Estimates Based on Partially Consistent Observations". *Econometrica* 16, no. 1 (1948): 1–32.

Piller, Charles. "FDA and NIH let clinical trial sponsors keep results secret and break the law". *Science* (2020).

Rao, Anita. "Strategic research and development investment decisions in the pharmaceutical industry". *Marketing Science* 39, no. 3 (2020): 564–586.

Sacks, Leonard V., et al. "Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012". *JAMA* 311, no. 4 (2014): 378–384.

Saito, Hiroki, et al. "How Frequently Do the Results from Completed US Clinical Trials Enter the Public Domain? - A Statistical Analysis of the ClinicalTrials.gov Database". Ed. by Vasee Moorthy. *PLoS ONE* 9, no. 7 (2014).

Scott Morton, Fiona M. "Entry Decisions in the Generic Pharmaceutical Industry". *The RAND Journal of Economics* 30, no. 3 (1999): 421–440.

Shapiro, Carl. "Competition and Innovation: Did Arrow Hit the Bull's Eye?" (2011): 361–404.

Waring, Michael J, et al. "An analysis of the attrition of drug candidates from four major pharmaceutical companies". *Nature Publishing Group* 14 (2015).

Wong, Chi Heem, Kien Wei Siah, and Andrew W. Lo. "Estimation of clinical trial success rates and related parameters". *Biostatistics* 20, no. 2 (2019): 273–286.