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Drug Deals: Policies to Increase the Availability of Effective Medications

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Management

by

Taylor Courtney Corcoran

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ABSTRACT OF THE DISSERTATION

Drug Deals: Policies to Increase the Availability of Effective Medications

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Doctor of Philosophy in Management

University of California, Los Angeles, 2019

Professor Fernanda Bravo Plaza, Co-Chair

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Two key issues faced by any policy maker in healthcare are providing effective treatments for ailments and ensuring that these treatments are available to patients. In this dissertation, we use contract theory, epidemic modeling, and queueing theory to study the effectiveness and availability of treatment in the context of medicines and vaccines.

In the first essay, "Flexible FDA Approval Policies", we analyze the problem faced by the Food and Drug Administration (FDA) of deciding whether to approve or reject novel drugs based on evidence of their safety and efficacy. Traditionally, the FDA requires clinical trial evidence that is statistically significant at the 2.5% level, but the agency often uses regulatory discretion when making approval decisions. Factors including disease severity, prevalence, and availability of existing therapies are qualitatively considered, but transparent, quantitative guidelines that systematically assess these characteristics are lacking. We develop a novel queueing model of the drug approval process which explicitly incorporates these factors, as well as obsolescence, or when newer drugs replace older formulas. We show that the optimal significance level is higher for diseases with lengthy clinical trials, greater attrition rates in the development stage, low intensity of research and development, or low levels of obsolescence among drugs on the market.

Using publicly available data, we estimate model parameters and calculate the optimal signifi-

cance levels for drugs targeting three diseases: breast cancer, HIV, and hypertension. Our results indicate that the current 2.5% significance level is too stringent for some diseases yet too lenient for others. A counterfactual analysis of the FDA's Fast Track program demonstrates that, by bringing drugs to patients more quickly, this program achieves a level of societal benefit that cannot be attained by solely changing approval standards.

The second essay, "Contracts to Increase the Effectiveness and Availability of Vaccines", studies contractual issues between global health organizations (GHOs) and pharmaceutical companies in the vaccine supply chain for neglected tropical diseases (NTDs). NTDs are a diverse group of conditions that affect over 1 billion individuals worldwide but which have historically received inadequate funding. Current funding mechanisms, such as the Advanced Market Commitment, do not incentivize pharmaceutical companies to exert costly research and development (R&D) effort to develop highly efficacious vaccines. We develop a joint game-theoretic and epidemic model that allows us to study different payment contracts and their impact on the spread of the disease. We show that traditional wholesale price contracts perform poorly and at best *mitigate* – diminish the number of cases – the spread of the disease, while performance-based contracts that directly link payment to vaccine efficacy have the potential to *eliminate* – reduce the number of cases to zero – the disease.

We formulate epidemic models for two NTDs: Chagas, a vector-borne disease most commonly found in Central and South America, and Ebola. We estimate model parameters and conduct a numerical analysis in which we explore the performance of each contract under a variety of cost scenarios. Our results indicate that, when the cost of treating the disease with no vaccine is sufficiently high, performance-based contracts have the potential to facilitate disease eradication, but when treatment costs are low, alternate disease containment methods such as vector control or mass drug administration may be more cost-effective.

The dissertation of Taylor Courtney Corcoran is approved.

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2019

DEDICATION

To my parents, for their never-ending support, and to Markov and Fuka, for all the love.

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Feeling gratitude and not expressing it is like wrapping a present and not giving it.

– William Arthur Ward

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Chapter 1 Introduction

Lack of access to treatment is one of the most complex problems faced by a health system. Initiatives for improving access are broad, and while many focus on affordability, there are a variety of other factors that determine whether patients obtain the medicines they need. In this dissertation, we explore two key components of treatment access: (i) availability – whether treatments exist and if so, whether they are present in sufficient quantities – and (ii) efficacy/effectiveness – whether the drug has the desired clinical effect in a controlled setting such as clinical trials (efficacy) or the extent to which the drug has the desired effect in the the general population (effectiveness).

In the first essay, "Flexible FDA Approval Policies", we study the problem faced by the Food and Drug Administration (FDA) of setting type I error thresholds for the approval of novel drugs. In the second essay, "Contracts to Increase the Efficacy and Availability of Vaccines", we consider the problem faced by an altruistic central planner of incentivizing pharmaceutical companies to develop highly efficacious vaccines for Neglected Tropical Diseases (NTDs). Both chapters examine the problem of increasing the availability of efficacious/effective medical products from the point of view of a healthcare policy maker – the FDA in the first essay and a central planner in the second. While one could additionally take the perspective of the patient or the pharmaceutical company, we chose to focus on the decisions made by a policy maker that must consider the impact of their choices on all aspects of the health system.

Each chapter explores ways that the policy maker can increase the availability of drugs or

vaccines. In "Flexible FDA Approval Policies", we propose a disease-specific approval policy that explicitly depends on characteristics including the severity and prevalence of the disease, the intensity of research and development (R&D) directed towards the disease, and the number of treatments currently available. By recommending stricter approval standards for diseases with many candidates in clinical trials and less stringent standards for diseases with a paucity of drugs in development, our model can incentivize pharmaceutical companies to invest in traditionally under-researched diseases with few available treatments. In "Contracts to Increase the Efficacy and Availability of Vaccines", we compare the advantages of developing a vaccine for NTDs (e.g., savings in treatment costs) against the costs (e.g, research and development, procurement, and distribution costs). Our model provides insight regarding the conditions under which a disease may benefit from the introduction of a vaccine (i.e., improved availability), as well as conditions under which the costs of vaccine development outweigh its benefits.

A key source of uncertainty faced by both policy makers is the effectiveness (efficacy) of drugs (vaccines). As the FDA is primarily concerned with how drugs perform in the general population, we consider uncertainty in drug effectiveness in the first chapter. Prior to approval, the FDA does not know a given drug's effectiveness, and thus they must take clinical trial evidence into account when making approval decisions. Relaxing approval standards – accepting drugs with less clinical evidence demonstrating effectiveness – may increase the chances of approving an effective treatment for patients, but comes at the risk of approving ineffective treatments. In the second chapter, we consider uncertainty in drug efficacy as a result of randomness in the vaccine development process. Due to minimum efficacy standards imposed by the World Health Organization, this uncertainty impacts whether or not a vaccine will successfully be developed. Furthermore, the realization of efficacy influences the progression of the epidemic – a highly efficacious vaccine may be able to fully contain a disease, while a less efficacious vaccine may only be able to mitigate its spread.

Chapter 2 Flexible FDA Approval Policies

Abstract

To approve a novel drug therapy, the U.S. Food and Drug Administration (FDA) requires clinical trial evidence demonstrating efficacy with 2.5% statistical significance, although the agency often uses regulatory discretion when interpreting these standards. Factors including disease severity, prevalence, and availability of existing therapies are qualitatively considered, yet current guidelines fail to systematically consider such characteristics in approval decisions.

New drug approval requires weighing the risks of type I and II errors against the potential benefits of introducing life-saving therapies. Approval standards tailored to individual diseases could improve treatment options for patients with few alternatives, potentially incentivizing pharmaceutical companies to invest in neglected diseases.

We propose a novel queueing framework to analyze the FDA's drug approval decision-making process that explicitly incorporates these factors, as well as obsolescence—when newer drugs replace older formulas—through the use of pre-emptive M/M/1/1 queues. Using public data encompassing all registered U.S. clinical trials and FDA-approved drugs, we estimate parameters for three high-burden diseases: breast cancer, HIV, and hypertension.

Given an objective of maximizing net societal benefits, including health benefits and the monetary value of drug approval/rejection, the optimal policy relaxes approval standards for drugs targeting diseases with long clinical trials, high attrition during development, or low R&D inten-

sity. Our results indicate that the current 2.5% significance level is too stringent for some diseases yet too lenient for others. A counterfactual analysis demonstrates that the FDA's Fast Track program—offering expedited review of therapies for life-threatening diseases—achieves a level of societal benefit that cannot be attained by solely changing approval standards.

Our study offers a transparent, quantitative framework that can help the FDA issue disease-specific approval guidelines based on underlying disease severity, prevalence, and characteristics of the drug development process and existing market.

2.1 Introduction

Since its establishment in 1906, the U.S. Food and Drug Administration (FDA) has approved over 1,500 novel drugs, with total annual sales exceeding $310 billion (Kinch et al., 2014; IMS Health, 2016). When deciding whether to approve a drug, the FDA must consider two key stakeholders: patients, whose health may be improved or possibly harmed by the drug, and pharmaceutical firms, which have invested hundreds of millions of dollars into developing the compound. The tension between providing sick patients with potentially beneficial remedies, while protecting consumers from harmful adverse events plays a key role in the FDA's decision-making. Despite undergoing rigorous evaluation, some FDA-approved drugs are later found to be ineffective or even detrimental to patients. In September 2004, for example, the anti-inflammatory drug Vioxx developed by Merck was withdrawn from global markets due to safety concerns after more than 160,000 patients suffered heart attacks or strokes and 38,000 patients died. Merck lost $25 billion in market capitalization on the day following the Vioxx recall and $4.85 billion in legal settlements (New York Times, 2007).

In this work, we develop a novel queueing modeling framework to study drug approval decisions. The model considers the process from compound development through evaluation, FDA approval or rejection, and obsolescence or market expiry. Our modeling framework can proffer insights for

the FDA's decision-making process, by permitting flexible approval standards based on differences in disease *severity*—a measure of a disease's impact on both mortality (length of life) and morbidity (quality of life), *prevalence*—the number of individuals afflicted, intensity of research and development (R&D), and the number of alternative treatments available. In this paper, we refer to a *drug* as a substance intended to diagnose, cure, treat, or prevent disease; we use this synonymously with the terms medication, therapy, compound, molecule, or drug candidate. The FDA also regulates medical devices, which we do not explicitly consider.

Current FDA policy requires pharmaceutical companies to first demonstrate that a candidate drug displays no evidence of adverse effects—known as drug *safety*—and second show improvement in a health outcome related to the target condition—known as drug *efficacy*. Drug safety and efficacy are usually established through a series of clinical trials, allowing FDA policy-makers to weigh the risk of approving an ineffective drug (*type I error*) against the risk of rejecting an effective drug (*type II error*), using statistical hypothesis testing. Traditionally, the probability of type I error is set to a tolerable level known as the *significance level*, α, and the probability of type II error is adjusted through experimental design such as changing the sample size or decreasing measurement error (Casella and Berger, 2002).

FDA guidelines recommend a constant threshold of $\alpha = 2.5\%$ for all diseases (FDA 2017e), which present both benefits and challenges. By prioritizing diseases equally and holding all drugs to the same efficacy standard, this policy is impartial. The choice of $\alpha = 2.5\%$ is arbitrary, however, and no compelling rationale exists for why this value was selected (Sterne and Smith, 2001). By considering only type I errors, this policy ignores the asymmetric costs of type I and type II errors across diseases. Rejecting an effective drug for mild pain that has many alternative treatment options, for example, is less costly than rejecting an effective drug for Alzheimer's disease, for which few treatments currently exist. A fixed threshold ignores the nuances of clinical trial design (e.g.,

rate of new molecule discovery, trial duration, rate of attrition), target population characteristics (e.g., disease prevalence and severity), and the post-approval market (e.g., availability of other drugs).

In recognition of the limitations of a fixed threshold, the FDA has introduced programs that provide the agency with regulatory discretion to address some aspects of (i) disease prevalence, (ii) disease severity, and (iii) the duration of the drug development and approval process.

(i) One regulatory mechanism that considers disease prevalence is the Orphan Drug Act of 1983. In an attempt to offset the high costs of drug development and incentivize investment in understudied conditions, Congress established tax credits and market exclusivity rights for drugs targeting rare, or "orphan" diseases (FDA 2017b). Nevertheless, wide variation exists in rates of drug development, with common diseases often lacking viable treatments. For example, 1.6 million new cancer diagnoses occur annually in the U.S. and more than 800 cancer-related drugs are in development; in contrast, Alzheimer's disease newly afflicts 476,000 people, yet fewer than 80 compounds are in development (PhRMA, 2015b, 2016b). One way to address this imbalance is via the FDA's choice of significance level. Raising the significance level, making approval easier, for diseases with few drugs in development increases the risk of approving an ineffective drug, but for patients with few alternatives, the benefits of approving more drugs may outweigh the costs.

(ii) The FDA's consideration of disease severity is indicated in the Federal Code of Regulations, which states that "patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses" and that "the benefits of the drug need to be evaluated in light of the severity of the disease being treated" (Code of Federal Regulations, 2018). For example, Lotronex, a drug used to treat irritable bowel syndrome, was voluntarily withdrawn from the market in 2000 after many patients experienced severe adverse reactions. Based on patient feedback, however, the

FDA re-approved Lotronex in 2002 with restricted use (FDA 2016a).

(iii) The FDA introduced four *Priority Review* programs to address the protracted timeline for drug development and approval, which typically lasts between ten and fifteen years (FDA 2015). The *Fast Track* program facilitates faster trial completion and FDA review of drugs that treat serious conditions and fill an unmet medical need. *Accelerated Approval* allows the FDA to base approval decisions on surrogate endpoints thought to predict clinical benefit (e.g., one surrogate endpoint for heart disease is cholesterol level). A *Breakthrough Therapy* designation expedites the development and review of drugs demonstrating significant clinical improvement over existing therapies. Finally, *Priority Review* requires the FDA to take action on a drug application within six months, compared to ten months under standard review. These programs are designed to benefit patients, who hopefully gain access to life-saving drugs more quickly, and pharmaceutical firms, who benefit financially from a shortened development timeline. Despite the benefits of such programs, a 2013 study found that nearly 45% of newly approved drugs failed to qualify for any expedited program, leaving room for improvement in the current approval process (Kesselheim et al., 2015). In this paper, we explore an alternative regulatory policy: vary the FDA's choice of significance level for each disease based on characteristics of the drug development process.

In their approval deliberations, the FDA considers other factors including a risk-benefit assessment of the drug, but these are weighed qualitatively (FDA 2017d). By developing a model that explicitly sets the significance level based on underlying disease characteristics, one can discern the relative importance of each factor on approval likelihood. Furthermore, the FDA is often accused of fostering opaque approval policies, and an objective model, in conjunction with existing FDA analyses, could improve transparency.

The contributions of this paper are as follows:

- We develop a framework to study the drug development process and analyze FDA-approval

decisions, accounting for disease severity and prevalence, R&D intensity, trial duration, and the availability of alternative treatments. We model the development process as a series of $M/M/\infty$ queues and the post-approval market as a set of $M/M/1/1$ and $M/M/\infty$ queues. Our study, to the best of our knowledge, is the first to formulate the drug approval process as a network of queues.

- We solve for the FDA's optimal approval policy by disease, assuming they are the primary decision-maker, to maximize expected societal benefits. These include the *health impact* accrued from FDA-approved drugs on the market, the *monetary value* associated with new drugs, and the costs of approving ineffective (type I error) and rejecting effective (type II error) drugs. We interpret *health impact* as the incremental gain in Quality-Adjusted Life Years (QALYs) associated with novel drugs and *monetary value* as the change in the market capitalization of publicly traded pharmaceutical firms following news of successful drug approval, rejection, or withdrawal. We show that, in accordance with intuition, the optimal significance level is higher (easier to approve) for diseases with lengthy clinical trials, high rates of attrition, and low R&D intensity.

- By constructing a new dataset encompassing all registered clinical trials and FDA drug approvals, we illustrate our approach for three high-burden diseases: breast cancer, HIV, and hypertension. We show how the optimal significance level relates to characteristics of the development process and post-approval market. Our numeric results highlight that a one-size-fits-all significance level for drug approval is sub-optimal on a societal level, and approval decisions should objectively consider both pre- and post-approval drug characteristics. To further test model robustness, we simulate the queueing network while relaxing several key assumptions. Although the expected net benefit is sensitive to our assumptions, the signifi-

cance level that maximizes the simulated objective function is relatively robust, differing by at most 0.004 from the optimal policy.

- We evaluate the existing Fast Track program for breast cancer through a counterfactual analysis with parameters estimated for a hypothetical approval process without this program. Our results indicate that, by bringing drugs to market more quickly, Fast Track increases both health benefits and societal monetary value. Furthermore, we find that Fast Track attains a level of health benefit that cannot be achieved by solely changing the significance level.

2.2 Related Literature

Drug Development and Approval. Three sources of inefficiency in the current approval process are the high costs of conducting lengthy clinical trials, frequent attrition during development, and a lack of transparency by the FDA. The Tufts Centre for the Study of Drug Development (2014) estimates an average cost of $802 million to $2.5 billion to develop a drug and bring it to market. Between 2003 and 2011, 7.5% of all novel drugs that initiated clinical trials ultimately gained approval, with lack of safety and efficacy accounting for more than 60% of failures (Hay et al., 2014). Additionally, the FDA has been criticized for fostering opaque approval policies. Downing et al. (2014) examine the strength of clinical trial evidence supporting drug approvals from 2005 to 2012. Despite the FDA's recommendation that drugs should be tested against an active comparator or placebo in two randomized, double-blind trials, more than 60% of drugs were approved on the basis of a single trial, 10% of trials were not randomized, 20% were not double-blind, and 12% did not use a comparator or placebo. While this demonstrates flexibility in considering a wide range of trial evidence, it obfuscates the agency's approval criteria. While these studies are descriptive and focus on identifying drug approval issues and quantifying their financial or health burden, our work

is more prescriptive and presents an objective modeling framework to help inform policy decisions.

Few studies have analyzed the FDA's decision-making process. One recent paper by Montazerhodjat et al. (2017) uses Bayesian Decision Analysis to show how FDA approval could depend on disease burden and patient preferences. The authors compute the optimal significance level for 23 cancers and argue that the traditional $\alpha = 2.5\%$ is too low for rare cancers with few treatment options and short survival times, and too high for more common cancers with many treatments and long survival times. Their choice of significance level depends on trial duration and the rate of new drug discovery. Our work incorporates these elements of the development pipeline, but also considers the post-approval market, such as substitution between drugs within a therapeutic class and obsolescence of older therapies, effects excluded by Montazerhodjat et al. (2017).

Randomized Controlled Trials (RCTs). One bottleneck in the drug approval process is the required sequence of clinical trials. A large body of research focuses on optimal trial design to shorten trial duration or minimize the number of volunteers exposed to a potentially unsafe drug. Ahuja and Birge (2016) dynamically adjust randomization probabilities so that patients are treated as effectively as possible without compromising the ability to learn about efficacy. Bertsimas et al. (2015) use discrete linear optimization to construct treatment groups for small samples, allowing for more powerful statistical inference. Small-sample trial design is important for ethical reasons, but also logistically, as recruiting a large number of volunteers with a rare disease is challenging. Montazerhodjat et al. (2017) incorporate the costs of treating patients with a potentially harmful drug and use expected cost analysis to determine the optimal sample size for a balanced two-arm RCT. Chick et al. (2018) use a Bayesian, decision-theoretic framework to design multi-arm, multi-stage trials that allows dynamic patient allocation decisions, based on prior observations. Other recent studies leverage existing clinical trial data to identify novel drug combinations or patient groups to target. For example, Bertsimas et al. (2016) use machine learning to predict chemotherapy

outcomes in cancer patients and suggest new drug combinations. Gupta et al. (2018) use robust optimization to identify patient subpopulations to maximize the effectiveness of an intervention. We do not explicitly model clinical trial design, but instead analyze how disease specifics drive the optimal significance level, assuming a standard balanced two-arm design.

New Product Development. The journey of a candidate drug from conception through R&D, testing, regulatory approval, and post-approval market penetration relates to new product development (NPD), the process of transforming product concepts into commodities. See Krishnan and Ulrich (2001) and Killen et al. (2007) for a comprehensive review.

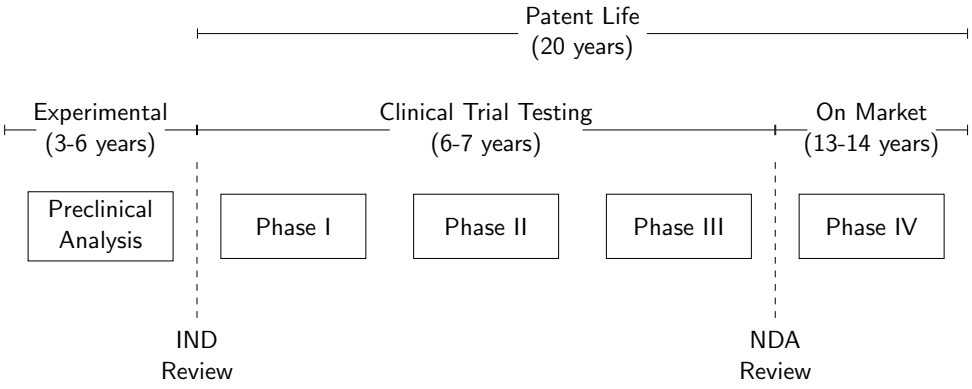
Adler et al. (1995) model a product development process as a queueing network, to identify bottlenecks and find opportunities to reduce time to market for new products. Our work similarly models the stages of drug development as a sequence of queues, but we also capture characteristics of the post-approval process, such as obsolescence among drugs. Adler et al. (1995) take the perspective of a single firm, with the objective of maximizing profit, while we assume the perspective of the social planner with a goal of maximizing expected societal benefit. Other research focuses on the marketing stage, examining topics such as how new products compete for market share. Ding and Eliashberg (2002) use dynamic programming to optimize a portfolio of projects to maximize expected profit, when the final products target the same market and compete for revenue. They define the number of projects pursued by a firm as a decision variable, whereas R&D intensity is an exogenous parameter in our work. Rather than studying market competition for revenue, we explore the role of obsolescence among FDA-approved drugs targeting the same condition.

2.3 Drug Development Overview

The drug approval process in the U.S. consists of a series of stages, beginning with the discovery of a potential new pharmaceutical compound and ending with the FDA deciding whether to grant

marketing approval to the drug. See Figure 2.1 for a summary and average duration of each stage (PhRMA, 2015a).

Figure 2.1: The FDA drug development and approval process



Note: For each new compound, the FDA reviews two applications submitted by the pharmaceutical company: an IND (Investigational New Drug) and an NDA (New Drug Application).

The creation of a new drug begins with extensive research on the target disease and identification of a novel chemical compound intended to treat the illness. Promising candidates are subjected to preclinical analysis, involving laboratory (*in vitro*) and animal (*in vivo*) testing. In addition to screening for potential safety issues, this testing aims to study how the candidate drug is eventually metabolized by the human body (*pharmacokinetics*) and to determine appropriate dosing levels. If a drug candidate raises no safety concerns, the sponsoring firm can submit an Investigational New Drug (IND) application to the FDA, presenting a plan for clinical trial testing. The firm may begin clinical trials within 30 days of filing an IND, provided the FDA does not respond with objections.

Clinical trials usually consist of three phases, designed to test if the candidate drug is both safe and effective in humans. Phase I entails testing in healthy volunteers to observe the drug's potential side effects and pharmacokinetics. If the therapy is well-tolerated in healthy volunteers, the drug can advance to Phase II, where it is administered to volunteers diagnosed with the target illness to establish drug efficacy while continuing to monitor side effects, by comparing patients receiving

the candidate drug to those treated with a placebo or standard therapy. The final stage of clinical testing, Phase III, aims to establish efficacy in a large patient cohort, and to assess interactions with other medications, reactions in different sub-populations, and dosage levels.

At any point during development, the sponsoring firm may withdraw the drug. Typical reasons for halting development include the inability to demonstrate efficacy, safety concerns, pharmacokinetic issues, market competition, and financial considerations (Arrowsmith and Miller, 2013). After completing Phase III, the firm can submit a New Drug Application (NDA) to the FDA, consisting of trial results and a proposal for manufacturing and labeling the drug. The FDA performs a risk-benefit assessment using this information, including data on demonstrated efficacy and reported adverse events, and decides whether the potential benefits of the medication outweigh its risks. Firms may be asked to perform additional testing before gaining marketing approval (FDA 2014b).

Drugs that ultimately gain FDA approval may then be legally marketed in the U.S and receive patenting and exclusivity rights. Patents are granted by the U.S. Patent and Trademark Office and typically expire 20 years after a sponsoring firm files a patent application. This usually occurs before the clinical trials begin, although applications can be submitted at any point during development. Exclusive marketing rights are granted by the FDA, with all new drugs receiving five years of exclusivity upon approval. Safety and efficacy of approved drugs continue to be monitored during post-marketing studies (Phase IV), with any adverse events caused by the drug reported to the FDA (FDA 2016b). Most approved drugs do not cause wide-scale adverse events and thus remain on the market while the firm continues to manufacture them. In rare cases, drugs with harmful side effects are withdrawn from the market by the sponsoring firm or the FDA (FDA 2017c).

2.3.1 Randomized Controlled Trial Design

RCTs are the gold standard for establishing efficacy of candidate drugs. For simplicity, we assume that all drugs tested using a two-arm balanced RCT, a common design that randomly assigns participants to a *treatment* or *control* group, which are equal in size. Individuals in the treatment arm receive the experimental regimen; those in the control arm receive standard therapy or a placebo. Before the trial begins, researchers must propose one or more *endpoints*—outcomes that represent direct clinical benefit—associated with the target disease that will be monitored throughout the study (Friedman et al., 2015; Jennison and Turnbull, 2000). For example, one endpoint in oncology is five-year progression-free survival. The FDA evaluates drugs using two criteria: *safety* is measured by the number and type of adverse events occurring in trial volunteers, and *efficacy* is assessed by monitoring one or more disease endpoints and comparing the treatment and control groups.

We present a standard framework for modeling drug efficacy (Section 2.3.2) drawn from the statistics literature, but we do not explicitly model drug safety given the multitude of possible adverse events. According to the FDA, "with the exception of trials designed specifically to evaluate a particular safety outcome of interest, in typical safety assessments, there are often no prior hypotheses ... and numerous safety findings that would be of concern" (FDA 2017e). In contrast, few clinical endpoints are used to assess efficacy. These endpoints must be specified before initiating the trial and can be objectively measured. We assume that one quantitative *primary endpoint* critical to establishing efficacy is monitored. Although multiple primary endpoints may be used in reality, these endpoints are often merged into a single combined endpoint. Cardiovascular studies, for example, often consolidate cardiac death, heart attack, and stroke into a single compound endpoint (FDA 2017e). Finally, we assume that higher endpoint values correspond to better health

outcomes, though a range of desirable values could exist.

2.3.2 A Statistical Framework for Drug Approval

Consider a two-armed, balanced, non-adaptive clinical trial with n patients in each arm. Let $x_1, \ldots, x_n$ denote independent observations of a single quantitative endpoint from patients in the treatment group, and let $y_1, \ldots, y_n$ denote independent observations from patients in the control group who receive standard therapy. Assume x_i is drawn from a distribution with mean μ_x and variance σ^2, and y_i is drawn from a distribution with mean μ_y and variance σ^2 (Jennison and Turnbull, 2000). The assumption of equal variance is made for simplicity and can be easily relaxed.

The quantity $\delta = \mu_x - \mu_y$ represents the treatment effect of the candidate drug. Our analysis focuses on superiority trials, which assumes that the experimental drug has no effect or a positive effect, compared to the standard therapy. We perform the following hypothesis test:

$$H_0 : \delta = 0 \text{ (drug is ineffective)}$$

$$H_1 : \delta > 0 \text{ (drug is effective)}$$

We compute the Wald statistic from the observed data:

$$Z_n = (\overline{x} - \overline{y}) \sqrt{I_n}$$

where $\overline{x} = \frac{1}{n} \sum_{i=1}^{n} x_i$ and $\overline{y} = \frac{1}{n} \sum_{i=1}^{n} y_i$ are the sample means, and $I_n = \frac{n}{2\sigma^2}$ is known as the *information* of the sample. By the Central Limit Theorem, Z_n is approximately normally distributed with mean $\delta\sqrt{I_n}$ and variance 1. If the p-value associated with Z_n is less than a threshold α, then H_0 is rejected and the drug is deemed effective. If the p-value $> \alpha$, then H_0 cannot be rejected, and the drug is considered ineffective.

Let the *approval policy* corresponding to significance level α be defined as follows: candidate drugs that complete clinical trials and undergo FDA review are approved if p-value $< \alpha$, and rejected otherwise. Let p be the *prior* probability that a candidate drug is actually effective. Given

an approval policy α and prior p, we use our statistical model to obtain joint probability expressions:

$$\begin{aligned}
\pi_{\mathrm{AE}}(\alpha) &= [1-\Phi(\Phi^{-1}(1-\alpha)-\delta\sqrt{I_n})]\,p && \text{Approved effective (AE) drug} \qquad (2.1)\\
\pi_{\mathrm{AI}}(\alpha) &= \alpha\,(1-p) && \text{Approved ineffective (AI) drug}\\
\pi_{\mathrm{RE}}(\alpha) &= \Phi(\Phi^{-1}(1-\alpha)-\delta\sqrt{I_n})\,p && \text{Rejected effective (RE) drug}\\
\pi_{\mathrm{RI}}(\alpha) &= (1-\alpha)\,(1-p) && \text{Rejected ineffective (RI) drug}
\end{aligned}$$

where Φ and Φ^{-1} are the cumulative distribution function and inverse cumulative distribution function, respectively, of the standard normal.

In this work, we consider the FDA's approval decision (i.e., their choice of significance level α), given a fixed sample size n, rather than simultaneously optimizing for both sample size and significance level, as in Montazerhodjat et al. (2017). We focus on the choice of significance level because, in practice, the size of the trial is determined by the pharmaceutical company, taking into account the costs and feasibility of patient recruitment as well as treatment costs.

2.4 A Queueing Framework for the Drug Approval Process

We introduce a queueing network to model the drug development process from clinical trials to post-approval (Figure 2.2). A summary of model parameters is provided in Table 2.1.

2.4.1 Queueing Network Model

Assume that candidate drugs begin clinical trials according to a Poisson process with rate λ. We combine the three phases into a single "clinical trials" queue, rather than consider each phase separately. This simplifies our analyses and does not change our key insights, as we demonstrate in the numerical simulation. Drugs either complete clinical trial assessment, or the sponsoring firm halts the trials early, typically due to financial or pharmacokinetic challenges. Data from clinicaltri-

als.gov demonstrate that an exponential distribution approximates total clinical trial duration (see Appendix A.2 for details). Hence, we model clinical trial duration as an exponential race between trial completion and abandonment, with rates μ_{CT} and μ_{AB}, respectively. Drugs advance to FDA review with probability $\frac{\mu_{CT}}{\mu_{CT}+\mu_{AB}}$ or exit the system with probability $\frac{\mu_{AB}}{\mu_{CT}+\mu_{AB}}$. The net rate at which drugs enter FDA review is denoted by $\tilde{\lambda} = \lambda \frac{\mu_{CT}}{\mu_{CT}+\mu_{AB}}$ and the net trial abandonment rate is $\tilde{\mu} = \lambda \frac{\mu_{AB}}{\mu_{CT}+\mu_{AB}}$. For simplicity, we assume trial completion and abandonment rates are identical across drug classes; our model could easily be extended to incorporate class-specific rates.

Modelling a drug candidate's progression through clinical trials as an $M/M/\infty$ queue with abandonment has several advantages over simply considering the probability of finishing a trial. An $M/M/\infty$ queue captures three key elements of all clinical trials: the initiation rate (λ), total duration ($1/\mu_{CT}$), and abandonment rate (μ_{AB}). Each parameter can differ widely across diseases (see Section 2.5), and our modeling framework can account for this heterogeneity, which would be lost in a simplified model that only considers the trial completion probability.

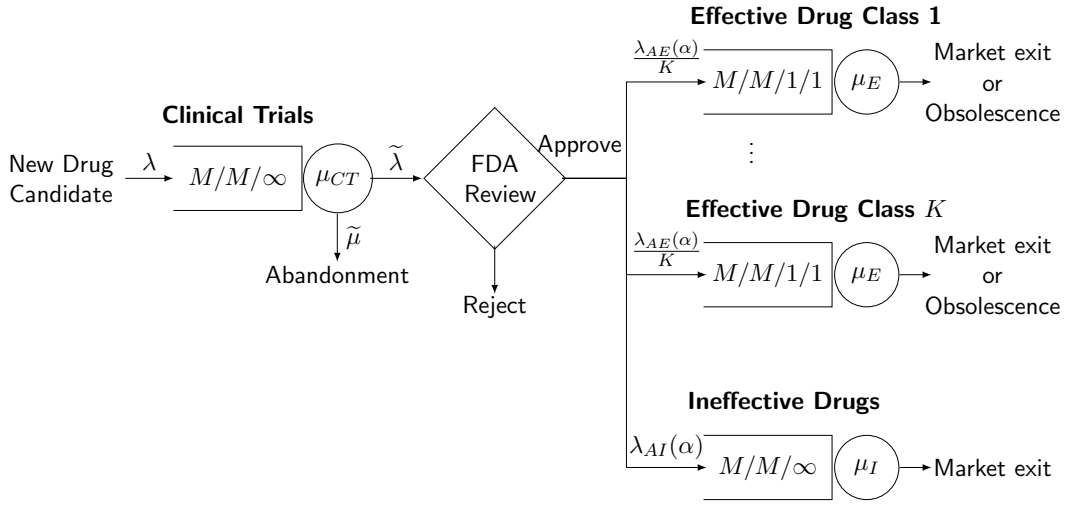
After FDA review, a drug is approved if the p-value associated with the clinical trial demonstrating efficacy is less than the significance level α, and is denied approval otherwise. In our model, the FDA's decision is instantaneous, though, in reality, the review process lasts between six months and two years. This delay could be accounted for by modeling the review stage as an $M/M/\infty$ queue, but would not substantially change our results. In steady state, the output of the FDA review stage constitutes a thinning of a Poisson process with the following arrival rates:

$$\lambda_{AE}(\alpha) = \tilde{\lambda}\pi_{AE}(\alpha), \quad \lambda_{AI}(\alpha) = \tilde{\lambda}\pi_{AI}(\alpha), \quad \lambda_{RE}(\alpha) = \tilde{\lambda}\pi_{RE}(\alpha), \quad \lambda_{RI}(\alpha) = \tilde{\lambda}\pi_{RI}(\alpha). \quad (2.2)$$

After undergoing FDA review, rejected drugs depart the system, while approved drugs enter the market. Approved *ineffective* drugs spend relatively little time on the market as they are more quickly discontinued by dissatisfied patients. Approved *effective* drugs typically spend decades on the market and may, eventually, become obsolete as newer drugs enter the market. Given

these differences, we model effective and ineffective FDA-approved drugs separately. Ineffective drugs are modeled using an $M/M/\infty$ queue, where "service" represents time on the market before withdrawal, with mean $1/\mu_I$. Effective drugs are modeled using a collection of K parallel preemptive $M/M/1/1$ queues with mean service time $1/\mu_E$. Each queue represents a therapeutic class and K denotes the number of unique classes available to treat a particular disease. Upon gaining FDA approval, we assume that effective drugs are equally likely to be in any of the K classes, for analytical tractability. However, we relax this assumption in the numerical simulation. Preemption is designed to account for older drugs becoming obsolete as newer therapies gain approval. Due to the relatively high market concentration within a drug class—a handful of drugs typically account for the majority of prescriptions— we consider the case where at most one drug within a class is on the market. For example, the top five hypertension medications (by market share) belong to five different drug classes (ACE inhibitors, beta blockers, calcium channel blockers, diuretics, and angiotensin receptor blockers) and collectively account for more than 50% of the market (Express Scripts Holding Company, 2017). If a drug class contains two or more comparable drugs, market share would be divided, but the net benefit to patients would remain largely unchanged. For a

Figure 2.2: Queueing network representing the drug development and approval process.



Note: $\tilde{\lambda} = \lambda \frac{\mu_{CT}}{\mu_{CT}+\mu_{AB}}$ and $\tilde{\mu} = \lambda \frac{\mu_{AB}}{\mu_{CT}+\mu_{AB}}$

Table 2.1: Summary of key model parameters.

Before FDA review		After FDA review	
σ	Standard deviation of the candidate drug response	K	Number of unique drug classes on the market
δ	Treatment effect of a candidate drug	Q_E	Per drug health benefit of an effective drug
p	Prior probability that candidate drug is effective	Q_I	Per drug health cost of an ineffective drug
n	Clinical trial enrollment	C_{AE}	Per drug monetary gain of approving effective drugs
λ	Rate that drugs initiate clinical trials	C_{AI}	Per drug monetary loss of approving ineffective drugs
μ_{CT}	Rate that clinical trials are completed	C_{RE}	Per drug monetary loss of rejecting effective drugs
μ_{AB}	Rate that firms abandon clinical trials	WTP	Willingness to pay per QALY
$\tilde{\lambda}$	Rate that drugs enter FDA review	$1/\mu_E$	Average market life of an effective drug
		$1/\mu_I$	Average market life of an ineffective drug

given condition, a drug falls into a single therapeutic class.

For tractability, we analyze the system in steady state with time invariant parameters. We consider two key components of the FDA's decision to approve or reject candidate drugs: the health benefits and monetary value of the drug. The importance of health benefits is explicitly given in the FDA's mission statement, which establishes the agency's role in protecting and advancing public health (FDA 2018j). Accounting for monetary value is in accordance with the agency conducting economic analyses of proposed regulations and comparing "both the incremental benefits and costs associated with increasing the stringency of regulation and the incremental foregone benefits and cost savings associated with decreasing the stringency of regulation" (FDA 2018f).

We measure health benefits in QALYs to account for a drug's effects on both length and quality of life. Consistent with patient health increasing as additional effective treatments become available—and decreasing if ineffective drugs reach the market—we assign an average health benefit Q_E per effective drug on the market, and an average health cost Q_I per ineffective drug. Additionally, a new drug approval or rejection by the FDA results in market gains or losses (measured in U.S. dollars) according to perceived changes in the lifetime profitability of the sponsoring firm. Let C_{AE} denote the average monetary gain associated with approving an effective drug, and let C_{AI} and C_{RE}, respectively, denote the average monetary losses resulting from approving ineffective (type I error) and rejecting effective (type II error) drugs. The monetary value of re-

jecting an ineffective drug is normalized to zero. To facilitate comparison between health benefits and monetary values, we multiply QALYs by willingness-to-pay (WTP), the amount that society values each additional QALY gained (Drummond et al., 2003).

The optimal approval policy α^* is chosen to maximize the expected net benefit $V(\alpha)$:

$$\alpha^* = \arg\max_{\alpha \in [0,1]} V(\alpha) \tag{2.3}$$

where

$$\begin{aligned} V(\alpha) &= \big\{\text{Net health impact} \cdot \text{WTP} + \text{Net monetary value}\big\} \\ &= \big\{\big(Q_E \mathbb{E}[N_E(\alpha)] - Q_I \mathbb{E}[N_I(\alpha)]\big)\text{WTP} + (C_{AE}\lambda_{AE}(\alpha) - C_{AI}\lambda_{AI}(\alpha) - C_{RE}\lambda_{RE}(\alpha))\big\}. \end{aligned}$$

The per drug health benefit or cost is multiplied by the expected number of effective or ineffective drugs, $\mathbb{E}[N_E(\alpha)]$ or $\mathbb{E}[N_I(\alpha)]$, respectively. Letting $\psi_E(\alpha) = \lambda_{AE}(\alpha)/(K\mu_E)$ and $\psi_I(\alpha) = \lambda_{AI}(\alpha)/\mu_I$, we can write these terms as:

$$\mathbb{E}[N_E(\alpha)] = \frac{K\psi_E(\alpha)}{1+\psi_E(\alpha)}, \qquad \mathbb{E}[N_I(\alpha)] = \psi_I(\alpha). \tag{2.4}$$

Each monetary value is multiplied by the corresponding approval or rejection rate, reflecting the societal benefits (or costs) associated with a new drug. Note that this is a one time gain/loss in monetary value (e.g., the market value increase of Pfizer upon obtaining approval of Lipitor).

2.4.2 Model Analysis

We first examine the structure of the optimal approval policy to gain insights into how the pre- and post-review characteristics of a drug affect the FDA's ultimate approval decision. All proofs are presented in Appendix A.

The following result shows that the optimal significance level α^* is unique and is the solution to a non-linear equation.

Theorem 1. *The expected net benefit function $V(\alpha)$ is concave in α, and the optimal policy α^**

satisfies the following first order condition:

$$\alpha^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}}\log\left(\frac{1-p}{p}\frac{C_{AI} + WTP \cdot Q_I/\mu_I}{WTP \cdot Q_E/(\mu_E(1+\psi_E(\alpha^*))^2) + C_{RE} + C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right). \quad (2.5)$$

Theorem 1 demonstrates that the optimal approval policy, α^*, weighs the steady-state monetary losses and health costs of approving ineffective drugs against the monetary gains (losses) and health benefits of approving (rejecting) effective drugs. Although no closed form expression for the optimal policy exists, we can analyze the comparative statics of α^* using the first order condition.

Proposition 1. *The optimal approval policy α^* is*

(a) increasing in Q_E, C_{AE}, C_{RE}, μ_I, and μ_{AB},

(b) decreasing in Q_I, C_{AI}, λ, and μ_{CT},

(c) increasing in p and decreasing in μ_E under the additional assumption that $\psi_E(\alpha^*) < 1$.

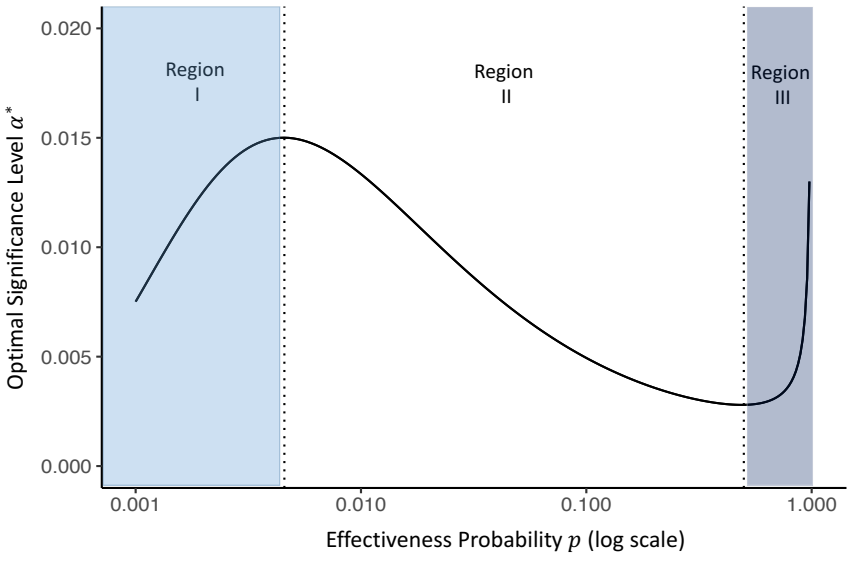
Proposition 1 indicates that the optimal approval policy is more stringent for diseases with many compounds in development (large λ) or short clinical trial durations (large μ_{CT}), and less stringent for diseases with high attrition rates (large μ_{AB}). As expected, drugs with greater health benefits Q_E or higher rejection costs C_{RE} (due to a type II error) have easier approval policies compared to those with higher approval costs C_{AI} (due to a type I error). Prolonging the time that ineffective drugs might spend on the market $1/\mu_I$ increases patient harm, thus discouraging FDA approval.

As the prior probability p of effectiveness increases, or as the average time that effective drugs spend on the market $1/\mu_E$ increases, one might expect that it is optimal to approve *more* drugs. Proposition 1 states that this intuition only holds under the condition $\psi_E(\alpha^*) = \lambda_{AE}(\alpha^*)/(K\mu_E) < 1$. In other words, the rate at which effective drugs in a given class are approved $\lambda_{AE}(\alpha^*)/K$ is less than the rate of market exit μ_E. Since we model this market as a collection of $M/M/1/1$ queues,

this condition is not needed for stability; rather it serves to limit crowding in the market. To understand the relationship between market crowding and non-monotonicity of the optimal policy (holding all other parameters constant), consider the following example, illustrated in Figure 2.3.

Consider a disease with a high rate of R&D intensity $\tilde{\lambda}$, and high health benefits associated with effective drugs Q_E relative to the health cost of ineffective drugs Q_I. For simplicity, suppose that there is no monetary value associated with approval or rejection, i.e. $C_{AE} = C_{AI} = C_{RE} = 0$. To illustrate the non-monotonic behavior of the optimal approval policy, we divide Figure 2.3 into three regions, characterized by the effectiveness probability p and the degree of crowding in the market among approved effective drugs, $\mathbb{E}[N_E(\alpha)]$. In this example, let's define drugs with a low effectiveness probability ($p < 0.5$) as *long shots*, and those with high effectiveness probability ($p \geq 0.5$) as *safe bets*. We consider the market *crowded* if many effective therapies are available ($\mathbb{E}[N_E(\alpha)] \approx K$) and *neglected* if few are available ($\mathbb{E}[N_E(\alpha)] << K$).

Figure 2.3: Example of the sensitivity of the optimal significance level α^* with respect to the effectiveness probability p if Proposition 1c is not satisfied.



Note: $\sigma = 1$, $\delta = 0.10$, $n = 500$, $\tilde{\lambda} = 8$, $K = 1$, $WTP = 1$, $Q_E = 1$, $Q_I = 0.1$, $\mu_E = 0.01$, $\mu_I = 0.10$, $C_{AE} = 0$, $C_{AI} = 0$, and $C_{RE} = 0$. Region I corresponds to $0 \leq p \leq 0.005$, Region II to $0.005 < p \leq 0.5$, and Region III to $0.5 < p \leq 1$.

Region I corresponds to diseases with neglected markets and long shot drugs. As the probability of effectiveness increases—despite its low value—the optimal policy approves *more* drugs because of the paucity of effective drugs available to patients. Region II comprises long shot drugs but a more crowded market. Here, the potential costs of approving an ineffective drug outweigh the benefits of approving an effective drug, as many alternative drugs are available. Therefore, as the effectiveness probably p increases, the optimal policy approves *fewer* drugs. Finally, in Region III, the market is crowded and each additional effective drug has diminishing marginal benefit, but the candidate drugs are reasonably safe bets, so each new approval generates a positive expected health benefit. Hence, the optimal policy in this region is to approve *more* drugs as p increases.

Our analysis thus far assumes a fixed number of unique drug classes K available to treat a particular disease. We next examine how the optimal policy changes as K increases, which can be interpreted as approving a *first-in-class* drug, one with a new and unique mechanism of action for disease treatment. First-in-class drugs potentially offer patients a more tolerable set of side effects or serve a patient population for whom current treatments are inadequate.

Let α_j^* denote the optimal policy and let V_j^* denote the optimal expected net benefit when j drug classes are on the market.

Proposition 2. *The optimal approval policies satisfy*

$$\alpha_0^* \leq \alpha_1^* \leq \cdots \leq \alpha_K^* \leq \cdots \leq \alpha_\infty^*$$

where

$$\alpha_0^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}} \log\left(\frac{1-p}{p}\frac{C_{AI} + WTP \cdot Q_I/\mu_I}{C_{RE} + C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right) \tag{2.6}$$

and

$$\alpha_\infty^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}} \log\left(\frac{1-p}{p}\frac{C_{AI} + WTP \cdot Q_I/\mu_I}{WTP \cdot Q_E/\mu_E + C_{RE} + C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right). \tag{2.7}$$

Proposition 2 states that the optimal approval policy is non-decreasing in the number of drug classes K, an intuitive result. As K increases, more opportunities exist for different therapy classes

and thus the optimal policy is to ease approval standards to fill the market. While α_0^* is purely a mathematical lower bound and does not have a direct interpretation in our model, the optimal policy α_1^* might represent a disease with limited treatment options, such as Alzheimer's disease or muscular dystrophy. The upper bound α_∞^* represents the optimal policy for a condition such as mild pain, for which a multitude of therapies are available.

Changing the number of drug classes on the market affects not only the optimal policy, but also the expected net benefit from approving and rejecting drugs.

Proposition 3. *The optimal expected net benefit functions satisfy*

$$V_0^* \leq V_1^* \leq \cdots \leq V_K^* \leq \cdots \leq V_\infty^*,$$

and, for all $K \geq 1$ *and for any* α*,*

$$V_{K+1}(\alpha) - V_K(\alpha) > V_{K+2}(\alpha) - V_{K+1}(\alpha).$$

The first result in Proposition 3 shows that, intuitively, increasing the number of drug classes K generates greater expected net benefit due to additional effective drugs on the market. For diseases with few drug classes (low K), increasing K with a first-in-class drug approval produces larger expected gains than for diseases with many existing drug classes (high K). Spurring innovation in drug development by easing approval standards is particularly beneficial for diseases with few available treatments.

2.5 Numerical Study

Using publicly available drug approval data, we conduct numerical analyses for three high-burden diseases: breast cancer, HIV, and hypertension. We compute the optimal approval policies for each disease, compared to a traditional policy of $\alpha = 2.5\%$. This analysis aims to (i) examine how characteristics of the drug development process affect the optimal approval policy, and (ii)

illustrate how our modeling framework could be used to gain insights about disease-specific approval recommendations.

2.5.1 Parameter Estimation

We provide an overview of our parameter estimation, with a detailed description and sources in Appendix B.

Clinical trial parameters. The pre-FDA review parameters are numerically estimated for each disease using clinical trial data from clinicaltrials.gov and historical drug approval data from Drugs@FDA. We estimate the clinical trial completion rate μ_{CT} using the mean durations of Phase I-III trials, and then calculate the probability that a drug completes all three phases, $\mathbb{P}$(Complete clinical trials). The trial abandonment rate is calculated as $\mu_{CT}\ \frac{1-\mathbb{P}(\text{Complete clinical trials})}{\mathbb{P}(\text{Complete clinical trials})}$. We estimate the NDA submission rate $\tilde{\lambda}$ using the average rate of drug approval for a disease (computed using exhaustive lists of approved drugs provided in Appendix Tables A.2-A.4) and estimates for the NDA approval probability from Thomas et al. (2016). The clinical trial initiation rate λ is estimated using $\tilde{\lambda}$ and $\mathbb{P}$(Complete clinical trials).

Clinical trial information $\delta\sqrt{I_n}$ is estimated by assuming that the statistical power of the trial—the probability of approval given the drug is effective—is 90%, assuming a traditional significance level of $\alpha = 2.5\%$. We calculate the prior probability p that a drug is effective so that the net approval probability equals estimates given by Thomas et al. (2016), assuming $\alpha = 2.5\%$.

Number of drug classes. We identify classes of drugs that are widely recognized among health care providers. Next, we use current treatment guidelines to remove classes rendered obsolete by newer therapies. Lists of all drug classes and references are provided in Appendix Table A.1.

Monetary values. We define the monetary gains and losses C_{AE}, C_{AI}, and C_{RE} as the average change in market capitalization of pharmaceutical firms in response to the approval of an

effective drug, approval of an ineffective drug, and rejection of an effective drug, respectively. We use published estimates of percent abnormal market returns at the time of initial review, the time a drug is announced as approvable, the approval (or rejection) announcement day, the day after the approval announcement, and following market withdrawal (Sarkar and de Jong, 2006; Ahmed et al., 2002). We estimate monetary values by combining these published estimates with the market capitalization of pharmaceutical companies to reflect the aggregate monetary gain or loss associated with a drug approval or rejection decision by the FDA. Note that this gain or loss is incurred once for each drug that is approved or rejected.

Health impacts. We interpret the per-drug health benefits and costs Q_E and Q_I as the change in QALYs associated with one additional effective or ineffective drug on the market, respectively. We calculate Q_E as the incremental per-drug per-person gain in QALYs associated with newly approved drugs, relative to the prevailing treatment option available at the time of FDA review (estimated by Chambers et al. (2017)), multiplied by the new drug's expected market size. We assume that patients with a particular disease are equally likely to take any of the K drug classes available. Market size is calculated as either the incidence (for acute diseases) or the prevalence (for chronic diseases) of the disease being treated, divided by the number of drug classes K, so that drugs have equal market share. In sensitivity analysis, we relax this assumption and consider a non-uniform distribution based on historical availability of different drug classes for each disease.

To calculate Q_I, we assume that the total health cost Q_I/μ_I is proportional to the total health benefit Q_E/μ_E. We use the ratio C_{AI}/C_{AE} of the monetary losses of approving ineffective drugs to the monetary gains of approving effective drugs as our constant of proportionality, with the idea that the relative stock market reactions of approving and withdrawing a drug may also reflect the relationship between expected health benefits or costs of approved drugs.

Market durations. The average time that effective drugs spend on the market $1/\mu_E$ equals

the sum of time on patent $1/\mu_{PAT}$ and as a generic or off-patent drug $1/\mu_{GEN}$. Assuming that firms file patents at the start of preclinical analysis (an average of 4.5 years before Phase I trials), we subtract the time in preclinical work and clinical trials from the 20 year standard patent life to obtain $1/\mu_{PAT}$ (PhRMA, 2015a). To obtain $1/\mu_{GEN}$, we examine FDA records of drugs (novel and generic) that were discontinued for reasons not related to safety or efficacy between the years of 2015 and 2017 (FDA 2017a).

The average time that ineffective drugs spend on the market $1/\mu_I$ is calculated as the average time until withdrawn drugs are removed, for each disease considered. This is likely an underestimate as withdrawn drugs often cause patient harm, which may accelerate their removal from the market. The list of withdrawn drugs and time on the market was obtained from Drugs@FDA and is included in Appendix Table A.5.

2.5.2 Case Study: Breast Cancer, HIV, and Hypertension

We conduct a numerical study of three high-burden diseases, which collectively accounted for over 10% of all drugs in development in 2016 (Murray et al., 2013; PhRMA, 2016a). Parameter estimates for each disease are summarized in Table 2.2, with additional details provided in Appendix B

Each year, 250,000 women in the U.S. are diagnosed with breast cancer and more than 40,000 die of the disease. Primary treatment consists of surgery, radiation, and/or chemotherapy and is typically completed within a year of diagnosis (Breast Cancer Society, 2018). Additional hormone or targeted therapies may be prescribed for several years after primary treatment to reduce recurrence risk. Women with metastatic breast cancer may take some form of oncological therapy for the remainder of their lives.

Currently 1.1 million people in the U.S. are living with Human Immunodeficiency Virus (HIV) and more than 6,000 die each year (CDC 2019). HIV attacks the body's immune system, leaving

individuals at risk for potentially deadly opportunistic infections. HIV+ patients are prescribed antiretroviral therapy, which suppresses viral load in the body, slows disease progression, and substantially prolongs life.

Chronic hypertension, or high blood pressure, afflicts 106 million people in the U.S. and is a precursor for heart disease, which is responsible for one in every four deaths (CDC 2017). Diagnosed individuals often take medications to control their blood pressure throughout their life.

Significant heterogeneity exists in the pre-FDA review timeline across these diseases (Table 2). Breast cancer has the highest R&D intensity λ, but also the highest clinical trial attrition rate μ_{AB} and the longest average trial duration $1/\mu_{CT}$, resulting in an NDA intensity $\tilde{\lambda}$ of 1.48 drugs per year. According to Arrowsmith and Miller (2013), this high rate of attrition stems from difficulty in establishing efficacy for oncology drugs in trials with relatively short durations. In contrast, hypertension has a low R&D intensity λ of 3.85 drugs per year, but also the lowest attrition rate and the shortest average clinical trial duration, leading to the highest NDA intensity of 2.34 drugs per year. The estimated probability p that a drug is effective, conditional on undergoing FDA

Table 2.2: Parameter estimates for selected diseases.

Parameter	Breast Cancer	HIV	Hypertension	Source
λ (drugs/year)	9.99	4.80	3.85	clinicaltrials.gov, BIO
μ_{CT} (drugs/year)	0.08	0.14	0.31	clinicaltrials.gov
μ_{AB} (drugs/year)	0.46	0.28	0.20	clinicaltrials.gov
$\tilde{\lambda}$ (drugs/year)	1.48	1.60	2.34	BIO
p	0.912	0.985	0.933	BIO
K (classes)	10	6	9	See Appendix Table A.1
C_{AE} (billion \$)	0.094	0.094	0.094	Ahmed et al. (2002), Sarkar and de Jong (2006)
C_{AI} (billion \$)	0.102	0.102	0.102	Ahmed et al. (2002), Sarkar and de Jong (2006)
C_{RE} (billion \$)	0.023	0.025	0.024	Ahmed et al. (2002), Sarkar and de Jong (2006)
Q_E (QALYs)	2,350	12,650	1,766,670	CDC.gov, Chambers (2017), NCI
Q_I (QALYs)	7,579	23,986	21,975,400	CDC.gov, Chambers (2017), NCI
WTP (\$/QALY)	100,000	100,000	100,000	Neumann et al. (2014)
μ_E (drugs/year)	0.043	0.039	0.036	FDA.gov, Drugs@FDA
μ_I (drugs/year)	0.128	0.069	0.455	See Appendix Table B6

Note: The clinical trial information $\delta\sqrt{I_n}$ is calculated assuming a 90% statistical power level.
Sources: clinicaltrials.gov (National Library of Medicine and National Institutes of Health, 2018); Biotechnology Innovation Organization (BIO) (Thomas et al., 2016); Centers for Disease Control and Prevention (2019); Centers for Disease Control and Prevention (2017c); National Cancer Institute (2018a); FDA (2018a)

Table 2.3: Optimal policies for selected diseases.

	Breast Cancer	HIV	Hypertension
Optimal Policy α^*	4.6%	6.3%	2.3%

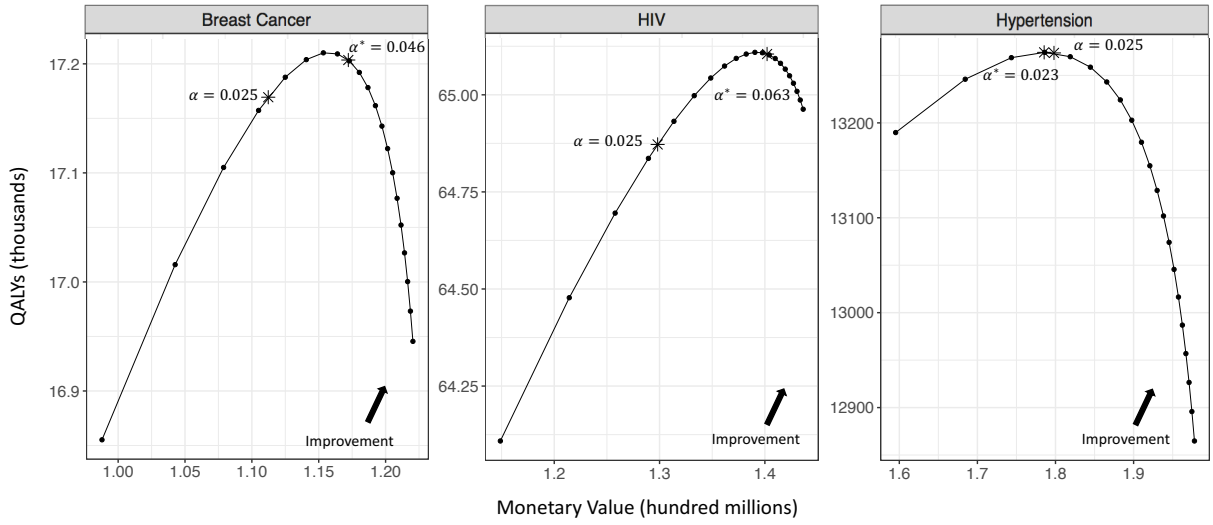
review, is similar across the examined conditions, with all estimated values exceeding 0.90.

Substantial variation also exists in the health impact associated with drugs used to treat these diseases. Hypertension has the greatest societal per-drug health benefit Q_E, while breast cancer medications have the least. This is driven by differences in both the incremental QALY gain, and the much larger market size for hypertension drugs. Hypertension drugs spend more time on the market under patent protection due to shorter average trial durations, compared to breast cancer drugs. Historically, ineffective hypertension drugs spend the shortest time on the market, potentially because blood pressure is easily monitored, leading to faster public awareness of a drug's ineffectiveness. The first case of HIV was identified in 1981, which may partly explain the paucity of drug classes for this disease compared to hypertension and breast cancer, for which treatments have been in development since the 1950s (Department of Health and Human Services, 2016).

Using the estimated parameter values, we calculate the optimal approval policies α^* for each disease (Table 2.3). Our model suggests that a stricter policy is optimal for hypertension drugs due to the higher rate of NDA submissions $\tilde{\lambda}$ and the substantial health costs incurred, given its high prevalence, if an ineffective drug gains FDA approval. In contrast, the optimal threshold for HIV is less stringent due to the lower NDA intensity, high prior probability of effectiveness p, and lack of available treatment alternatives.

Figure 2.4 depicts the trade-off between net monetary value accrued ($C_{AE}\lambda_{AE}(\alpha) - C_{AI}\lambda_{AI}(\alpha) - C_{RE}\lambda_{RE}(\alpha)$) and the health benefits (QALYs) achieved ($Q_E\mathbb{E}[N_E(\alpha)] - Q_I\mathbb{E}[N_I(\alpha)]$) for approval policies ranging from $\alpha = 1\%$ (far left point) to $\alpha = 10\%$ (far right point). In these plots, moving

Figure 2.4: Comparison of the monetary value and QALYs achieved by different approval policies.



Note: Each point on the curve represents a different approval policy α. We vary α from 0.01 (far left point in each plot) to 0.10 (far right point in each plot).

to the upper right is favorable, as both monetary value and QALYs increase. For each disease, increasing α from 1% to 10% results in higher monetary value because the marginal gains from approving effective drugs outweigh the potential losses of approving ineffective or rejecting effective drugs. Increasing α generates more QALYs initially as more drugs enter the market, but eventually reduces net QALYs because of market saturation and drug obsolescence. For breast cancer or HIV, the optimal policy α^* strictly dominates—offers more societal benefits (33 QALYs for breast cancer, 232 QALYs for HIV) and higher net monetary value ($6 million for breast cancer, $10.5 million for HIV)—than the *status quo* policy. The optimal policy for hypertension offers 567 more QALYs, but slightly lower net monetary value ($1.5 million), in part because the *status quo* policy is quite close to the optimal threshold for this disease.

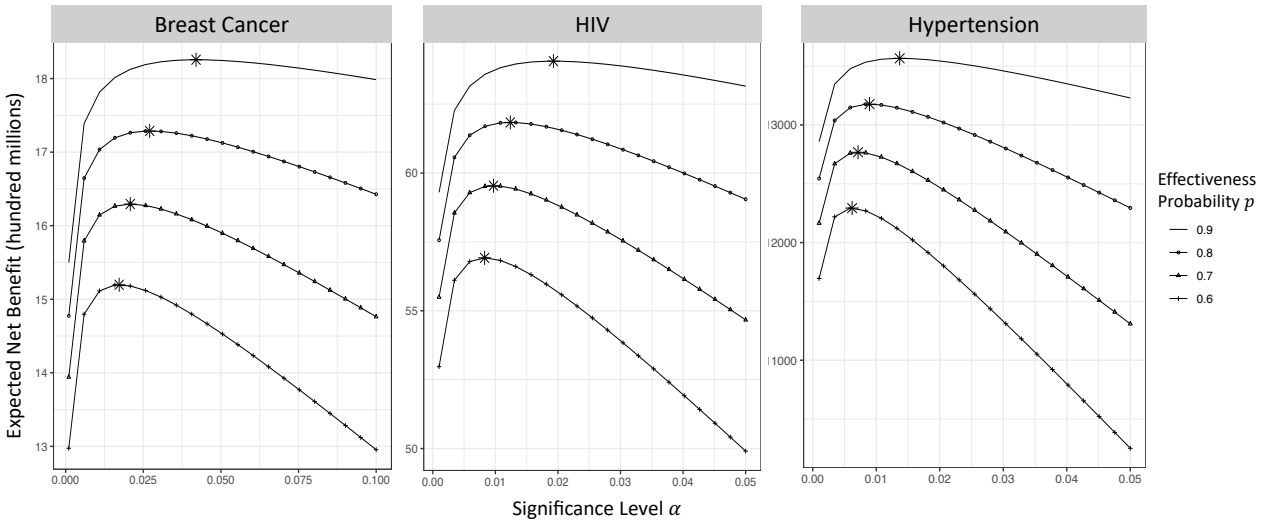
2.5.3 Sensitivity Analysis

We conduct sensitivity analysis of the optimal approval policies and expected net benefit with respect to the nominal parameter values (Table 2.2), focusing on three key parameters: the prior

probability p of effectiveness, NDA intensity $\tilde{\lambda}$ (which comprises the pre-review parameters λ, μ_{CT}, and μ_{AB}), and the average time effective drugs spend on the market $1/\mu_E$.

For each parameter, we plot the value of the expected net benefit as a function of α for different values of the parameter. On each curve, we indicate the optimal significance level for the given value of the parameter.

Figure 2.5: Sensitivity of the optimal approval policy and expected net benefit to the prior probability p that a drug is effective.



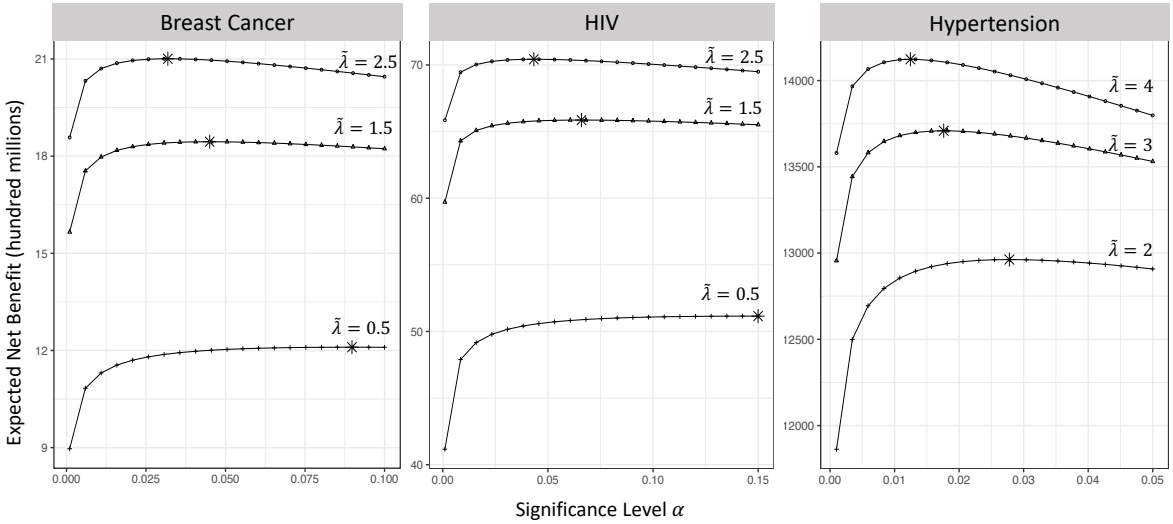
Sensitivity to effectiveness probability. We consider a range of $p = 0.6$ to $p = 0.9$, assuming the FDA is most likely to approve drugs for which its prior belief of effectiveness is high. Over this range, Figure 2.5 shows that the optimal policy is increasing in p for all diseases. Furthermore, we see that the curvature of the expected net benefit is quite sensitive to the value of p. For low effectiveness probabilities, the objective function has high curvature, meaning that a deviation from the optimal policy results in a larger drop in the expected net benefit as compared to high effectiveness probabilities. As our initial estimates of p are 0.912 (breast cancer), 0.985 (HIV), and 0.933 (hypertension), we can conclude that the objective function is fairly flat around the optimal policy α^* for our estimated parameter values.

Sensitivity to NDA intensity. For each disease, we consider three values for the rate of NDA

submissions: one value that is similar to the estimated NDA intensity given in Table 2.2, one value that reflects one fewer NDA submission each year, and one that reflects an additional submission. As indicated by Proposition 1, the optimal approval policy α^* is decreasing in $\tilde{\lambda}$ (Figure 2.6). As more candidate drugs for a particular disease go up for FDA review, the agency can afford to be more stringent, given the diminishing marginal returns of additional drugs treating the same underlying condition joining the market.

For hypertension, an increase in the NDA intensity $\tilde{\lambda}$ also affects the curvature of the objective. For low values of $\tilde{\lambda}$, there are few drugs going up for approval, and so a deviation from the optimal significance level α^* has a small impact on the number of drugs that are ultimately approved and rejected (and thus the expected net benefit). On the other hand, when $\tilde{\lambda}$ is high and many NDAs are being submitted, a small change in the approval policy has a large impact on the number of approved and rejected drugs.

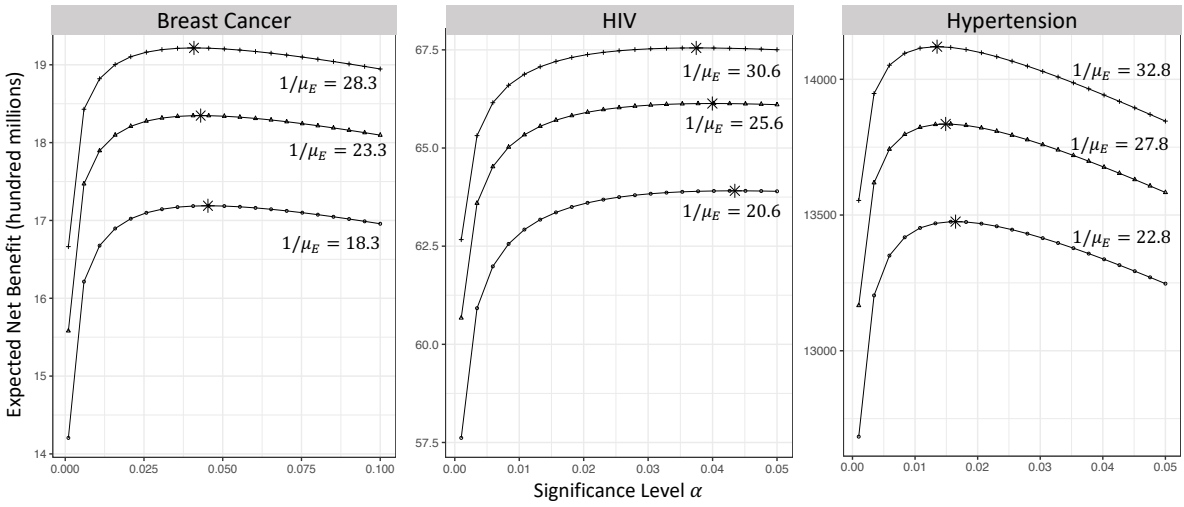
Figure 2.6: Sensitivity of the optimal approval policy and expected net benefit to the NDA intensity $\tilde{\lambda}$



Sensitivity to market duration. As in our analysis of the NDA intensity, we consider three values of the market duration $1/\mu_E$ for each disease: the value given in Table 2.2, one value that reflects five additional years on the market, and one value that reflects five fewer years. For the

range of values we consider, the optimal policy is stricter for drugs that spend more time on the market due in order to avoid overcrowding and increasing the rate of obsolescence among therapies within the same drug class. Compared to the effectiveness probability p and the NDA intensity $\tilde{\lambda}$, the optimal policy is less sensitive to changes in the average time that effective drugs spend on the market, and the curvature of the expected net benefit appears to remain the same for different market durations.

Figure 2.7: Sensitivity of the optimal approval policy and expected net benefit to the average time effective drugs spend on the market.



2.5.4 FDA Expedited Programs for Serious Conditions

Our framework can be used to examine the FDA's four expedited programs for serious conditions: Accelerated Approval, Breakthrough Therapy, Fast Track, and Priority Review. These programs, whose qualifying criteria and features are summarized in Table 2.4, aim to benefit patients suffering from serious conditions by reducing the time to bring new drugs to market.

We illustrate our approach for one expedited program (Fast Track), applied to one disease (breast cancer). Fast Track is chosen because of its impact on both the clinical trial and review durations, and because the Breakthrough Therapy designation, which similarly reduces these du-

rations, was only recently introduced in 2012. Breast cancer is selected because 48% of these drugs utilize the Fast Track program, compared to 35% for HIV and only 1% for hypertension (Kesselheim et al., 2015). We perform a counterfactual analysis by estimating parameters of the FDA review process in the absence of Fast Track, and comparing the monetary value and QALYs obtainable under this scenario to the current system with Fast Track.

Fast Track aims to reduce the time spent in clinical trials and NDA review, but to not affect other aspects of the drug development and approval process (FDA 2014a). We model this as an increase in the clinical trial completion rate μ_{CT}, and the per drug monetary gains and losses, health benefits and costs, market durations, and effectiveness probability are unchanged. Although Fast Track may seem like an obvious improvement, its potential downsides include approving more ineffective drugs and increasing drug obsolescence post-approval.

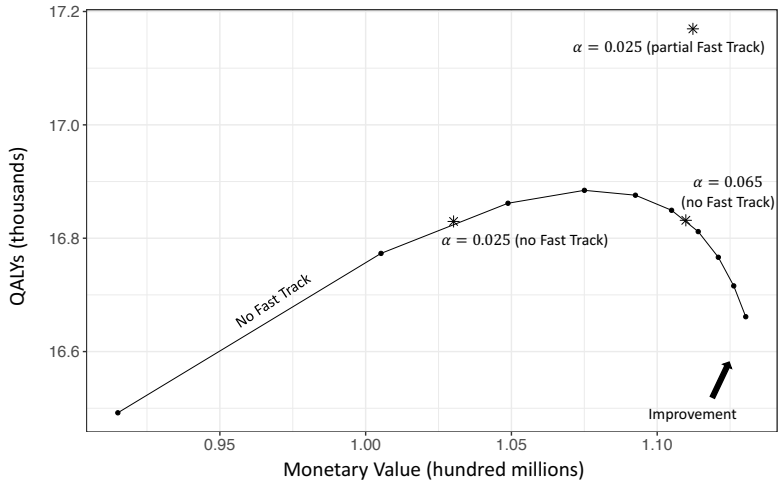
Let μ_{CT} denote the clinical trial completion rate under the current system, where 48% of breast cancer drugs use Fast Track. Let μ_0 denote the completion rate if 0% of drugs use Fast Track, and let μ_1 denote the rate if 100% of drugs participate. We denote the current system as partial Fast

Table 2.4: Overview of FDA expedited programs.

Program	Qualifying Criteria	Features
Accelerated Approval (1992)	A drug that treats a serious condition and provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint likely to predict clinical benefit.	Approval based on an effect on a surrogate endpoint.
Breakthrough Therapy (2012)	A drug that treats a serious condition and that preliminary evidence indicates may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies.	Intensive guidance on drug development; Rolling review.
Fast Track (1997)	A drug that treats a serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need.	Actions to expedite development/review.
Priority Review (1992)	A drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.	6-month FDA review (10-month standard)

Notes: Accelerated Approval was established under the 1992 Code of Federal Regulations, Breakthrough Therapy under the Food and Drug Administration Safety and Innovation Act of 2012, Fast Track under the Food and Drug Administration Modernization Act of 1997, and Priority Review under the Prescription Drug User Fee Act of 1992. Source: FDA 2014a.

Figure 2.8: Comparison of the monetary value and QALYs achieved under the current system (with partial Fast Track) and a system with no Fast Track.



Note: The approval policy α for the standard system varies from $\alpha = 0.01$ (far left point) to $\alpha = 0.10$ (far right point).

Track. We previously estimated $\mu_{CT} = 0.08$ for breast cancer (Section 2.5.2). Assume the duration of existing clinical trials $\frac{1}{\mu_{CT}}$ is a weighted average of the durations with 0% and 100% of drugs on Fast Track. We set $\frac{1}{\mu_1} = 0.95\frac{1}{\mu_{CT}}$ based on a report showing that Fast Track reduced total trial and review time by 5% across all drugs (Tufts Center for the Study of Drug Development, 2008).

Figure 2.8 depicts the trade-off between monetary value and QALYs of varying α between 1% and 10% (no Fast Track), and the current approval policy (partial Fast Track) with a fixed $\alpha = 2.5\%$. Compared to no Fast Track, the current system offers greater monetary value and QALYs. In other words, given a fixed approval policy, adding Fast Track *dominates* the approval process without this program. In the absence of Fast Track, no approval policy can achieve the QALYs obtainable under Fast Track. Eliminating Fast Track while setting $\alpha = 6.5\%$ generates similar monetary value as the current system (because a similar number of drugs are approved/rejected) but significantly fewer QALYs because drugs spend longer in clinical trials and thus less time on the market.

We assume that Fast Track shortens only the clinical trial completion rate μ_{CT}, but this program could also reduce the prior probability p of drug effectiveness. Shorter clinical trials mean less

time to investigate interactions with other medicines or recruit different patient populations, while shorter FDA review times might mean less time to evaluate trial results. Given a fixed $\alpha = 2.5\%$, for small changes in p, the current system continues to dominate the approval process with no Fast Track, both in terms of monetary value and QALYs. However, if $p < 0.84$ (from $p = 0.912$), then an approval system with no Fast Track is preferred.

2.5.5 Simulation

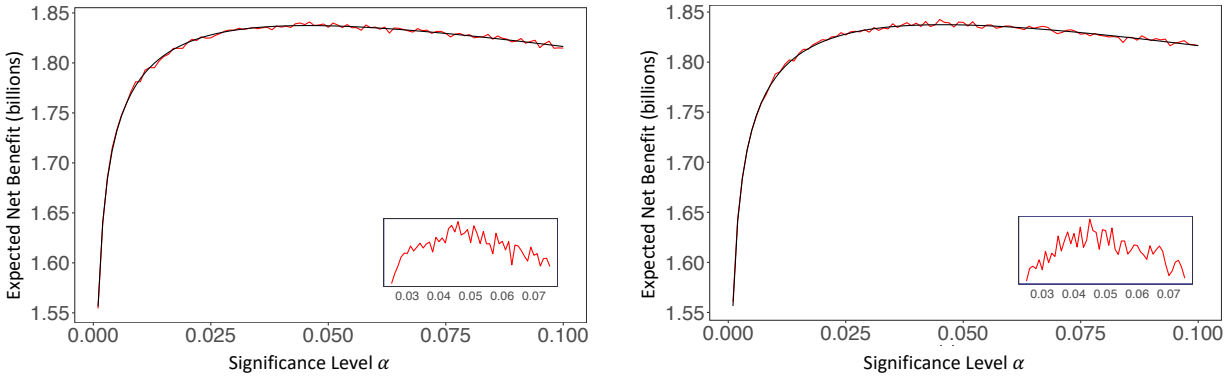
To test the robustness of our queueing model, we conduct a simulation while relaxing several key assumptions of the base model described in Section 2.4. We focus our analysis on breast cancer and simulate the drug approval process under various assumptions for a period of 10,000 years, for significance levels ranging from $\alpha = 0.1\%$ to $\alpha = 10\%$. For each value of α, we run 100 iterations and compute the expected net benefit after a burn-in period of 5,000 years.

Clinical Trials. In the base model, clinical trials are modeled as a single phase with an exponential race between abandonment and service completion. To test this assumption, we split the trials into three phases and either (i) model each phase as an exponential race with specific completion and abandonment rates, or (ii) sample each phase duration using historical breast cancer trial data from clinicaltrials.gov. In both scenarios, the probability of each phase completion is based on all oncology drugs given in Thomas et al. (2016). The rate at which drugs initiate clinical trials is adjusted so that the rate $\tilde{\lambda}$ of drugs entering NDA review is unchanged.

Figure 2.9 shows the expected net benefit for simulations (i) and (ii), which both closely match the base model results. The significance level maximizing the simulated objective function is (i) $\alpha = 4.6\%$ and (ii) $\alpha = 4.5\%$, compared to $\alpha^* = 4.6\%$ under the base model, suggesting that our earlier analysis is robust to structural variations in the pre-review queueing model.

Drug Class Distribution. In the base model, effective drugs that gain FDA approval are

Figure 2.9: Expected net benefit from simulation (red line) and base model (black line) for clinical trial assumption relaxations (i) (left) and (ii) (right).



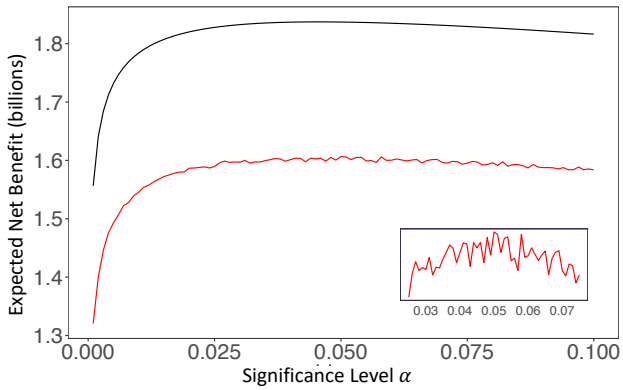
Note: The inset plots show the simulated expected net benefit function for $\alpha = 2.5\%$ to $\alpha = 7.5\%$.

equally likely to belong to any of the K drug classes on the market. We relax this assumption by setting the probability distribution across drug classes using historical data on breast cancer drug approvals (Appendix table A.2). Two of the ten approved drug classes for breast cancer account for nearly 60% of all approvals: combination chemotherapy (37%) and targeted biological therapy (20%). This imbalance means that drugs in these two classes are at risk for becoming obsolete—as newer therapies gain FDA approval—and thus removed from the market prematurely, before patent expiry. As a result, the remaining eight classes receive relatively few new drugs, decreasing the expected total number of approved effective drugs and, hence, decreasing expected net benefits (Figure 2.10). To compensate for this reduction in effective drugs, the significance level that maximized simulated net benefits increases slightly to $\alpha = 5.0\%$.

Time on Market. Lastly, we relax the $M/M/1/1$ queueing assumption that the time approved effective drugs spend on the market is exponentially distributed. We instead use a $M/G/1/1$ queue with lognormally distributed time on the market, assuming the same mean. We vary the coefficient of variation (CV) $= \frac{\sigma}{\mu}$ in the simulated queue assuming CV$= 0.5$, CV$= 1$, or CV$= 2$.

When CV$= 0.5$ or CV$= 1$, the simulated expected net benefit significantly increases, as more probability mass is placed on longer market durations, increasing health benefits, compared to the exponential distribution (Figure 2.11). If CV$= 2$, more mass is placed on shorter market durations,

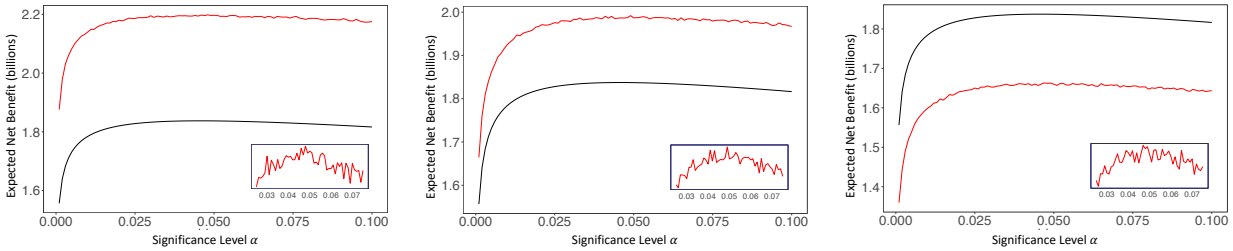
Figure 2.10: Expected net benefit from simulation (red line) and base model (black line) for relaxation of uniform drug class distribution assumption.



The inset plot shows the simulated expected net benefit function for $\alpha = 2.5\%$ to $\alpha = 7.5\%$.

leading to fewer health benefits. The preferred significance levels based on these simulations fall between $\alpha = 4.7\%$ and $\alpha = 4.9\%$, relatively close to the optimal policy for breast cancer, $\alpha^* = 4.6\%$.

Figure 2.11: Expected net benefit from simulation (red line) and base model (black line) for lognormally distributed time on market with CV= 0.5 (left), CV= 1 (middle), and CV= 2 (right).



The inset plots show the simulated expected net benefit function for $\alpha = 2.5\%$ to $\alpha = 7.5\%$.

2.6 Discussion

Our queueing framework presents a novel scheme for analyzing a disease-specific FDA-approval policy, accounting for both the pre-review drug development process and post-approval market characteristics. Our model considers three drivers of the shortfall of therapies available to treat some diseases: (i) lack of innovation in new drug formulation (i.e., a low *arrival rate*), (ii) lengthy clinical trials (i.e., a low *service rate*), and (iii) frequent attrition during development (i.e., a high *abandonment rate*). Over the years, the FDA has introduced multiple expedited programs designed

to spur R&D. Our approach could help evaluate their relative health benefits and monetary value and identify the program(s) best suited to a particular disease to offer the largest societal benefit.

Disease-specific drug approval policies offer a fundamentally different way of addressing imbalances in the number of treatments available to patients. For example, the FDA's *Orphan Drug Designation* aims to increase the research funding allotted to rare diseases by providing incentives, such as tax credits for clinical trials, to companies developing treatments for these conditions. Another way to address low research intensity is to ease approval standards for diseases with few drugs in the early stages of development (i.e., a low clinical trial arrival rate). This approach could potentially encourage pharmaceutical companies to reduce investment in diseases with many competitor drugs and instead focus R&D efforts on therapies more likely to gain approval.

Our work relates to Montazerhodjat et al. (2017), who use Bayesian Decision Analysis to find the significance levels that minimize the expected type I and type II error costs for oncology drugs. They find an optimal level of 17.6% for breast cancer—seven times higher than the traditional 2.5%. In contrast, our model recommends a significance level of 4.6% for breast cancer. One driver of these contrasting results relates to how the post-approval market is modeled. We use an $M/M/\infty$ queue to model ineffective drugs and, in an attempt to incorporate obsolescence, we model effective drugs with a collection of K $M/M/1/1$ queues. As a result, our model captures the diminishing returns of approving additional drugs, and thus recommends stricter approval standards.While our work accounts for obsolescence within each drug class, Montazerhodjat et al. (2017) ignore these effects and model effective and ineffective drugs identically, resulting in more lenient approval policies. Furthermore, the authors focus solely on the health costs of approval decisions, while we additionally consider the monetary gains or losses, based on stock price movements of the sponsoring pharmaceutical company, following news of a new drug approval, rejection, or withdrawal.

We focus our analysis on FDA drug approval, but our framework could readily apply to other

settings. Drugs developed in the U.S. and Europe both undergo clinical trial testing, but the review and approval processes differ substantially. All drugs in the U.S. undergo centralized review by the FDA, whereas in Europe, there are four possible paths to approval: a centralized process overseen by the European Medicines Agency, application to the regulatory body of a single European Union (EU) state, application for approval in all EU states following approval in one state, and independent application in multiple EU states (Van Norman, 2016). Our queueing framework could analyze the trade-offs of different approval pathways and to compare the European and U.S. systems.

2.6.1 Limitations

Drug efficacy is based on a single quantitative endpoint arising from a balanced, two-arm randomized clinical trial. Modern trial designs are often unbalanced, have more than two arms, and involve multiple endpoints. Our model could be easily adapted for unbalanced trials, but incorporating multiple arms and endpoints would require a more sophisticated hypothesis testing framework and queueing model (e.g., incorporating Bonferroni adjustment of the Type I error for multiple endpoints). Breast cancer trials, for example, often measure tumor size and time until recurrence, and establishing drug efficacy from these multiple endpoints requires multi-criteria decision-making (FDA 2017e). Such disease-specific complexity could render our model analytically intractable.

We make several simplifying assumptions regarding FDA decision-making. Qualitative aspects, such as concerns over trial design or manufacturing capacity, are ignored. We do not consider that the FDA may ask a firm to revise and resubmit an NDA, which occurs in 30% of reviews (Downing et al., 2014). We assume that NDA filing and FDA review occur immediately; in reality, these reviews last six to ten months, on average. Finally, we make several assumptions when computing expected net benefit: all queues are in steady state, the number of drug classes K is fixed, and clinical trial attrition rates are equal across drug classes.

Employing more complex queueing methodology may provide a more realistic model, but would likely sacrifice our analytical insights—how specific aspects of drug development affect the optimal approval policy—that we gain from a more parsimonious model. Simulation results suggest that our queueing model is relatively robust to several assumptions. A simple model that captures the key elements of drug development and post-approval market is more interpretable to decision-makers than a complex model that obscures the rationale behind the optimal approval policy.

2.6.2 Future Work

One natural extension of our approach is to analyze the drug development process using a game theoretic model with two players: the FDA selects the significance level α, and a pharmaceutical company selects the clinical trial size n. Conditions under which a firm should not invest in clinical trials to assess drug efficacy (i.e., $n = 0$), or when they should conduct additional trials after an NDA rejection, could be explored. A multi-firm model with competitive (e.g., innovation races) or cooperative (e.g., clinical trial cost-sharing and joint marketing) players could also be analyzed.

2.6.3 Conclusions

Faced with regulating thousands of drugs in a nation where millions are newly afflicted with severe diseases, the FDA must find the correct balance between ensuring the safety and effectiveness of drugs while spurring development of novel therapeutics and bringing life-saving products to market in a timely manner. Our study offers a transparent, quantitative framework that can provide the FDA with insights regarding how disease severity, prevalence, and other characteristics of the drug development process and existing market could change approval standards. Such a model could augment the complex decision-making and statistical analyses conducted by the FDA, providing a more customized approach to policy-making.

Appendices

Appendix A Flexible FDA Approval Policies

A.1 Proofs

We suppress the dependence of various terms on α for readability and only explicitly note it when needed for clarity. For all derivatives, the variable of differentiation is α unless otherwise specified.

Proof of Theorem 1: To show that $V(\alpha)$ is concave in α, we argue that $Q_E\mathbb{E}[N_E(\alpha)]$, $-Q_I\psi_I(\alpha)$, $C_{AE}\lambda_{AE}(\alpha)$, $-C_{AI}\lambda_{AI}(\alpha)$, and $-C_{RE}\lambda_{RE}(\alpha)$ are all concave functions of α, and thus the sum of concave functions is concave. Direct computation shows that $\mathbb{E}[N_E(\alpha)]$ is concave increasing in $\psi_E(\alpha)$ and that $\psi_E(\alpha)$ is concave in α. Thus $\mathbb{E}[N_E(\alpha)]$ is concave. Establishing concavity of the remaining terms is similarly straightforward. We note that in the case that $\alpha > 0$, $-C_{AI}\psi_{AI}(\alpha)$ and $-C_{RE}\lambda_{RE}(\alpha)$ are strictly concave in α and thus so is $V(\alpha)$. ■

Proof of Proposition 1: By the Implicit Function Theorem, we have that

$$\frac{\partial \alpha^*}{\partial x} = -\frac{\frac{\partial V'(\alpha^*)}{\partial x}}{\frac{\partial V'(\alpha^*)}{\partial \alpha}} \tag{A.1}$$

where x is the parameter of interest. The fact that $V(\alpha)$ is concave in α means the denominator is negative and thus the sign of $\frac{\partial \alpha^*}{\partial x}$ is given by the sign of $\frac{\partial V'(\alpha^*)}{\partial x}$. We use the equation

$$\begin{aligned} V'(\alpha) &= \left(Q_E \frac{\partial \mathbb{E}[N_E(\alpha)]}{\partial \psi_E}\frac{\partial \psi_E(\alpha)}{\partial \alpha} - Q_I \frac{\partial \mathbb{E}[N_I(\alpha)]}{\partial \psi_I}\frac{\partial \psi_I(\alpha)}{\partial \alpha}\right) WTP \\ &+ \left(C_{AE}\frac{\partial \lambda_{AE}(\alpha)}{\partial \alpha} - C_{AI}\frac{\partial \lambda_{AI}(\alpha)}{\partial \alpha} - C_{RE}\frac{\partial \lambda_{RE}(\alpha)}{\partial \alpha}\right) \end{aligned} \tag{A.2}$$

to find the sign of the effect of each parameter on α^*:

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial Q_E}\right) = \operatorname{sgn}\left(\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E}\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\right) \geq 0 \tag{A.3}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial Q_I}\right) = \operatorname{sgn}\left(-\frac{\partial \mathbb{E}[N_I(\alpha^*)]}{\partial \psi_I}\frac{\partial \psi_I(\alpha^*)}{\partial \alpha}\right) \leq 0 \tag{A.4}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial C_{AE}}\right) = \operatorname{sgn}\left(\frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha}\right) \geq 0 \tag{A.5}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial C_{AI}}\right) = \operatorname{sgn}\left(-\frac{\partial \lambda_{AI}(\alpha^*)}{\partial \alpha}\right) \leq 0 \tag{A.6}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial C_{RE}}\right) = \operatorname{sgn}\left(-\frac{\partial \lambda_{RE}(\alpha^*)}{\partial \alpha}\right) \geq 0 \tag{A.7}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \mu_I}\right) = \operatorname{sgn}\left(-Q_I\frac{\partial^2 \psi_I(\alpha^*)}{\partial \alpha \partial \mu_I}\right) \geq 0 \tag{A.8}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \tilde{\lambda}}\right) = \operatorname{sgn}\left(\text{WTP}\cdot Q_E\left(\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E}\frac{\partial^2 \psi_E(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} + \frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E^2}\frac{\partial \psi_E(\alpha^*)}{\partial \tilde{\lambda}}\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\right)\right. \tag{A.9}$$
$$\left. -\text{WTP}\cdot Q_I\frac{\partial^2 \psi_I(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} + C_{AE}\frac{\partial^2 \lambda_{AE}(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} - C_{AI}\frac{\partial^2 \lambda_{AI}(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} - C_{RE}\frac{\partial^2 \lambda_{RE}(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}}\right)$$

Multiplying both sides by $\tilde{\lambda} > 0$ (which does not change the sign) gives

$$\begin{aligned}\operatorname{sgn}\left(\tilde{\lambda}\frac{\partial \alpha^*}{\partial \tilde{\lambda}}\right) &= \operatorname{sgn}\left(\text{WTP}\cdot Q_E\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E}\frac{\partial \psi_E(\alpha^*)}{\partial \alpha} - \text{WTP}\cdot Q_I\frac{\partial \psi_I(\alpha^*)}{\partial \alpha} + C_{AE}\frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha}\right. \qquad \text{(A.10)}\\ &\quad \left. -C_{AI}\frac{\partial \lambda_{AI}(\alpha^*)}{\partial \alpha} - C_{RE}\frac{\partial \lambda_{RE}(\alpha^*)}{\partial \alpha} + \text{WTP}\cdot Q_E\frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E^2}\psi_E(\alpha^*)\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\right)\\ &= \operatorname{sgn}\left(\text{WTP}\cdot Q_E\frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E^2}\psi_E(\alpha^*)\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\right) \leq 0 \qquad \text{(A.11)}\end{aligned}$$

The second equality is due to the first order condition for α^*. The sign of the last expression is negative due to the concavity of $\mathbb{E}[N_E]$ with respect to ψ_E and the fact that ψ_E is increasing in α.

We claim that $\frac{\partial \alpha^*}{\partial \mu_E}$ and $\frac{\partial \alpha^*}{\partial p}$ are non-monotonic and that $\psi_E(\alpha^*) < 1$ is a sufficient condition to ensure that $\frac{\partial \alpha^*}{\partial \mu_E} \leq 0$ and $\frac{\partial \alpha^*}{\partial p} \geq 0$. The proof of this is given by straightforward differentiation:

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \mu_E}\right) = \operatorname{sgn}\left(-\frac{\tilde{\lambda}}{\mu_E^2}pe^{\Phi^{-1}(1-\alpha^*)\delta\sqrt{I_n}-\frac{\delta^2 I_n}{2}}\left(\frac{1-\psi_E(\alpha^*)}{(1+\psi_E(\alpha^*))^3}\right)\right) \tag{A.12}$$

$$\begin{aligned}\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial p}\right) = \operatorname{sgn}\left(\tilde{\lambda}e^{\Phi^{-1}(1-\alpha^*)\delta\sqrt{I_n}-\frac{\delta^2 I_n}{2}}\left(\text{WTP}\cdot Q_E\left(1-\psi_E(\alpha^*)\right) + C_{AE} + C_{RE}\right)\right. \qquad \text{(A.13)}\\ \left. +\text{WTP}\cdot Q_I\frac{\tilde{\lambda}}{\mu_I} + C_{AI}\tilde{\lambda}\right)\end{aligned}$$

The condition $\psi_E(\alpha^*) < 1$ is sufficient to guarantee that $\frac{\partial \alpha^*}{\partial \mu_E} \leq 0$ and $\frac{\partial \alpha^*}{\partial p} \geq 0$. ■

Proof of Proposition 2: We begin by demonstrating that $\alpha_1^* \leq \alpha_2^* \leq \cdots \leq \alpha_K^*$. To do this, we show that $V_K'(\alpha_{K+1}^*) \leq 0$ for any $K \geq 1$. The concavity of $V_K(\alpha)$ will imply the desired

inequality. Consider the following expression, where the notation $\mathbb{E}[N_E^K]$ and ψ_E^K is used to denote the expected number of effective drugs when there are K drug classes and the traffic intensity for each class, respectively:

$$V_K'(\alpha_{K+1}^*) - V_{K+1}'(\alpha_{K+1}^*) = WTP \cdot Q_E \left(\frac{\partial \mathbb{E}[N_E^K(\alpha_{K+1}^*)]}{\partial \psi_E^K} \frac{\partial \psi_E^K}{\partial \alpha} - \frac{\partial \mathbb{E}[N_E^{K+1}(\alpha_{K+1}^*)]}{\partial \psi_E^{K+1}} \frac{\partial \psi_E^{K+1}}{\partial \alpha} \right) \quad \text{(A.14)}$$

$$= -\frac{Q_E}{\mu_E} \frac{\partial \lambda_{AE}}{\partial \alpha} \frac{WTP}{(1+\psi_E^K)^2(1+\psi_E^{K+1})^2} \left(\frac{2\psi_E^K}{K+1} + \frac{(\psi_E^K)^2(2K+1)}{(K+1)^2} \right) \quad \text{(A.15)}$$

From the optimality of α_{K+1}^*, we know that $V_{K+1}'(\alpha_{K+1}^*) = 0$, and thus noting that (A.15) is negative gives $V_K'(\alpha_{K+1}^*) \leq 0$. As this holds for any K, we obtain the desired result. Consider a system in which $K = 0$. Applying the same argument as above gives

$$V_0'(\alpha_1^*) - V_1'(\alpha_1^*) = -WTP \cdot \frac{Q_E}{\mu_E} \frac{\partial \lambda_{AE}}{\partial \alpha} \frac{1}{(1+\psi_E^1)^2} \quad \text{(A.16)}$$

Noting that this expression is negative and that V_0' is concave in α, we see that

$$\alpha_0^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}} \log\left(\frac{1-p}{p} \frac{C_{AI} + WTP \cdot Q_I/\mu_I}{C_{RE} + C_{AE}} \right) + \frac{\delta\sqrt{I_n}}{2} \right) \leq \alpha_1^* \quad \text{(A.17)}$$

where α_0^* is found by solving $V_0'(\alpha) = 0$. Next, consider a system in which $K = \infty$. We demonstrate that $\alpha_K^* \leq \alpha_\infty^*$. Note that $\mathbb{E}[N_E^K] = \frac{K\lambda_{AE}}{K\mu_E + \lambda_{AE}}$, and thus taking the limit of this expression as K goes to infinity gives $\mathbb{E}[N_E^\infty] = \frac{\lambda_{AE}}{\mu_E}$. Once again, we use the concavity of $V_K(\alpha)$ to establish the result. Consider the following expression:

$$V_K'(\alpha_\infty^*) - V_\infty'(\alpha_\infty^*) = WTP \cdot Q_E \left(\frac{\partial \mathbb{E}[N_E^K(\alpha_\infty^*)]}{\partial \psi_E^K} \frac{\partial \psi_E^K}{\partial \alpha} - \frac{\partial \mathbb{E}[N_E^\infty(\alpha_\infty^*)]}{\partial \alpha} \right) \quad \text{(A.18)}$$

$$= -WTP \cdot \frac{Q_E}{\mu_E} \frac{\lambda_{AE}}{\partial \alpha} \left(2\psi_E^K + (\psi_E^K)^2 \right) \quad \text{(A.19)}$$

By the optimality of α_∞^*, we have that $V_\infty'(\alpha_\infty^*) = 0$, and thus $V_K'(\alpha_\infty^*) \leq 0$. As a result, we have

$$\alpha_K^* \leq \alpha_\infty^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}} \log\left(\frac{1-p}{p} \frac{C_{AI} + WTP \cdot Q_I/\mu_I}{WTP \cdot Q_E/\mu_E + C_{RE} + C_{AE}} \right) + \frac{\delta\sqrt{I_n}}{2} \right) \quad \text{(A.20)}$$

where α_∞^* can be found by solving $V_\infty'(\alpha) = 0$. ■

Proof of Proposition 3: We begin by demonstrating that $V_K(\alpha_K^*) \leq V_{K+1}(\alpha_{K+1}^*)$, which first involves showing $V_K(\alpha) \leq V_{K+1}(\alpha)$ for all α. The following calculation shows that this is the case:

$$V_K(\alpha) - V_{K+1}(\alpha) = WTP \cdot Q_E \left(\frac{K\lambda_{AE}}{K\mu_E + \lambda_{AE}} - \frac{(K+1)\lambda_{AE}}{(K+1)\mu_E + \lambda_{AE}} \right) \quad (A.21)$$

$$= \frac{-WTP \cdot Q_E \cdot \lambda_{AE}^2}{(K\mu_E + \lambda_{AE})((K+1)\mu_E + \lambda_{AE})} \quad (A.22)$$

The series of inequalities $V_K(\alpha_K^*) \leq V_{K+1}(\alpha_K^*) \leq V_{K+1}(\alpha_{K+1}^*)$ completes this demonstration.

Next, we show that $V_K(\alpha_K^*) \leq V_\infty(\alpha_\infty^*)$. To do this, we first show that $V_K(\alpha) \leq V_\infty(\alpha)$ for all α as follows:

$$V_K(\alpha) - V_\infty(\alpha) = WTP \cdot Q_E \left(\frac{K\lambda_{AE}}{K\mu_E + \lambda_{AE}} - \frac{\lambda_{AE}}{\mu_E} \right) \quad (A.23)$$

$$= -\frac{WTP \cdot Q_E \cdot \lambda_{AE}^2}{\mu_E(K\mu_E + \lambda_{AE})} \quad (A.24)$$

The remainder of the proof follows from the series of inequalities $V_K(\alpha_K^*) \leq V_\infty(\alpha_K^*) \leq V_\infty(\alpha_\infty^*)$.

Next, we show $V_{K+1}(\alpha) - V_K(\alpha) > V_{K+2}(\alpha) - V_{K+1}(\alpha)$ by direct computation:

$$V_{K+1}(\alpha) - V_K(\alpha) - (V_{K+2}(\alpha) - V_{K+1}(\alpha)) \quad (A.25)$$

$$= WTP \cdot Q_E \left[\left(\frac{(K+1)\lambda_{AE}}{(K+1)\mu_E + \lambda_{AE}} - \frac{K\lambda_{AE}}{K\mu_E + \lambda_{AE}} \right) - \left(\frac{(K+2)\lambda_{AE}}{(K+2)\mu_E + \lambda_{AE}} - \frac{(K+1)\lambda_{AE}}{(K+1)\mu_E + \lambda_{AE}} \right) \right]$$

$$= \frac{2 \cdot WTP \cdot Q_E \cdot \mu_E}{((K+1)\mu_E + \lambda_{AE})\,((K+2)\mu_E + \lambda_{AE})\,(K\mu_E + \lambda_{AE})} \quad \blacksquare \quad (A.26)$$

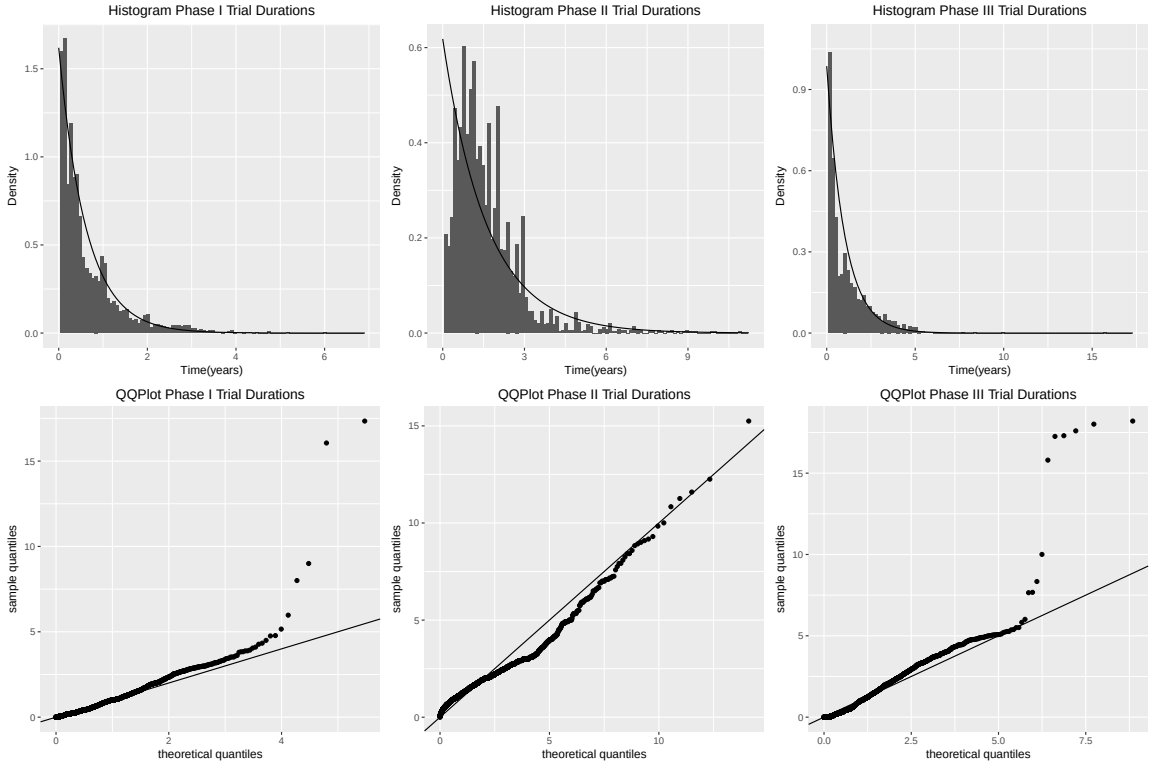
A.2 Exponential Assumptions

In order to test the assumption that the duration of clinical trials is exponentially distributed, we downloaded 10,000 (the maximum permitted) phase I, phase II, and phase III clinical trial records from clinicaltrials.gov with trial start dates from January 2000 to September 2018 (clinical trial registration was not required before 2000). To ensure that we had a large enough sample size for our analysis, we examined data for trials targeting any condition rather than limiting ourselves to the three diseases studied in the paper. Using maximum likelihood estimation, we estimate exponential distribution parameters for each phase of clinical trials. Figure A.1 shows histograms and qqplots of the duration of trials in each phase of clinical trials. Note that the curve shown in

each histogram is the density of the estimated exponential distribution.

Figure A.1 shows that the distribution of clinical trial durations in each phase is unimodal and right skewed. Examining the qqplots, we see that our data fits an exponential distribution well for trials with short durations, but the data has some trials with longer durations than predicted. For phase I, these are trials that last more than 3 years, while for phase III, these are trials whose durations exceed 6 years. However, as these trials constitute 4.6% and 1.6% of the phase I and phase III data, respectively, we believe that the exponential distribution is a reasonable model for clinical trial duration.

Figure A.1: Histograms and qqplots of the duration of phase I, phase II, and phase III clinical trials.



A.3 Parameter Estimation

Clinical trial parameters. For each of the diseases (breast cancer, HIV, and hypertension), we perform an Advanced Search on clinicaltrials.gov with the following field settings: Search Terms:

(insert disease here); Study Type: Interventional Studies; Conditions: (insert disease here) ; Interventions: Drug. All other field settings were left blank. After downloading the data that resulted from this search, we remove trials that met the following exclusion criterion: (i) Non-drug intervention (Behavioral, Biological, Device, Dietary Supplement, Other, Procedure, Genetic, Radiation), (ii) Conditions other than the disease of interest, (iii) Enrollment = 0 or NULL, (iv) Study Completion Date or Study Start Date NULL, (v) Duration of study = 0 or NULL, (vi) Study Start Date before January 2000 or Study Completion Date after January 2017, (vii) Title or Condition fields do not indicate relevance of the trial to the disease of interest, (viii) Drug listed in intervention was not related to treating the disease of interest. Using the trial data that remain after imposing exclusion criterion (i)-(viii), we estimate the following parameters.

- **Rate of clinical trial completion.** Let D_i denote the mean duration of Phase i trials, where i =I,II,III. We estimate $1/\mu_{CT}$ as $D_{\text{I}} + D_{\text{II}} + D_{\text{III}}$.

- **Rate of abandonment.** Recall that the probability of a drug completing clinical trials is given by

$$\mathbb{P}(\text{complete clinical trials}) = \frac{\mu_{CT}}{\mu_{CT} + \mu_{AB}} \tag{A.27}$$

  For each drug intervention in our data, we define a binary variable `Completed Phase III` to be one if there is a Phase III or Phase IV trial associated with that intervention, and zero otherwise. Our estimate of the probability of completing clinical trials is the mean of `Completed Phase III`. Given our estimates of μ_{CT} and $\mathbb{P}$(complete clinical trials), we use equation A.27 to solve for our estimate of μ_{AB}.

- **Rate of clinical trial initiation and NDA submission.** In order to estimate the NDA submission rate λ and clinical trial initiation rate $\tilde{\lambda}$, we first note that the rate $\lambda_{AE} + \lambda_{AI}$ at which drugs are approved is the product of the rate at which NDAs are submitted $\tilde{\lambda}$ and the

probability that a submitted NDA is approved, $\mathbb{P}$(Approve NDA). We estimate the average rate $\lambda_{AE} + \lambda_{AI}$ at which drugs were historically approved using exhaustive lists of drugs approved to treat a disease (Tables A.2 - A.4), and we use estimates for $\mathbb{P}$(Approve NDA) from Thomas et al. (2016). Using our estimates of $\lambda_{AE} + \lambda_{AI}$ and $\mathbb{P}$(Approve NDA), we obtain our estimate of $\tilde{\lambda}$ as $\tilde{\lambda} = (\lambda_{AE} + \lambda_{AI})/\mathbb{P}$(Approve NDA). The rate at which drugs begin clinical trials λ is then estimated as $\lambda = \tilde{\lambda}/\mathbb{P}$(Complete clinical trials).

- **Clinical trial information.** The clinical trial information $\delta\sqrt{I_n}$ is estimated by assuming the statistical power of the trial—the probability of approving a drug conditional on the drug being effective (given by π_{AE}/p)—is 90%, given a traditional statistical significance level of $\alpha = 2.5\%$. Mathematically, our estimate $\delta\sqrt{I_n}$ is chosen to satisfy $.90 = 1 - \Phi\left(\Phi^{-1}(1 - 0.025) - \delta\sqrt{I_n}\right)$.

- **Effectiveness probability.** To estimate the prior probability p that a drug is effective, we select the value of p that makes the probability of approving a drug in our model equal to the estimated probability that an NDA is approved, assuming $\alpha = 2.5\%$. Thus our estimate p satisfies $\mathbb{P}(\text{Approve NDA}) = \pi_{AE}(\alpha) + \pi_{AI}(\alpha) = \left[1 - \Phi\left(\Phi^{-1}(1 - 0.025) - \delta\sqrt{I_n}\right)\right] p + (1 - 0.025)p$.

Monetary Values. To estimate C_{AE}, C_{AI}, and C_{RE}, we multiply the median pharmaceutical market capitalization $Market\ Cap$ by the percent change in market capitalization as a result of approving effective, approving ineffective, and rejecting effective drugs, respectively. We use published estimates from Sarkar and de Jong (2006) and Ahmed et al. (2002) of percent abnormal market returns at the time of initial review $r_{initial}$, the time a drug is announced as approvable $r_{approvable}$, the approval announcement day $r_{approval\ day}$ (or the rejection announcement day $r_{rejection}$), the day after the approval announcement $r_{day\ after\ approval}$, and following market with-

drawal $r_{withdrawal}$. We combine these values with the median pharmaceutical market capitalization to obtain the following monetary value estimates:

$$C_{AE} = (r_{initial} + r_{approvable} + r_{approval\ day} + r_{day\ after\ approval}) \cdot Market\ Cap \quad (A.28)$$

$$C_{AI} = C_{AE} - (r_{withdrawal}) \cdot Market\ Cap \quad (A.29)$$

$$C_{RE} = (r_{initial} + r_{approvable} - r_{rejection}) \cdot Market\ Cap \cdot p. \quad (A.30)$$

Note that the probability p that a drug is effective appears in our estimate for C_{RE}, but not in our estimates for C_{AE} or C_{AI}. In the case of approved drugs, we assume that it is possible to distinguish the monetary value of effective and ineffective drugs using the market reaction to drug withdrawals. In the case of rejected drugs this differentiation is not possible, so instead we multiply the change in market capitalization by the probability that a drug is effective.

Table A.1: Drug classifications by disease.

Disease	**Drug Class**	**Source**
Breast cancer	Alkylating Agents	QLHC (2017), NCCN (2016)
	Anthracyclines	QLHC (2017), NCCN (2016)
	Anti-Estrogen Drugs	QLHC (2017), NCCN (2016)
	Aromatase Inhibitors	QLHC (2017), NCCN (2016)
	Combination Chemo	QLHC (2017), NCCN (2016)
	Ovarian Suppression	QLHC (2017), NCCN (2016)
	Platinum Drugs	QLHC (2017)
	Targeted Biological Therapy (HER-2)	QLHC (2017), NCCN (2016)
	Taxanes	QLHC (2017)
	Vinca Agents	QLHC (2017)
HIV	Combination Therapy	DHHS (2016)
	Integrase Inhibitors	WHO (2016)
	Non-Nucleoside Reverse Transcriptase Inhibitors	WHO (2016)
	Nucleoside Reverse Transcriptase Inhibitors	WHO (2016)
	Pharmacokinetic Enhancers	DHHS (2016)
	Protease Inhibitors	WHO (2016)
Hypertension	Angiotensin Converting Enzyme (ACE) Inhibitors	AHRQ (2011)
	Angiotensin II Receptor Blockers (ARB)	AHRQ (2011)
	Antiadrenergics	AHRQ (2011)
	Beta Blockers	AHRQ (2011)
	Calcium Channel Blockers	AHRQ (2011)
	Combination Products	AHRQ (2011)
	Diuretics	AHRQ (2011)
	Other Renin-Angiotensin System Antagonists	AHRQ (2011)
	Vasodilators	AHRQ (2011)

Sources: Quantum Leap Healthcare Collaborative (2018); National Comprehensive Cancer Network (2016); Department of Health and Human Services (2016); World Health Organization (2016); Agency for Healthcare Research and Quality (Townsend et al., 2011).

Table A.2: FDA-approved breast cancer drugs.

Drug (Brand Name)	Approval	Drug Class
Thiotepa (Tepadina)	March 1959	Alkylating Agents
Cyclophosphamide (Cytoxan)	May 2008	
Methotrexate (Trexall)	Aug 1959	Other Chemotherapy
Vinblastine (Velban)	Aug 1987	
Vincristine (Oncovin)	Apr 1988	
Fluorouracil 5-FU (Adrucil)	Aug 1991	
Gemcitabine (Gemzar)	May 1996	
Irinotecan (Camptosar)	Jun 1996	
Capecitabine (Xeloda)	Apr 1998	
Temozolomide (Temodar)	Aug 1999	
Ixabepilone (Ixempra)	Oct 2007	
Eribulin (Halaven)	Nov 2010	
Topotecan (Hycamtin)	Dec 2010	
Megestrol Acetate (Megace)	Aug 1971	Other Hormone Therapy
Cisplatin (Platinol)	Dec 1978	Platinum Drugs
Carboplatin (Paraplatin)	Mar 1989	
Goserelin (Zoladex)	Dec 1989	Ovarian Suppression
Leuprolide (Lupron)	Apr 1993	
Abarelix (Plenaxis)	Nov 2003	
Buserelin (Suprefact)	N/A	
Paclitaxel (Taxol)	Dec 1992	Taxanes
Docetaxel (Taxotere)	May 1996	
Paclitaxel (Abraxane)	Jan 2005	
Vinorelbine (Navelbine)	Dec 1994	Vinca Agents
Toremifine (Fareston)	May 1997	Anti-Estrogen Drugs
Tamoxifen (Nolvadex)	Feb 2003	
Raloxifene (Evista)	Dec 1997	
Fulvestrant (Faslodex)	Apr 2002	
Trastuzumab (Herceptin)	Sep 1998	Targeted Biologics
Bevacizumab (Avastin)	Feb 2004	
Everolimus (Afinitor)	Mar 2009	
Pertuzumab (Perjeta)	Jun 2012	
Ado-trastuzumab emtansine (Kadcyla)	Feb 2013	
Palbociclib (Ibrance)	Feb 2015	
Tykerb (Lapatinib)	Sep 2015	
Ribociclib (Kisqali)	Mar 2017	
Neratinib maleate (Nerlynx)	July 2017	
Abemaciclib (Verzenio)	Sep 2017	Targeted Biologics
Olaparib (Lynparza)	Jan 2018	(Continued)
Zoledronate (Zometa)	Aug 2001	Biphosphonate Therapy
Pamidronate (Aredia)	May 2002	
Alendronate (Fosamex)	Feb 2008	
Denosumab (Xgeva)	Jun 2010	
Ibandronate (Boniva)	Apr 2012	
Risedronate (Actonel)	Jun 2014	
Doxorubicin (Adriamycin)	Dec 1987	Anthracyclines
Mitoxantrone (Novantrone)	Apr 2006	
Epirubicin (Ellence)	Sep 2008	
Liposomal Doxorubicin (Doxil)	Feb 2013	
Anastrozole (Arimidex)	Jun 2010	Aromatase Inhibitors
Exemestane (Aromasin)	Apr 2011	
Letrozole (Femara)	Jun 2011	
Docetaxel & Cyclophosphamide	N/A	Combination Chemotherapy
Docetaxel, Doxorubicin & Cyclophosphamide	N/A	
Docetaxel & Carboplatin	N/A	
Paclitaxel & Capecitabine	N/A	
Docetaxel & Capecitabine	N/A	
Docetaxel & Carboplatin	N/A	
Paclitaxel & Carboplatin	N/A	
Paclitaxel & Capecitabine	N/A	
Paclitaxel & Carboplatin	N/A	
Irinotecan & Temozolomide	N/A	
Gemcitabine & Carboplatin	N/A	
Ixabepilone & Capecitabine	N/A	

Sources: National Cancer Institute (2018b); FDA (2018e)

Table A.2: FDA-approved breast cancer drugs (continued).

Drug (Brand Name)	Approval	Drug Class
Doxorubicin & Cyclophosphamide	N/A	Combination Chemotherapy
Doxorubicin, Cyclophosphamide & Paclitaxel	N/A	(Continued)
Doxorubicin, Cyclophosphamide & Docetaxel	N/A	
Epirubicin & Cyclophosphamide	N/A	
Cyclophosphamide, Doxorubicin, & Fluorouracil	N/A	
Cyclophosphamide, Methotrexate & 5-Flourouracil	N/A	
5-Flourouracil, Doxorubicin & Cyclophosphamide	N/A	
5-Flourouracil, Epirubicin & Cyclophosphamide	N/A	

Sources: National Cancer Institute (2018b); FDA (2018e)

Table A.3: FDA-approved HIV drugs.

Drug (Brand Name)	Approval	Drug Class
Zidovudine (Retrovir)	Mar 1987	Nucleoside
Didanosine (Videx)	Oct 1991	Reverse
Stavudine (Zerit)	Jun 1994	Transcriptase
Lamivudine (Epivir)	Nov 1995	Inhibitors
Abacavir (Ziagen)	Dec 1998	(NRTIs)
Didanosine (Videx EC)	Oct 2000	
Tenofovir Disoproxil Fumarate (Viread)	Oct 2001	
Emtricitabine (Emtriva)	Jul 2003	
Saquinavir (Invirase)	Dec 1995	Protease
Idinavir (Crixivan)	Mar 1996	Inhibitors
Ritonavir (Norvir)	Mar 1996	
Nelfinavir (Viracept)	Mar 1997	
Atazanavir (Reyataz)	Jun 2003	
Fosamprenavir (Lexiva)	Oct 2003	
Tipranavir (Aptivus)	Jun 2005	
Darunavir (Prezista)	Jun 2006	
Nevirapine (Viramune)	Jun 1996	Non-Nucleoside
Delavirdine (Rescriptor)	Apr 1997	Reverse
Efavirenz (Sustiva)	Sep 1998	Transcriptase
Etravirine (Intelence)	Jan 2008	Inhibitors
Nevirapine (Viramune XR)	Mar 2011	(NNRTIs)
Rilpivirine (Edurant)	May 2011	
Lamivudine & Zidovudine (Combivir)	Sep 1997	Combination
Lopinavir & Ritonavir (Kaletra)	Sep 2000	Medications
Abacavir, Lamivudine & Zidovudine (Trizivir)	Nov 2000	
Abacavir & Lamivudine (Epzicom)	Aug 2004	
Emtricitabine & Tenofovir Disoproxil Fumarate (Truvada)	Aug 2004	
Efavirenz, Emtricitabine & Tenofovir Disoproxil Fumarate (Atripla)	Jul 2006	
Emtricitabine, Rilpivirine & Tenofovir Disoproxil Fumarate (Complera)	Aug 2011	
Cobicistat, Elvitegravir, Emtricitabine & Tenofovir Disoproxil Fumarate (Stribild)	Aug 2012	
Abacavir, Dolutegravir & Lamivudine (Triumeq)	Aug 2014	
Atazanavir & Cobicistat (Evotaz)	Jan 2015	
Cobicistat & Darunavir (Prezcobix)	Jan 2015	
Cobicistat, Elvitegravir, Emtricitabine & Tenofovir Alafenamide Fumarate (Genvoya)	Nov 2015	
Emtricitabine, Rilpivirine & Tenofovir Alafenamide Fumarate (Odefsey)	Mar 2016	
Emtricitabine and Tenofovir Alafenamide (Descovy)	Apr 2017	
Dolutegravir & Rilpivirine (Juluca)	Nov 2017	
Bictegravir & Emtricitabine & Tenofovir & Alafenamide (Bictegravir)	Feb 2018	
Enfuvirtide (Fuzeon)	Mar 2003	Fusion Inhibitors
Maraviroc (Selzentry)	Aug 2007	Entry Inhibitors
Raltegravir (Isentress)	Oct 2007	Integrase
Dolutegravir (Tivicay)	Aug 2013	Inhibitors
Elvitegravir (Vitekta)	Sep 2014	
Cobicistat (Tybost)	Sep 2014	Pharmacokinetic Enhancers

Sources: AidsInfo (2018); FDA (2018b,e)

Table A.4: FDA-approved hypertension drugs.

Drug (Brand Name)	Approval	Drug Class
Reserpine (Raudixin)	Mar 1955	Antiadrenergic
Guanadrel (Hylorel)	Dec 1982	
Methyldopa (Aldomet)	Feb 1986	
Clonidine (Catapres)	Jul 1987	
Prazosin (Minipress)	Sep 1988	
Guanabenz	Apr 1995	
Phentolamine (Regitine)	Mar 1998	
Terazosin (Hytrin)	Mar 1998	
Doxazosin (Cardura)	Oct 2000	
Guanfacine (Tenex)	Oct 2012	
Phenoxybenzamine (Dibenzyline)	Jan 2017	
Guanethidine (Ismelin)	N/A	
Deserpidine (Harmonyl)	Apr 1957	Angiotensin Converting
Captopril (Capoten)	Feb 1996	Enzyme (ACE) Inhibitor
Enalapril (Vasotec)	Jan 2001	
Lisinopril (Prinivil)	Jul 2002	
Moexipril (Univasc)	May 2003	
Benazepril (Lotensin)	Feb 2004	
Fosinopril (Monopril)	May 2005	
Quinapril (Accupril)	Jun 2006	
Trandolapril (Mavik)	Jun 2007	
Ramipril (Altace)	Jun 2008	
Perindopril (Coversyl)	Nov 2009	
Amlodipine & Perindopril (Prestalia)	Jan 2015	
Chlorothiazide (Diuril)	Sep 1958	Diuretics
Polythiazide (Renese)	Sep 1961	
Hydrochlorothiazide (Microzide)	Jan 1973	
Furosemide (Lasix)	Oct 1981	
Methyclothiazide	Jun 1982	
Hydroflumethiazide (Saluron)	May 1985	
Amiloride (Midamor)	Jan 1986	
Spironolactone (Aldactone)	Jul 1986	
Triamterene-Hydrochlorothiazide (Dyazide)	Dec 1987	
Atenolol-Chlorthalidone (Tenoretic)	Jul 1992	
Indapamide (Lozol)	Jul 1995	
Bumetanide (Bumex)	Nov 1996	
Metolazone (Zaroxolyn)	Dec 2003	
Torsemide (Demadex)	May 2005	
Ethacrynic Acid (Edecrin)	Jul 2015	
Deserpidine-Methyclothiazide (Enduronyl)	Aug 1961	Combination Therapy
Reserpine-Polythiazide (Renese-R)	Oct 1963	
Reserpine-Chlorthalidone (Regroton)	May 1964	
Reserpine-Methyclothiazide (Diutensen-R)	Sep 1975	
Reserpine-Hydrochlorothiazide (Hydroserpine)	Jan 1977	
Hydralazine-Reserpine-Hydrochlorothiazide (Hydrap-ES)	Sep 1977	
Hydralazine-Hydrochlorothiazide (Apresazide)	Sep 1977	
Timolol-Hydrochlorothiazide (Timolide)	Dec 1981	
Reserpine-Chlorothiazide (Diupres)	May 1982	
Reserpine-Hydroflumethiazide	Mar 1983	
Reserpine-Trichlormethiazide	Apr 1983	
Methyldopa-Hydrochlorothiazide (Aldoril)	Feb 1987	
Propranolol-Hydrochlorothiazide (Inderide)	Apr 1987	
Spironolactone-Hydrochlorothiazide (Aldactazide)	Jul 1987	
Triamterene-Hydrochlorothiazide (Dyazide)	Dec 1987	
Clonidine-Chlorthalidone (Combipres)	Dec 1987	
Amiloride Hydrochlorothiazide (Moduretic)	May 1988	
Atenolol-Chlorthalidone (Tenoretic)	Jul 1992	
Enalapril-Diltiazem (Teczem)	Oct 1996	
Enalapril Felodipine (Lexxel)	Dec 1996	

Table A.4: FDA-approved hypertension drugs (continued).

Drug (Brand Name)	Approval	Drug Class
Captopril-Hydrochlorothiazide (Capozide)	Dec 1997	
Bisoprolol-Hydrochlorothiazide (Ziac)	Sep 2000	
Enalapril-Hydrochlorothiazide (Vaseretic)	Sep 2001	
Eprosartan-Hydrochlorothiazide (Teveten HCT)	Nov 2001	
Lisinopril-Hydrochlorothiazide (Zestoretic)	Jul 2002	
Benazepril-Hydrochlorothiazide (Lotensin HCT)	Feb 2004	
Metoprolol-Hydrochlorothiazide (Lopressor HCT)	Aug 2004	
Moexipril-Hydrochlorothiazide (Uniretic)	Mar 2007	
Nadolol-Bendroflumethiazide (Corzide)	Mar 2007	
Amlodipine-Benazepril (Lotrel)	May 2007	
Quinapril-Hydrochlorothiazide (Accuretic)	Aug 2007	
Aliskiren-Valsartan (Valturna)	Sep 2009	
Losartan-Hydrochlorothiazide (Hyzaar)	Oct 2010	
Aliskiren-Hydrochlorothiazide (Amturnide)	Dec 2010	
Telmisartan-Hydrochlorothiazide (Micardis)	Sep 2011	
Irbesartan-Hydrochlorothiazide (Avalide)	Sep 2012	
Valsartan-Hydrochlorothiazide (Diovan)	Sep 2012	
Candesartan-Hydrochlorothiazide (Atacand)	Dec 2012	
Amlodipine-Valsartan (Exforge)	Mar 2013	
Amlodipine-Atorvastatin (Caduet)	Nov 2013	
Amlodipine-Telmisartan (Twynsta)	Jan 2014	
Amlodipine-Valsartan-Hydrochlorothiazide (Exforge HCT)	Jun 2015	
Olmesartan-Hydrochlorothiazide (Benicar HCT)	Oct 2016	
Amlodipine-Olmesartan (Azor)	Nov 2016	
Deserpidine-Hydrochlorothiazide	N/A	
Guanethidine-Hydrochlorothiazide (Esimil)	N/A	
Methyldopa-Chlorothiazide (Aldoclor)	N/A	
Hydralazine (Apresoline)	Oct 1978	Vasodilators
Minoxidil	Jul 1999	
Mecamylamine (Inversine)	Mar 2013	
Propranolol (Inderal)	Nov 1985	Beta Blockers
Penbutolol (Levatol)	Dec 1987	
Atenolol (Tenormin)	Jan 1992	
Nadolol (Corgard)	Oct 1993	
Metoprolol (Lopressor)	Dec 1993	
Pindolol (Visken)	Jan 1994	
Acebutolol (Sectral)	Apr 1995	
Timolol (Betimol)	Mar 1997	
Labetalol (Trandate)	Aug 1998	
Betaxolol (Kerlone)	Oct 1999	
Carteolol (Ocupress)	Jan 2000	
Bisoprolol (Zebeta)	Jun 2001	
Esmolol (Brevibloc)	May 2005	
Carvedilol (Coreg)	Sep 2007	
Nebivolol (Bystolic)	Jul 2015	
Penbuterol	N/A	
Verapamil (Calan)	Jul 1992	Calcium Channel Blockers
Nicardipine (Cardene)	Dec 1996	
Diltiazem (Cardizem)	Dec 1999	
Isradipine (DynaCirc)	Apr 2006	
Amlodipine (Norvasc)	Jun 2007	
Felodipine (Plendil)	Apr 2008	
Nifedipine (Procardia)	Jun 2010	
Nisoldipine (Sular)	Jan 2011	
Aliskiren (Tekturna)	Mar 2007	Other Renin-Angiotensin
Eplerenone (Inspra)	Aug 2008	System Antagonists
Losartan (Cozaar)	Oct 2010	Angiotensin II Receptor
Eprosartan (Teveten)	Nov 2011	Blockers
Azilsartan and Chlorthalidone (Edarbyclor)	Dec 2011	
Irbesartan (Avapro)	Oct 2012	
Candesartan (Atacand)	Jan 2014	
Telmisartan (Micardis)	Jul 2014	
Valsartan (Diovan)	Jun 2015	
Nevivolol and Valsartan (Byvalson)	Jun 2016	
Amlodipine and Olmesartan (Olmesartan)	Oct 2016	

Sources: FDA (2018e)

Table A.5: List of FDA-approved drugs that were withdrawn from the market.

Disease	**Drug**	**Approval**	**Withdrawal**	**Time on Market**
Breast cancer	Avastin*	Feb 2004	Nov 2011	7.8 years
HIV	Hivid	Jun 1992	Dec 2006	14.5 years
Hypertension	Ticrynafen	May 1979	Jun 1982	2.7 years
Hypertension	Posicor	Jun 1997	Jun 1998	1.0 year
Hypertension	Valturna	Sep 2009	Jul 2012	2.8 years

* Avastin's indication for breast cancer was removed but the drug itself remained on the market.
Sources: Avastin - Drugsite Trust (2018a), Hivid - FDA (2018i), International Association of Providers of Aids Care (2017), Ticrynafen - Manier et al. (1982), Posicor - Bradbury (1998), Valturna - Drugsite Trust (2018b), FDA (2016b)

Chapter 3 Contracts to Increase the Efficacy and Availability of Vaccines

Abstract

Neglected Tropical Diseases (NTDs) affect 1 in 6 individuals worldwide and disproportionately occur in low and middle income countries. Existing funding mechanisms, such as Advance Market Commitments have failed to stimulate investment in these conditions and provide no incentive for companies to develop a vaccine that exceeds minimum efficacy standards imposed by the World Health Organization.

The leading NTDs – ascariasis, hookworm, and trichuriasis – affect 1.5 billion individuals, result in more than 3 million disability adjusted life years lost, and lead to nearly 5,000 deaths annually. Vaccines with high *efficacy* – the fraction of a vaccinated population who are immune from contracting the disease – reduce the number of people who are ultimately infected, and if sufficiently high, can eliminate the disease altogether in region. Vaccines can result in improved population health, but developing and administering a vaccine may be prohibitively costly. Two key players in vaccine markets are Global Health Organizations (GHOs), who procure vaccines for low and middle income countries, and profit-maximizing manufacturers who develop and produce vaccines. We develop a joint game-theoretic and epidemic model to study how different performance-based contracts (i.e., contracts that tie some portion of payment to the vaccine's resulting efficacy), might

simultaneously incentivize pharmaceutical firms to invest in vaccine R&D and GHOs to procure such vaccines, and the resultant effect on disease spread in a population. We consider two such contracts: (i) a lump sum contract in which manufacturers receive one per-unit price for exceeding the minimum efficacy standard and a different (possibly higher) price for a vaccine efficacious enough to eliminate the disease, and (ii) a contract in which the price is a linear function of vaccine efficacy.

Compared to wholesale price contracts, which can at best ensure a reduction in the number of cases, performance-based contracts are able to guarantee disease elimination. We formulate epidemic models and estimate parameters for two NTDs: Chagas, a vector-borne disease, and Ebola, which is spread via bodily fluids. The difference in the mode of transmission leads to epidemic models with fundamentally different structures. Our results indicate that, across a variety of cost scenarios, the use of a linear contract rather than a lump sum contract results in an average reduction in R&D and manufacturing costs of 7.5% and 11.3% while only increasing the per-unit price by 17.5% and 4.1% for Chagas and Ebola, respectively.

Performance-based contracting has been used to improve the overall quality of care in a variety of health care settings. Recent initiatives have demonstrated the benefits of outcome-based pricing for drugs, but currently there is no analogous proposal for vaccines. Our work highlights the potential for these contracts to reduce the burden of disease in the world's poorest countries.

3.1 Introduction

The control of infectious diseases using vaccines is widely considered to be one of the greatest public health achievements of the last two centuries (Centers for Disease Control and Prevention, 1999, 2011). Vaccination has eradicated smallpox worldwide, contained cases of polio to just three nations, and dramatically reduced annual cases of other deadly conditions such as measles and

tetanus (Kotar and Gessler, 2013; WHO, 2019a). Despite these successes, billions of individuals continue to contract infectious diseases, with the number of emerging outbreaks increasing in recent years. More than 1.6 billion individuals suffer from one or more neglected tropical diseases (NTDs), a group of 20 conditions identified by the World Health Organization (WHO) that occur primarily in low-income countries in sub-Saharan Africa, Asia, and Latin America (WHO, 2019b). The term "neglected" describes the disparity in funding for these conditions (a combined $2.9 billion in 2016) compared to the "big three" infectious diseases – HIV/AIDS, malaria, and tuberculosis ($11.7 billion, $5.7 billion, and $5.6 billion, respectively, in 2016), which collectively afflict 2.5 billion people worldwide (WHO, 2018e).

Global health organizations (GHOs) such as Gavi, the Vaccine Alliance or the United Nations Children's Fund (UNICEF) play a key role in facilitating disease control in low and middle income countries. These organizations purchase vaccines in bulk from manufacturers and then provide these vaccines to countries in an effort to reduce their disease burden. Furthermore, GHOs often

Table 3.1: Selected Neglected Tropical Diseases.

Disease	Prevalance	Annual Deaths	Annual DALYs*	Transmission Mode
Ascariasis	799 million	4,800	1.3 million	Parasitic worm
Hookworm	450 million	N/A	1.6 million	Parasitic worm
Trichuriasis	435 million	N/A	0.3 million	Parasitic worm
Schistosomiasis	189 million	10,000	1.8 million	Parasitic worm
Lymphatic Filariasis	29 million	N/A	1.2 million	Parasitic worm
River Blindness	14 million	N/A	0.9 million	Parasitic worm
Chagas Disease	7.2 million	7,000	0.2 million	Vector-borne
Dengue	6 million	37,000	2.9 million	Vector-borne
Leishmaniasis	4.8 million	13,000	0.9 million	Vector-borne
Trachoma	3.3 million	N/A	0.2 million	Bodily fluids
Leprosy	$<$ 1 million	N/A	0.03 million	Bodily fluids

Table 3.2: Source: Vos et al. (2016)
$*$ Disability Adjusted Life Years (DALYs) are a measure of overall disease burden which include the number of years lost due to impaired health, disability, or early death.
A value of N/A for annual deaths is used to indicate that death from this condition is rare and thus statistics on the number of deaths are unavailable.

procure and administer medications to treat infected individuals.

In this work, we develop a joint game-theoretic and epidemic model to study contractual issues between a vaccine manufacturer that invests in the development of a new vaccine for a NTD, and a GHO that seeks to procure the vaccine on behalf of low and middle income countries. Using this model, we analyze the impact of different payment contracts on the price and *efficacy* – the performance of the vaccine under ideal circumstances, such as those in controlled clinical trials – of the vaccine, as well as the resulting progression of the underlying epidemic.

Efforts to eradicate NTDs have largely focused on prevention via improvement of sanitation systems and control of the disease vector (e.g, parasitic worms, flies, or mosquitoes). While these strategies have proven successful for certain conditions (e.g., guinea worm cases dropped from 3.5 million in 1986 to just 30 in 2017) they have been less effective for others (e.g., cases of dengue fever have increased in the past 50 years, despite substantial efforts to control its spread) (Bowman et al., 2016; WHO, 2018b). Some progress has occurred in developing treatments for NTDs (e.g., Mectizan for the treatment of river blindness), and mass drug administration (MDA) programs have focused on providing these therapies to entire communities in affected countries. MDAs, however, face significant drawbacks, particularly when compared to immunization programs. Drug treatment does not provide individuals with immunity, meaning that MDA success is critically tied to community participation rates. If an infected individual chooses not to receive MDA, they can compromise the health of others by reintroducing the condition to other susceptible individuals. In contrast, vaccines provide individuals with some degree of protection against the disease, and, more importantly, contribute to *herd immunity*, a positive externality that confers some protection to unvaccinated individuals, as long as a critical vaccination threshold is attained. MDA also needs to be performed on an annual or semi-annual basis to the entire infected community, a significant logistical challenge, compared to vaccination, which is typically administered only once or twice

during an individual's lifetime (Cheah and White, 2016).

Despite the public health challenges of MDA programs, there are several reasons why developing a drug treatment may be a more attractive investment to pharmaceutical companies than a vaccine. Drugs earn profits over a lifetime of patient use and do not provide immunity to the disease, while vaccines are administered infrequently and make the overall population less vulnerable to future infection (Kremer and Snyder, 2003). Companies that invest in vaccine development often focus on infectious diseases, such as measles or human papillomavirus (HPV), with large markets in wealthy countries, allowing for recoupment of research and development (R&D) costs via *tiered pricing*, in which high-income countries are charged higher prices for the same product than low- and middle-income nations. NTDs have smaller markets that primarily exist in low- and middle-income countries, making these settings less attractive to vaccine developers.

In response to the dearth of investment in NTDs, governments and international organizations have proposed several policy initiatives to incentivize pharmaceutical companies to develop drugs and vaccines for these conditions. One such initiative is the AMC for pneumococcal vaccine. Launched in 2009, the AMC aims to eliminate demand uncertainty by guaranteeing the purchase of a given quantity from manufacturers at a high initial price of $7 per dose for a period of 10 years in exchange for guaranteed long-term supply at a lower price of $3.50 per dose (Gavi, the Vaccine Alliance, 2019b). While the pneumococcal vaccine does not target diseases classified as NTDs by the WHO (the vaccine targets bacteria that cause pneumonia and meningitis), it was selected in order to demonstrate the AMC's ability to incentivize the development and production of novel vaccines. However, the mechanism's potential for incentivizing new vaccine development is unclear because the participating manufacturers (GlaxoSmithKline and Pfizer) both committed to supply doses of each firm's *existing* pneumococcal vaccines (Gavi, the Vaccine Alliance, 2019a).

Another challenge with the AMC is that, by setting a price ceiling, it does not reward phar-

maceutical companies for developing superior products. The WHO defines a mandatory set of product attributes (including safety and efficacy) required of vaccines purchased by UNICEF and other GHOs, as described in each disease's *Target Product Profiles* (WHO, 2019c). Under the current funding mechanism, no incentive exists for companies to exert costly R&D effort to develop a more efficacious vaccine than a competitor, or as required by the WHO. High efficacy vaccines are desirable not only from a patient perspective, but also from a broader public health perspective. The higher the efficacy of a vaccine, the lower the *critical vaccination threshold*, or the minimum fraction of the population that needs to be vaccinated in order to achieve herd immunity. If herd immunity is established and maintained in a population for long enough, the disease can be *eliminated* — the number of cases falls to zero — in that region. *Eradication*, or the worldwide elimination of a disease, brings benefits including savings in healthcare costs, improved population health, and the ability to redirect resources towards the elimination of other diseases.

In this paper, we propose using performance-based contracts that explicitly link vaccine price and efficacy to incentivize the development of highly efficacious vaccines that facilitate disease elimination. Our contributions are as follows:

We develop a joint game-theoretic and epidemic model to study the impact of different payment contracts between the GHO and manufacturer on the spread of the disease. We incorporate R&D and manufacturing costs borne by the manufacturer and treatment/vaccine administration costs borne by the GHO in the case that (i) no vaccine that meets minimum efficacy standards is produced, (ii) a vaccine is produced that is efficacious enough to *mitigate* – reduce the number of cases– but not to eliminate, is produced, and (iii) a vaccine is produced that is efficacious enough to eliminate the disease. Our study, to the best of our knowledge, is the first to focus on uncertainty in efficacy in the context of vaccine development.

We analyze two different performance-based contracts in which a per-unit price is paid for a

vaccine, conditional on its realized efficacy: (i) a lump sum contract that offers one of two different per-unit prices depending on whether the vaccine is efficacious enough to mitigate or eliminate, and (ii) a contract where the payment is a linear function of vaccine efficacy. Our results indicate that performance-based contracts have two main advantages over wholesale price contracts. First, these contracts can lead to reduced R&D, manufacturing, and treatment/vaccine administration costs compared to a wholesale price contract. Second, performance-based contracts have the potential to achieve disease elimination, while a wholesale price contract can at best ensure mitigation.

We illustrate our joint game-theoretic and epidemic modeling approach for two NTDs: Chagas, a vector-borne disease found primarily in South and Central America, and Ebola, the majority of cases of which have occurred in west Africa. We use numerical estimates for each parameter, where available, and vary others over plausible ranges and compute the optimal per-unit price and efficacy for the lump sum and linear contracts. Our results show that, across a variety of cost scenarios, the use of a linear contract leads to an average reduction in non-procurement costs of 7.5% for Chagas and 11.33% for Ebola. Furthermore, we find that, while vaccines purchased under the linear contract are more expensive per-unit, these additional costs are moderate and translate to a price increase of 17.5% per unit for Chagas and 4.1% for Ebola.

3.2 Related Literature

Epidemic Modeling and Vaccination. Infectious disease modeling has been widely used to study how a disease spreads, predict the trajectory of an outbreak (i.e., the total number of infected individuals or the duration of the epidemic), to evaluate the effectiveness of different public health interventions (e.g., quarantine, vaccination, treatment) and to optimize resource allocation for epidemic control (Anderson and May, 1991). A common class of models are *compartmental models*, which divide a population into several homogeneous groups (compartments) and use differential

equations to describe movement between groups due to disease transmission, recovery, or death. For example, the SIR model assumes that individuals in the population are either *susceptible* to infection, *infected* and infectious, or *removed* (either recovered or dead). A key component in the analysis of these models is the computation of the *basic reproduction number*, denoted by R_0, which is the expected number of secondary infections caused by a typical infected individual in an otherwise susceptible population. If $R_0 < 1$, then the disease will be eliminated in the long run, while if $R_0 > 1$ then the disease remains *endemic* in the population. Models that include vaccination derive the basic reproduction number as a function of the vaccine *coverage* level — the fraction of the population that is vaccinated — and the vaccine's efficacy, which is typically defined in terms of three aspects: take (the fraction of those vaccinated in whom the vaccine has an effect), degree (the reduction in the probability of infection upon exposure), and duration (the length of time for which vaccinated individuals are protected from infection) (McLean and Blower, 1993).

In this work, we use variations on the SIR model featuring vaccination with an imperfect vaccine to evaluate payment contracts between a vaccine manufacturer and a GHO, where different contracts result in varying levels of vaccine efficacy.

Vaccine Market Coordination. Vaccine markets consist of multiple players with competing objectives, including profit-maximizing manufacturers (suppliers), group-interested countries (buyers), public health-oriented global health organizations (procurers), and self-interested individuals (consumers). A large body of research examines the inefficiencies that arise in vaccine markets — and potential remedies — when the incentives of one or more players are misaligned; a comprehensive review is given by Duijzer et al. (2018).

Prior studies have modeled contracts between a vaccine manufacturer and one or more countries, but typically focus on production *yield* uncertainty — the number of vaccine doses a manufacturer produces — and the resulting coverage levels. Deo and Corbett (2009) study Cournot competition

between manufacturers in the U.S. influenza vaccine market, in which yield uncertainty impacts the net production quantity, and hence profits, ultimately deterring a firm from entering the market. Mamani et al. (2013) study governments' optimal vaccination coverage levels when cross-border transmission is possible. The authors find that decentralized decision-making by each country leads to shortages of vaccines in some countries and excesses in others, and they propose a coordinating contract to allow for vaccine transfers between countries.

Chick et al. (2008) use a game-theoretic model to study the decisions of a profit-maximizing vaccine manufacturer that bears the risk of yield uncertainty, and a government seeking to maximize the health benefits of vaccination less the administration costs. Without intervention, they show that vaccine coverage is below the societally optimal level, but that this can be remedied with a cost-sharing contract that shares the risk of yield uncertainty. Chick et al. (2016) extend Chick et al. (2008) by considering the case where the manufacturer can exert costly effort to fulfill the demand that was unsatisfied due to yield uncertainty.

Our work differs from Mamani et al. (2013) in that we study a single GHO and a single manufacturer, who decides how much to invest to *improve* vaccine efficacy, while their work studies multiple countries, with a manufacturer producing the desired quantity of vaccines with *fixed* efficacy. Unlike Deo and Corbett (2009), Chick et al. (2008) and Chick et al. (2016), who consider *yield* uncertainty, a risk borne by the manufacturer assuming a quantity-based payment contract, we allow for uncertain *efficacy*, which can result in lack of payment to the manufacturer if the resulting efficacy falls below the WHO's minimum standard.

Vaccine Pricing and Subsidies. The process of developing, testing, and licensing a new vaccine is expensive and lengthy, taking an estimated 10 years and between $200 million and $500 million (Serdobova and Kieny, 2006). Given the uncertainty in market demand, relatively smaller market sizes (as compared to pharmaceuticals) and international pressure to provide vaccines at low

prices, firms who decide to pursue vaccine development have an incentive to set high prices in order to recoup their substantial R&D costs. However, high prices not only create a financial burden for low- and middle-income countries, they also exacerbate free riding, in which susceptible individuals forgo vaccination by taking advantage of herd immunity in the population (Harvard Gazette, 2010). Several papers in the operations management literature explore how these challenges can be resolved through the use of subsidies to either the manufacturer, consumers, or both.

Arifoğlu et al. (2012), Adida et al. (2013), and Arifoglu and Tang (2019) extend the joint game-theoretic and epidemic model of Chick et al. (2008) to incorporate strategic consumer behavior, and propose supply-side (manufacturer) or demand-side (individuals) subsidies to resolve inefficiencies resulting from such strategic behavior. Levi et al. (2016) and Yamin and Gavious (2013) consider the use of subsidies to increase the consumption of malaria drugs and vaccines, respectively. Unlike the preceding studies, which use subsidies to increase either the production quantity or consumption of vaccines, we investigate the ability of contracts that link price and efficacy to incentivize manufacturers to develop highly efficacious vaccines.

Advance Market Commitments. In an AMC, one or more sponsors pre-commit to purchasing a given quantity of vaccines at a guaranteed price, in exchange for the manufacturer agreeing to a reduced price on additional purchases. The rationale behind an AMC is that it encourages investment in new vaccines by removing the element of demand uncertainty and ensuring that manufacturers will recover a large portion of their R&D costs, while at the same time ensuring the affordability of these vaccines in the long run (Kremer, 2000a,b).

Both Kremer et al. (2015) and Martin et al. (2018) examine the problem of how to optimally design an AMC, which involves determining the quantity of vaccines that sponsors will commit to purchase as well as the initial (higher) and long-run (lower) per-unit prices. Similar to an AMC, the contracts that we examine aim to encourage the development of novel vaccines. However, while the

price paid in an AMC is tied to efficacy only through a minimum efficacy threshold, the contracts proposed in our work explicitly reward manufacturers for developing marginally more efficacious vaccines. Moreover, neither Martin et al. (2018) nor Kremer et al. (2015) consider the impact of their proposed contracts on the evolution of the epidemic, while we design performance-based contracts with the goal of either mitigating or eliminating the disease.

Performance-Based Contracting in Healthcare. Performance-based contracting is a contracting framework in which at least some portion of payment is linked to the evaluation of outputs or outcomes rather than required inputs, activities or processes (Martin, 2007).

Within the context of performance-based contracting in healthcare, research in the operations management community has largely focused on contracts between a service provider (e.g., hospital or clinic) and regulatory bodies (e.g., a government agency), where payment for service is conditional on patient health outcomes or waiting times. So and Tang (2000) examine a setting in which a health clinic prescribes medication to a patient and is only reimbursed if the patient's measured health score meets a specified threshold. Savva et al. (2018) empirically study how yardstick competition – a reimbursement scheme in which a provider's payment is linked to their performance relative to other comparable providers – performs in service systems such as hospital emergency departments, where a regulator seeks to incentivize reductions in both costs and waiting time. Jiang et al. (2012) analyze an outpatient care setting in which a service provider allocates capacity among different categories of patients in order to meet a waiting-time target. Unlike the majority of research in this area, which links payment to health outcomes of individual patients or patients within a healthcare center, our work studies contracts that link payment to vaccine efficacy, which impacts the overall health of the country.

Outside of healthcare, performance-based contracting has been applied to study after-sales supply chains (Kim et al., 2007), product reliability (Guajardo et al., 2012) and collaborative

services (Roels et al., 2010), among others; see Selviaridis and Wynstra (2015) for an exhaustive review.

3.3 Model

We propose a joint game-theoretic and epidemic model featuring an immunization supply chain consisting of a single GHO and a single vaccine manufacturer. Our game-theoretic model consists of a Stackelberg game between the GHO (the leader), who offers a per-unit price for the vaccine, and the manufacturer (the follower), who sets a desired, or target, efficacy level. Given the fraction of the population immunized, the efficacy of the vaccine developed by the manufacturer, and the underlying disease dynamics, our epidemic model captures the resulting progression of the disease. We detail the model for a general vaccine, and in Section 3.4 we show how this base model can be modified for specific diseases. Appendix B.1 provides a summary of the model notation.

We first provide an overview of our model and relevant assumptions. Section 3.3.1 considers a centralized system in which the GHO and manufacturer operate as a single entity that develops a vaccine in order to minimize R&D, manufacturing, and treatment/administration costs. Sections 3.3.2 and 3.3.3 consider a decentralized system with a profit-maximizing manufacturer and cost-minimizing GHO. In Section 3.3.2, we demonstrate the sub-optimal behavior of the wholesale price contract and analyze the lump sum performance-based contract, while in Section 3.3.3 we consider the linear performance-based contract.

Immunization Process. Individuals typically receive immunizations through *routine immunization* – nationally organized programs which seek to vaccinate individuals (typically infants) according to a defined immunization schedule – or *mass vaccination* – programs that seek to increase coverage by immunizing large numbers of susceptible individuals, regardless of their age. Mass vaccination is considered a supplementary activity to routine immunization and is most com-

monly used for the influenza vaccine; for these reasons, we assume that all vaccinated individuals receive their vaccinations via a routine immunization program (Chakrabarti et al., 2019). Given this assumption, we consider the *target population* – the intended recipients of the vaccine – to be newborn babies, as this is the case for the majority of routine immunization programs; nine of the ten WHO-recommended vaccines are first given shortly after birth, with subsequent doses delivered three to six months later (WHO, 2018f).

In order to vaccinate a fraction f of the target population of newborns, the GHO purchases a quantity Q of vaccines from the manufacturer. The resulting fraction immunized (and thus the corresponding quantity of vaccines ordered) is exogenous and is *not* a decision made by the GHO; rather, is a function of factors such as what portion of the population lives in urban areas (it is logistically more challenging to vaccinate individuals in rural areas), and can range from just 26% in South Sudan to over 95% in the United States for the DTP3 vaccine (WHO, 2018a). Although in practice GHOs may order excess vaccines to account for wastage, we assume that the GHO minimizes costs and thus orders the minimum number of vaccines needed to immunize the fraction f of the target population.

GHO Actions. The GHO offers a price $p(e)$ per unit for a vaccine with efficacy e, provided that the vaccine exceeds the minimum efficacy η_1. These efficacy standards may be imposed by recipient countries or by the WHO, which publishes Target Product Profiles detailing the minimum efficacy required for the prequalification of new vaccines. For example, the WHO's Target Product Profile for Zika specifies a minimum efficacy of 70% (WHO, 2017b).

Manufacturer Actions. Taking into account the quantity Q of vaccines demanded by the GHO and the offered price $p(e)$, the manufacturer invests in developing a vaccine with target efficacy level t and incurs a corresponding R&D cost that is convex increasing in the target. For analytic tractability, we consider the case where the R&D cost is quadratic in the target efficacy and is given

by rt^2. Due to uncertainty in the manufacturing and development process, the *realized* efficacy e of the vaccine may differ from its target t. Sources of efficacy uncertainty include (i) patient reactions to the vaccine caused by genetic factors or previous exposure to the disease (Thomas and Moridani, 2010), (ii) antigenic variation, or the ability of an infectious agent to alter its makeup to avoid triggering an immune response in the host (Oyston and Robinson, 2012), (iii) variation in conferred immunity due to different strains of the disease (WHO, 2018d), or (iv) variation in the development of the vaccine itself, such as when mutations occur with live attenuated vaccines after injecting a virus into a foreign host (Shimizu et al., 2004). We consider the realized efficacy e to be given by $t + \epsilon$, where $\epsilon \sim U[-u, u]$.

Manufacturer Costs and Revenue. If the resulting efficacy exceeds the minimum standard η_1, the manufacturer produces Q doses of the vaccine at a cost c per unit, and receives payment $p(e)$ per unit. Otherwise, the manufacturer receives no payment and does not produce the vaccine.

GHO Costs. Given the realized vaccine efficacy e, the GHO incurs procurement costs $p(e)$ per unit and may additionally incur costs associated with administering the vaccine and treating infected individuals. Equation 3.1 summarizes the administration and treatment costs as a function of the realized efficacy e. If the realized efficacy falls below the minimum standard η_1, the GHO incurs the lump-sum cost K_1 of treating the disease with no vaccine to help attenuate its spread. If the realized efficacy is above the minimum standard η_1, but below the threshold η_2 needed to eliminate the disease in the population, then the GHO incurs the lump-sum cost K_2, which includes the cost of administering the vaccine and treating infected individuals, along with the payment $p(e)Q$ to the manufacturer. In this case we say that the disease has been *mitigated* – a positive number of cases of infection remain in the population, but fewer than if no vaccine were available – but not eliminated – no cases of infection remain. Finally, in the case that the realized efficacy is above the threshold η_2, the disease is eliminated and thus the GHO bears no cost of

treatment and is only responsible for the payment to the manufacturer as well as the lump-sum cost K_3 of administering the vaccine.

$$\text{GHO's Administration and Treatment Costs} = \begin{cases} K_1 & \text{if } e \leq \eta_1 \\ K_2 & \text{if } \eta_1 < e \leq \eta_2 \\ K_3 & \text{if } e > \eta_2 \end{cases} \tag{3.1}$$

While recipient countries may pay a portion of the total costs, a 2016 analysis by the WHO found that, in countries with a per-capita GDP of less than $1000 (which tend to have high rates of NTDs), 78% of routine immunization expenditures and 88% of expenditures on vaccines were externally funded (WHO, 2016). With this in mind, we focus on the relationship between the GHO and the vaccine manufacturer, and do not consider the costs incurred by the recipient country. Furthermore, we assume that the GHO's vaccine supply is the country's only source of immunization for the given disease.

Key Assumptions. We assume that $K_1 > K_2 > K_3$. The condition $K_1 > K_2$ states that mitigating the disease prevents enough infections to offset the cost of adding the vaccine to the routine immunization program. In practice this condition likely holds, as vaccination costs are in general less expensive than disease treatment costs. For example, an analysis of 94 low- and middle-income countries found that the average per-person cost of a vaccine program is between $2 and $4; in contrast, the average cost to treat a case of dengue fever is $150 (Portnoy et al., 2015a; Shepard et al., 2016). We note that $K_2 > K_3$ by definition, as K_2 includes both treatment costs and administration costs, while K_3 only includes administration costs (which are the same in the case of mitigation and elimination).

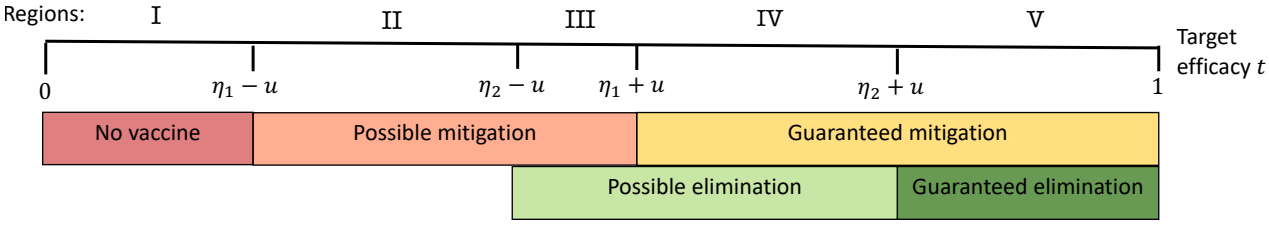
In summary, the GHO decides the per-unit vaccine price to minimize societal costs, while the manufacturer decides the target vaccine efficacy level to maximize their individual profits. We make a mild assumption on the relationship between parameters introduced above.

Assumption 1. *The difference between the threshold for elimination η_2 and the minimum efficacy threshold η_1 is less than twice the uncertainty in efficacy u.*

Assumption 1 states that the difference between the mitigation and elimination thresholds is small compared to the uncertainty in vaccine production. Recall that the mitigation threshold η_1 is the minimum efficacy at which the GHO will purchase the vaccine (which is typically imposed by the WHO), while the elimination threshold η_2 is derived from the epidemiology of the disease and the fraction f of individuals immunized. The WHO could choose to set a low mitigation threshold (i.e., accept lower efficacy vaccines), which would have the benefit of providing a vaccine to recipient countries, but doing so would be costly, would make elimination less likely (compared to a higher threshold), and, depending on how low the efficacy is, fail to substantially reduce the burden of disease. Thus Assumption 1 argues that the WHO sets the mitigation threshold η_1 relatively close to the elimination threshold in order to facilitate elimination of the disease.

Figure 3.1 displays the possibility of mitigating ($e > \eta_1$) or eliminating ($e > \eta_2$) the disease, given a target efficacy t. We use the terms "no mitigation/elimination" to indicate that, given the target efficacy in a region, mitigation or elimination occurs with probability zero. The terms "possible mitigation/elimination" designate regions where the probability of these events is positive, but less than one, while "guaranteed mitigation/elimination" is used for regions where these events occur with probability one. Under Assumption 1, the interval $(\eta_1 - u, \eta_1 + u)$ on which mitigation is possible and the interval $(\eta_2 - u, \eta_2 + u)$ on which elimination is possible overlap. We use red to indicate Region I, where no vaccine is produced, orange for Regions II and III, where mitigation is possible, yellow for Regions IV and V where mitigation is guaranteed, light green for Regions III and IV where elimination is possible, and dark green for Region V where elimination is guaranteed.

Figure 3.1: Possibility of eliminating and mitigating the disease as a function of the target vaccine efficacy t under Assumption 1.



3.3.1 Centralized System

In order to evaluate the performance of different contracts and determine what target efficacy level t is desirable, we analyze a centralized system consisting of both the GHO and manufacturer. In this system, the two decision-makers operate as a single entity that selects a target efficacy t to minimize the total expected cost of developing and manufacturing the vaccine, as well as the expected administration and treatment costs. All proofs are presented in Appendix B.2.

The *first-best* minimizes the total costs for the immunization supply chain:

$$\Pi(t) = rt^2 + K_1\mathbb{P}(e < \eta_1) + (cQ + K_2)\mathbb{P}(\eta_1 < e < \eta_2) + (cQ + K_3)\mathbb{P}(e > \eta_2)$$

The centralized cost is a piecewise convex, continuous function of the target efficacy t, but is not continously differentiable. The marginal cost $\Pi'(t)$ has a piecewise linear structure, exemplified in Figure 3.2. Note that all line segments have the same slope $2r$, which corresponds to the R&D costs of developing a marginally more efficacious vaccine. Figure 3.2 displays three vertical shifts of the line $\Pi' = 2rt$, the magnitude of which are designated by D_1, D_2, and D_3, respectively.

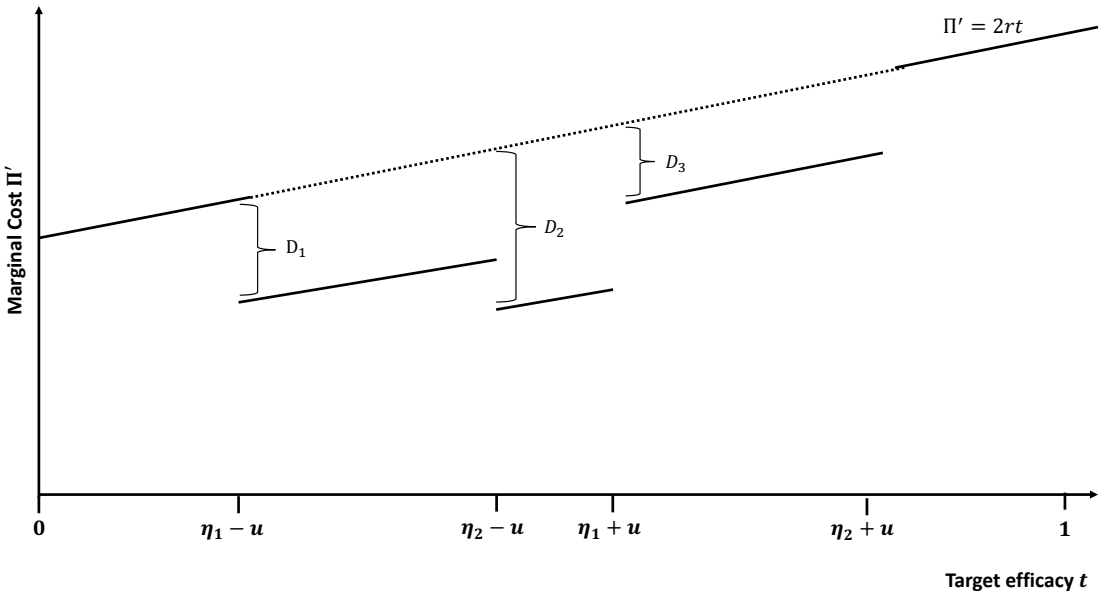
The first shift occurs when t is in Region II ($t \in (\eta_1 - u, \eta_2 - u)$) where mitigation is possible. In addition to the known R&D costs incurred on this region, the central planner incurs probabilistic costs; either K_1 in the case of no mitigation, and $K_2 + cQ$ if mitigation occurs. On this region, the marginal increase in the probability of mitigation associated with an increase in the target efficacy t is $\frac{1}{2u}$. Thus $D_1 = \frac{K_1 - (K_2 + cQ)}{2u}$ gives the marginal expected savings to the central planner associated

with increasing the target t.

The next vertical shift occurs on Region III ($t \in (\eta_2 - u, \eta_1 + u)$) on which both mitigation and elimination are possible. In addition to the R&D cost, the central planner incurs K_1 if no mitigation occurs, $K_2 + cQ$ if mitigation occurs but elimination does not, and $K_3 + cQ$ if elimination occurs. On this region, an increase in the target efficacy t generates two types of marginal expected savings: $\frac{K_1 - (K_2 + cQ)}{2u}$, which compares the costs under mitigation and no mitigation, and $\frac{K_2 + cQ - (K_3 + cQ)}{2u}$ which compares the costs under mitigation but no elimination and elimination. Adding these two savings gives $D_2 = \frac{K_1 - K_3 - cQ}{2u}$.

The last shift occurs on Region IV ($t \in (\eta_1 + u, \eta_2 + u)$) where mitigation is guaranteed and elimination is possible. Because mitigation is guaranteed on this region, the central planner incurs manufacturing costs cQ as well as the R&D costs. Additionally, the central planner incurs costs K_2 and K_3 if elimination does not or does occur, respectively. Thus the marginal expected savings associated with developing a marginally more efficacious vaccine on this region is $D_3 = D_2 - D_1$.

Figure 3.2: Marginal costs of the centralized problem as a function of the target efficacy.



All line segments have the same slope $2r$. $D_1 = \frac{K_1 - K_2 - cQ}{2u}$, $D_2 = \frac{K_1 - K_3 - cQ}{2u}$, $D_3 = D_2 - D_1 = \frac{K_2 - K_3}{2u}$

While Figure 3.2 shows an example where each of the three shifts translates to a reduction in marginal costs, we note that in general these shifts can result in either higher (if $D_i < 0$) or lower (if $D_i > 0$) marginal costs. Given our assumption that $K_1 > K_2 > K_3$, we have that $D_3 > 0$, but the sign of D_1 and D_2 depends on the total manufacturing costs.

Rather than analyzing the centralized system in full generality, we impose sufficient conditions to ensure that the objective is unimodular and thus has a unique optimum.

Assumption 2. *The problem parameters satisfy* $D_2 < 2r(\eta_2 - u)$.

Assumption 2 states that the centralized costs $\Pi(t)$ are increasing on Region III in which both mitigation and elimination are possible, meaning that it is never optimal for the central planner to choose a target on the interior of this region. Instead, the central planner would prefer to either lower the target so that only mitigation is possible and save on R&D costs, or raise the target so that mitigation or elimination is guaranteed and save on treatment costs.

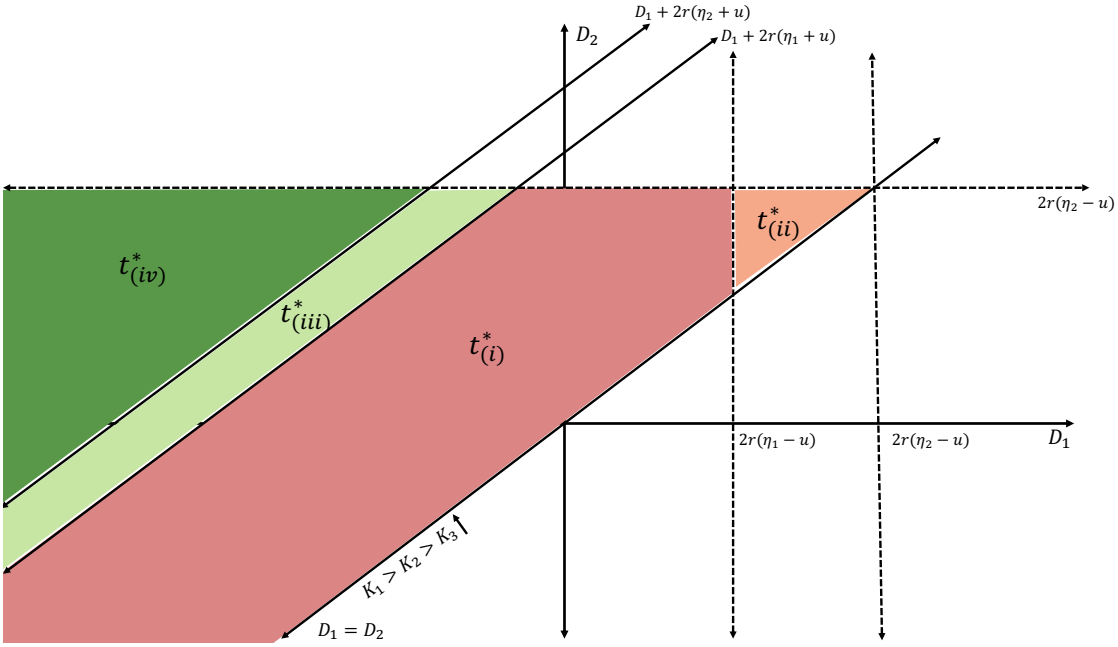
Under Assumption 2, we find that there are a total of four possible optima; Proposition 4 graphically presents these first-best target efficacy levels.

Proposition 4. *Under Assumption 2, the centralized problem is unimodular. The first-best target efficacy levels* t^* *are given in Figure 3.3, where* $t_i^* = 0$, $t_{ii}^* = \frac{D_1}{2r}$, $t_{iii}^* = \frac{D_3}{2r}$, *and* $t_{iv}^* = \eta_2 + u$.

Figure 3.3 displays the first-best target efficacy levels, where each region is colored according to the best possible epidemic outcome, using the same color scheme as Figure 3.1. For example, solution $t_{(iii)}^*$ is in Region IV, where mitigation is guaranteed and elimination is possible. Thus we color the region associated with this solution light green, which corresponds to the best epidemic outcome of possible elimination.

We see that, depending on the problem parameters, a variety of targets are possible, ranging from having no vaccine to eliminating the disease with probability one. Under target $t_{(i)}^*$ (red

Figure 3.3: First-best target efficacy levels.



$t^*_{(i)} = 0$, $t^*_{(ii)} = \frac{D_1}{2r}$, $t^*_{(iii)} = \frac{D_3}{2r}$, and $t^*_{(iv)} = \eta_2 + u$.

region), no vaccine is produced, and the epidemic progresses as it would without intervention. If target $t^*_{(ii)}$ (orange region) is selected, then it is possible that the disease will be mitigated, but the target is too low for elimination. Under target $t^*_{(iii)}$ (light green region) the disease will be mitigated with probability one, and elimination is possible. Finally, target $t^*_{(iv)}$ (dark green region) is the minimum value needed to ensure that elimination is guaranteed.

Figure 3.3 highlights how the first-best target efficacy depends on the marginal expected savings associated with having no vaccine vs mitigation (D_1) and the marginal expected savings associated with having no vaccine vs elimination (D_2). We see that the highest targets are associated with negative values of D_1 and positive values of D_2, meaning that eliminating the disease is more attractive from a cost savings perspective than mitigating. Furthermore, we see that, for a fixed value of D_1, increasing D_2 may result in a higher target. For example, for low values of D_1, we see that by increasing D_2, the optimal target changes from $t^*_{(i)}$ (no vaccine) to $t^*_{(iii)}$ (possible elimination) to $t^*_{(iv)}$ (guaranteed elimination).

3.3.2 Lump Sum Contract

The first contract we consider is a generalization of a wholesale price contract, a popular contract both among practitioners and academics in the vaccine market setting (Dai et al., 2016; Chick et al., 2008). In a traditional wholesale price contract, one party purchases a product from another at a fixed price per unit. The contract we consider differs from a traditional wholesale price contract in that it is performance-based, meaning that at least some portion of payment is linked to the evaluation of outputs (Martin, 2007). In particular, given that the efficacy exceeds the minimum standard, the contract we study offers the manufacturer a per-unit price p_1 if the efficacy falls below the elimination threshold η_2, and a different per-unit price p_2 if the efficacy exceeds this threshold. The intuition behind this contract is that, by offering a substantially high price p_2, the GHO can entice the manufacturer to set a target high enough to exceed the elimination threshold.

Under the lump sum contract, the GHO sets the prices p_1 and p_2 to minimize the expected cost $\widehat{\Pi}_G$ of procuring the vaccine, as well as the administration and treatment costs – K_1 in the case of no vaccine, K_2 in the case of mitigation, and K_3 in the case of elimination – subject to ensuring that the manufacturer participates (i.e., has a non-negative expected profit). The GHO problem is as follows:

$$\min_{p_1,p_2} \widehat{\Pi}_G(p_1,p_2) = K_1\mathbb{P}(e<\eta_1) + (K_2+p_1Q)\mathbb{P}(\eta_1<e<\eta_2) + (K_3+p_2Q)\mathbb{P}(e>\eta_2)$$

$$\text{s.t. } \widehat{\Pi}_M(t(p_1,p_2)) \geq 0$$

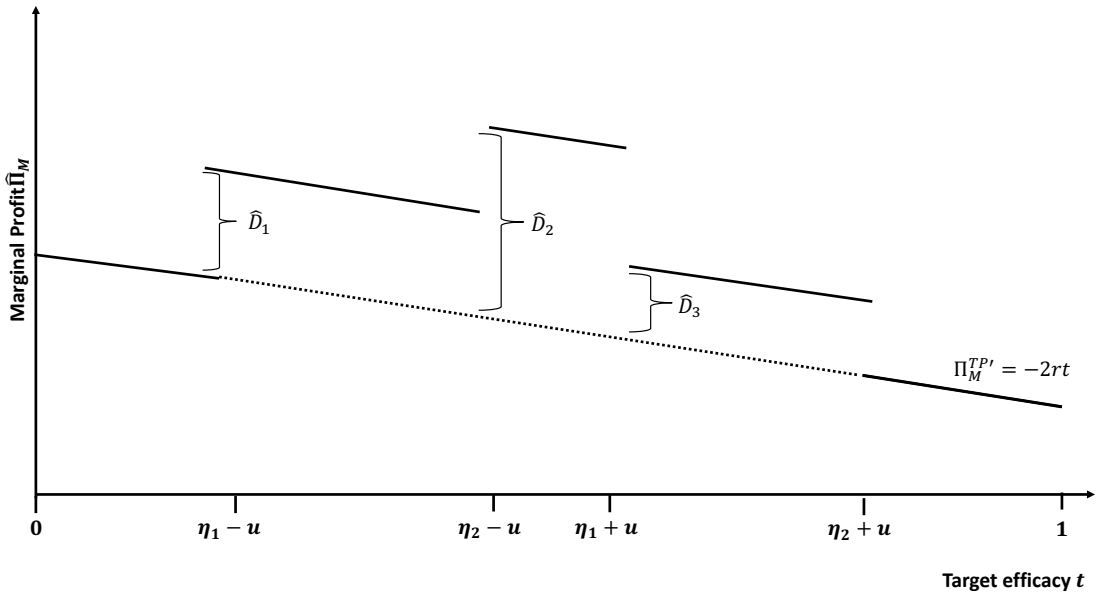
Given the prices selected by the GHO, the manufacturer chooses the vaccine efficacy target t to maximize their expected profits $\widehat{\Pi}_M$, which consist of the expected revenues from selling Q units of the vaccine ($p_1Q\mathbb{P}(\eta_1<e<\eta_2) + p_2Q\mathbb{P}(e>\eta_2)$), less the R&D costs rt^2 and manufacturing costs cQ. The manufacturer's problem is as follows:

$$\max_{t\in[0,1]} \widehat{\Pi}_M(t) = -rt^2 + (p_1-c)Q\mathbb{P}(\eta_1<e<\eta_2) + (p_2-c)Q\mathbb{P}(e>\eta_2)$$

We solve the manufacturer and GHO problems by backward induction. Given fixed prices p_1 and p_2, we solve the manufacturer's problem to find the optimal target $t(p_1, p_2)$ as a function of the contract prices. We then use this characterization of the optimal target to solve the GHO problem for the optimal prices.

The manufacturer's profit is piecewise continuous, and the marginal profit $\widehat{\Pi}'_M(t)$ has a piecewise linear structure (depicted in Figure 3.4) where all line segments have the same slope $-2r$, corresponding to the marginal R&D costs. Figure 3.4 displays three vertical shifts of the line $\widehat{\Pi}'_M = -2rt$, which have magnitudes $\widehat{D}_1$, $\widehat{D}_2$, and $\widehat{D}_3$, respectively.

Figure 3.4: Marginal costs of the manufacturer's problem as a function of the target efficacy under the lump sum contract.



All line segments have the same slope $-2r$. $\widehat{D}_1 = \frac{(p_1-c)Q}{2u}$, $\widehat{D}_2 = \frac{(p_2-c)Q}{2u}$, and $\widehat{D}_3 = \widehat{D}_2 - \widehat{D}_1$.

The quantities $\widehat{D}_1$, $\widehat{D}_2$, and $\widehat{D}_3$ can be interpreted in a similar manner as D_1, D_2, and D_3 in the centralized system. We see that $\widehat{D}_1 = \frac{(p_1-c)Q}{2u}$ is the marginal expected revenue associated with an increase in the target efficacy t on Region II, and is obtained by comparing the manufacturer's profit when no mitigation occurs (and no vaccine is purchased) versus when mitigation occurs (and the vaccine is purchased at p_1 per unit). The quantity $\widehat{D}_2$ is the marginal expected revenue on

Region III and is the sum of the marginal expected increases in revenue associated with mitigation ($\frac{(p_1-c)Q}{2u}$) and elimination ($\frac{(p_2-c)Q}{2u} - \frac{(p_1-c)Q}{2u}$). Finally, $\widehat{D}_3 = \frac{(p_2-p_1)Q}{2u} = \widehat{D}_2 - \widehat{D}_1$ reflects the marginal expected increase in revenue on Region IV, which compares the profit under the scenarios when elimination does and does not occur.

Figure 3.4 illustrates an example where each of the three vertical shifts translates to an increase in marginal profit, but in general these shifts can result in either higher (if $\widehat{D}_i > 0$) or lower (if $\widehat{D}_i < 0$) marginal profit.

Similarly to the centralized setting, we impose sufficient conditions to ensure that the manufacturer's profit function is unimodular and thus has a unique optimum.

Assumption 3. *The problem parameters satisfy* $\widehat{D}_2 < 2r(\eta_2 - u)$.

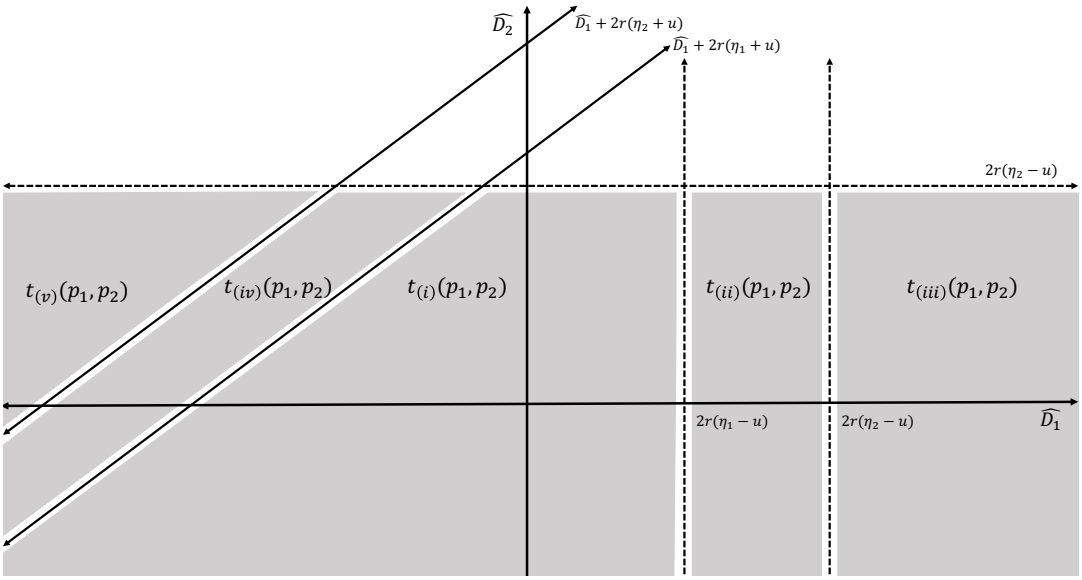
Assumption 3 states that the GHO selects prices so that manufacturer's profit is decreasing on Region III in which both mitigation and elimination are possible, meaning that the manufacturer never selects a target on the interior of this region. In other words, this means that the GHO would rather incentivize the manufacturer to select a lower target so that only mitigation is possible and save on procurement costs, or incentivize the manufacturer to select a higher target so that mitigation or elimination is guaranteed and save on treatment costs.

Given Assumption 3, Proposition 5 graphically presents the manufacturer's best response target efficacy level as a function of the contract prices p_1 and p_2.

Proposition 5. *Under Assumption 3, the manufacturer's problem is unimodular. The manufacturer's best response target efficacy levels* $t(p_1, p_2)$ *are displayed in Figure 3.5, where* $t_{(i)}(p_1, p_2) = 0$, $t_{(ii)}(p_1, p_2) = \frac{\widehat{D}_1}{2r}$, $t_{(iii)}(p_1, p_2) = \eta_2 - u$, $t_{(iv)}(p_1, p_2) = \frac{\widehat{D}_3}{2r}$, *and* $t_{(v)}(p_1, p_2) = \eta_2 + u$.

Given the manufacturer's best response $t(p_1, p_2)$, the GHO selects the prices p_1 and p_2 to minimize its costs, subject to ensuring the participation of the manufacturer. We find that there

Figure 3.5: Manufacturer's best response target efficacy levels $t(p_1, p_2)$ under the lump sum contract.



$t_{(i)}(p_1, p_2) = 0$, $t_{(ii)}(p_1, p_2) = \frac{\widehat{D}_1}{2r}$, $t_{(iii)}(p_1, p_2) = \eta_2 - u$, $t_{(iv)}(p_1, p_2) = \frac{\widehat{D}_3}{2r}$, $t_{(v)}(p_1, p_2) = \eta_2 + u$.

are five equilibrium targets t^{TP} that can be obtained, two of which align with the first-best targets. Proposition 6 details the equilibrium targets and prices. For several target efficacy levels, there are multiple values of p_1 and/or p_2 that induce the manufacturer to select this target. For brevity, we include any additional conditions in Appendix B.2. Figure 3.6 graphically presents the equilibrium targets and their correspondence with the manufacturer's best response targets.

Proposition 6. *The equilibrium target efficacy level $\widehat{t}$ and prices $\widehat{p}_1$ and $\widehat{p}_2$ under the lump sum contract are given as follows:*

1. $\widehat{t}_{(i)} = 0$; $\widehat{p}_{1(i)} < \frac{4ru(\eta_1 - u)}{Q} + c$; $\widehat{p}_{2(i)} < \min\{\frac{4ru(\eta_2 - u)}{Q} + c, \frac{8ru\eta_1}{Q} + c\}$

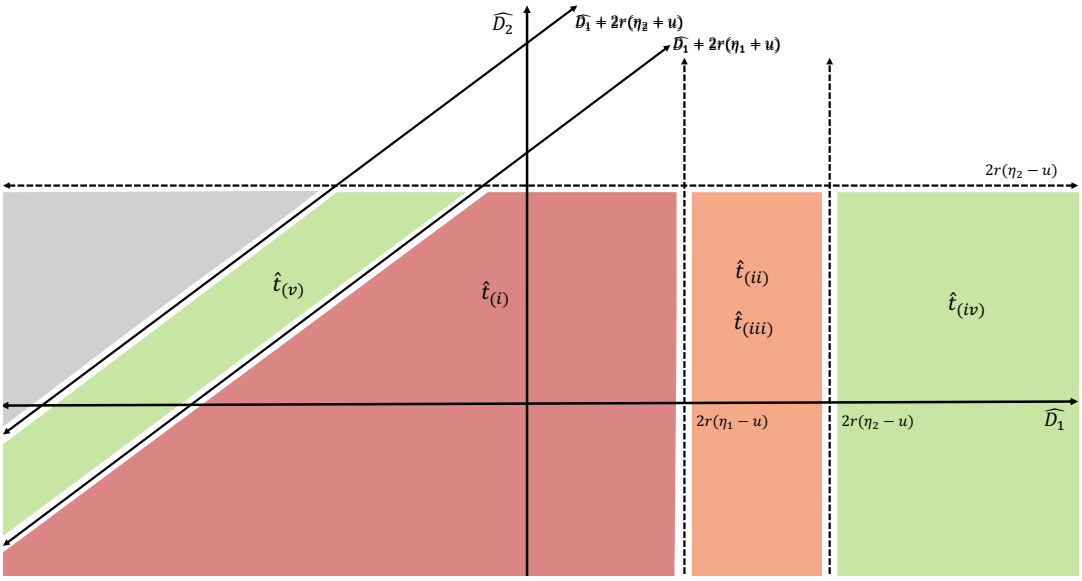
2. $\widehat{t}_{(ii)} = 2(\eta_1 - u) \in (\eta_1 - u, \eta_2 - u)$; $\widehat{p}_{1(ii)} = \frac{8ru(\eta_1 - u)}{Q} + c$; $\widehat{p}_{2(ii)} < \min\{\frac{8ru(\eta_1 - u)}{Q} + \frac{4ru(\eta_1 + u)}{Q} + c, \frac{4ru(\eta_2 - u)}{Q} + c\}$

3. $\widehat{t}_{(iii)} = \frac{D_1}{4r} + \frac{\eta_1 - u}{2} \in (\eta_1 - u, \eta_2 - u)$; $\widehat{p}_{1(iii)} = \frac{c}{2} + \frac{2ru(\eta_1 - u) + K_1 - K_2}{Q}$; $\widehat{p}_{2(iii)} < \min\{\frac{4ru(\eta_2 - u)}{Q} + c, \frac{4ru(\eta_1 + u)}{Q} + \frac{c}{2} + \frac{2ru(\eta_1 - u)}{Q} + \frac{K_1 - K_2}{Q}\}$

4. $\widehat{t}_{(iv)} = \eta_2 - u$; $\widehat{p}_{1(iv)} = c + \frac{2ru(\eta_1 - u)^2}{Q(\eta_2 - \eta_1)}$; $\widehat{p}_{2(iv)} < \min\{\frac{4ru(\eta_2 - u)}{Q} + c, \frac{4ru(\eta_1 + u)}{Q} + c + \frac{2ru(\eta_2 - u)^2}{Q(\eta_2 - \eta_1)}\}$

5. $\widehat{t}_{(v)} = \frac{D_3}{2r} \in (\eta_1 + u, \eta)2 + u)$; $\widehat{p}_{1(v)} = c + \frac{K_2 - K_3}{2Qu}\left(\eta_2 - u - \frac{(K_2 - K_3)}{8ru}\right)$; $\widehat{p}_{2(v)} = c + \frac{K_2}{Q} + \frac{K_2}{2Qu}\left((\eta_2 - u) - \frac{K_2}{8ru}\right)$

Figure 3.6: Equilibrium target efficacy levels under the lump sum contract.



$\widehat{t}_{(i)} = 0$, $\widehat{t}_{(ii)} = 2(\eta_1 - u)$, $\widehat{t}_{(iii)} = \frac{D_1}{4r} + \frac{\eta_1 - u}{2}$, $\widehat{t}_{(iv)} = \eta_2 - u$, $\widehat{t}_{(v)} = \frac{D_3}{2r}$.

Figure 3.6 displays the target efficacy levels under the lump sum contract, where each region is colored in a similar manner as Figure 3.3, which presents the first-best targets. By comparing Figures 3.5 and 3.6, we are able to map the manufacturer's best response target to its resulting equilibrium target. For example, we see that the best response $t_{(i)}(p_1, p_2) = 0$ induces an equilibrium target $\widehat{t}_{(i)} = 0$ which results in no vaccine, while the best response target $t_{(ii)}(p_1, p_2) = \frac{\widehat{D}_1}{2r}$ can induce targets $\widehat{t}_{(ii)} = 2(\eta_1 - u)$ or $\widehat{t}_{(iii)} = \frac{D_1}{4r} + \frac{\eta_1 - u}{2}$ which both result in possible mitigation. The best response $\widehat{t}_{(v)}(p_1, p_2) = \eta_2 + u$ is not an equilibrium and thus this region is shaded in grey.

From Proposition 6, we see that the lump sum contract is able to achieve the first-best target $\frac{D_3}{2r}$ $(t^*_{(iii)})$ in Region IV where elimination is possible, but is not able to achieve the lower target $\frac{D_1}{2r}$ $(t^*_{(ii)})$ in Region II where mitigation is possible. This behavior, where high first-best targets can be achieved but low ones cannot, is driven by the dual roles that prices in this contract play; prices

both shape the value of $\widehat{t}$ and ensure participation of the manufacturer. If the manufacturer's best response $t(p_1, p_2)$ falls below $\eta_2 - u$ (in which case elimination is not possible), then the contract becomes a function of p_1 only as the target is too low for the manufacturer to receive p_2 per unit. On the other hand, when the manufacturer's best response $t(p_1, p_2)$ is above $\eta_2 - u$, then the manufacturer has a non-zero probability of receiving either price. With this additional degree of freedom, the contract is able to simultaneously achieve the first-best target and guarantee participation.

In addition to being unable to achieve the first-best target $\frac{D_1}{2r}$ (t^*_{ii}), the lump sum contract cannot achieve the highest first-best target $\eta_2 + u$ $(t^*_{(iv)})$, which is the minimum value needed to guarantee elimination. While setting the target high enough to guarantee elimination ensures that the manufacturer earns a per-unit price of p_2, it is more profitable for the manufacturer to set a slightly lower target, save on R&D costs, and gamble that the realized efficacy falls above η_2.

Of the four first-best targets, the lump sum is able to induce the manufacturer to select two of them: $t = 0$ and $t = \frac{D_3}{2r}$. As detailed in Proposition 7, it is sometimes possible for the central planner to select prices p_1 and p_2 to coordinate the vaccine efficacy target to $\frac{D_1}{2r}$, but no prices can incentivize the manufacturer to select the target $t = \eta_2 + u$. For brevity, all additional conditions needed are provided in Appendix B.2.

Proposition 7. *If $\frac{D_1}{2r} \geq 2(\eta_1 - u)$ and $\eta_1 < \frac{\eta_2 + u}{2}$, then the lump sum contract with $p_1 = \frac{K_1 - K_2}{Q}$ and $p_2 < \min\{\frac{4ru(\eta_1+u)}{Q} + p_1, \frac{4ru(\eta_2-u)}{Q} + c\}$ coordinates the manufacturer's target efficacy level $\frac{\widehat{D}_1}{2r}$ to the first-best value $\frac{D_1}{2r}$. Furthermore, there are no prices p_1 and p_2 that coordinate the manufacturer's target to the first-best level $\eta_2 + u$.*

This result shows that the lump sum contract can sometimes align the decisions of the decentralized system with the first-best decisions, with the notable exception being when the first-best target is just high enough to guarantee elimination $(\eta_2 + u)$, in which case there are no coordinating

prices p_1 and p_2.

Next, we consider a wholesale price contract, which can be obtained as a special case of the lump sum contract in which $p_1 = p_2$. Under the wholesale price contract, the manufacturer is paid a per-unit price $p_1 = p_2$, provided that the realized efficacy exceeds the minimum threshold η_1. We find that the manufacturer's profit function under this contract is piecewise continuous and unimodular. Proposition 8 summarizes the target efficacy levels that can be achieved with this contract.

Proposition 8. *(Wholesale Price Contract) Under a wholesale price contract, there are six possible equilibrium targets, all of which are at most $\eta_1 + u$ and only one of which ($t = 0$) aligns with the first-best targets. Furthermore, there is no price that coordinates the vaccine efficacy target to a first-best level greater than $\eta_1 + u$.*

Under the wholesale price contract, any target above $\eta_1 + u$ is guaranteed to have a realized efficacy greater than η_1, and thus it is clear that the manufacturer has no incentive to set a high target, as this contract does not reward the manufacturer for producing vaccines with efficacy greater than η_1.

3.3.3 Linear Contract

The second performance-based contract we consider is a linear contract in which the manufacturer receives a per-unit price p_1 plus a bonus per-unit payment $p_2 e$, provided the realized efficacy exceeds the minimum threshold η_1. The intuition behind this contract is that, by rewarding the manufacturer for producing a marginally more efficacious vaccine, the GHO can incentivize the manufacturer to set a high efficacy target so as to minimize the number of individuals infected by the disease.

Under the linear contract, the GHO selects prices p_1 and p_2 to minimize the expected cost $\widetilde{\Pi}_G$

of procuring the vaccine, as well as the administration and treatment costs, subject to ensuring the manufacturer's participation. The GHO problem is as follows:

$$\min_{p_1,p_2} \widetilde{\Pi}_G(p_1,p_2) = K_1\mathbb{P}(e<\eta_1) + K_2\mathbb{P}(\eta_1<e<\eta_2) + K_3\mathbb{P}(e>\eta_2) + \mathbb{P}(e>\eta_1)\mathbb{E}[(p_1+p_2e)Q|e>\eta_1]$$

$$\text{s.t. } \widetilde{\Pi}_M(t(p_1,p_2)) \geq 0$$

where $t(p_1,p_2)$ is the manufacturer's optimal target level, which is anticipated by the GHO for given prices p_1 and p_2.

Given the prices offered by the GHO, the manufacturer selects a target efficacy to maximize their expected profits $\widetilde{\Pi}_M(t)$, which consist of the expected revenues from selling the vaccine $Q(p_1 + p_2\mathbb{E}_{e>\eta_1}[e])$, less the R&D costs rt^2 and manufacturing costs cQ. The manufacturer's problem is as follows:

$$\max_{t\in[0,1]} \widetilde{\Pi}_M(t) = -rt^2 + \mathbb{E}_{e>\eta_1}[p_1+p_2e-c]Q\mathbb{P}(e>\eta_1)$$

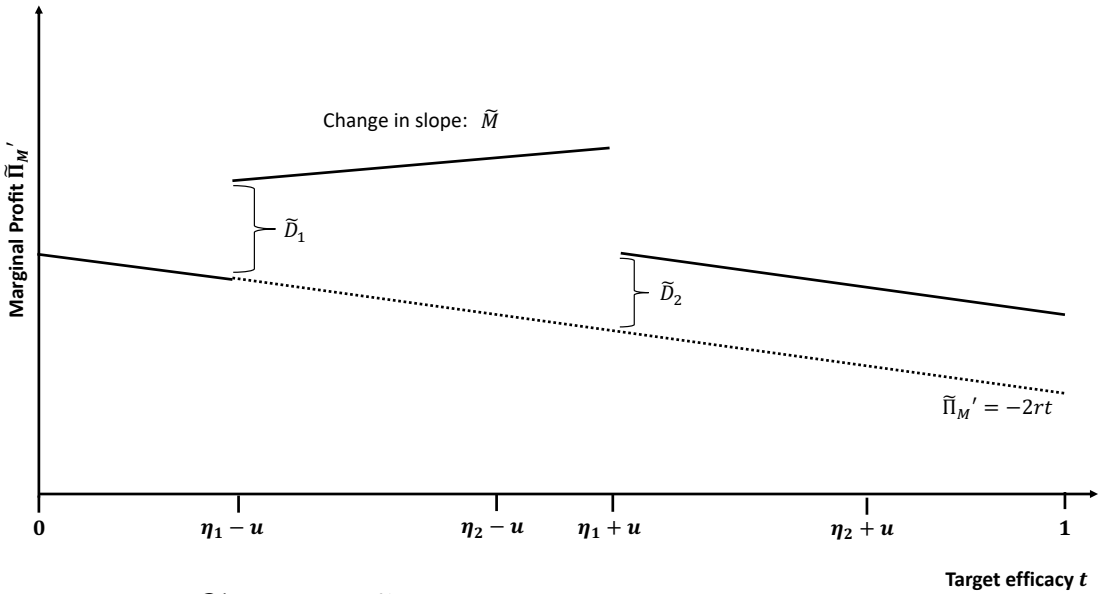
We solve the manufacturer and GHO problems by backward induction. Similarly to the lump sum contract, we find that the manufacturer's profit is a piecewise concave, continuous function of the target efficacy t, and the marginal profit $\widetilde{\Pi}'_G$ is piecewise linear. However, unlike the lump sum contract, in which all segments of the marginal profit have the same slope $-2r$, the slope of the marginal profit under the linear contract varies, as depicted in Figure 3.7.

From Figure 3.7, we see that the linear contract divides the target efficacy space into three regions: $(0,\eta_1-u)$, on which no vaccine is produced, (η_1-u,η_1+u), on which mitigation is possible (and elimination is possible if $e\geq\eta_2-u$), and $(\eta_1+u,1)$, on which mitigation is guaranteed (and elimination is guaranteed if $e\geq\eta_2+u$).

On the first region, the target efficacy is too low for the contract to come into play, and thus the marginal profit curve is just given by $\widetilde{\Pi}'_M = -2rt$. On the second region, the linear contract impacts the marginal profit in two ways. First, there is a vertical shift of magnitude $\widetilde{D}_1 = \frac{(p_1-c)Q+p_2Qu}{2u}$,

which is the expected change in marginal revenue associated with producing a vaccine and receiving payment $p_1 Q + p_2 Q \mathbb{E}_{e>\eta_1}[e]$ less the manufacturing costs cQ, compared to producing no vaccine. Second, the linear contract increases the slope of the marginal profit curve by $\tilde{M} = \frac{p_2 Q}{2u}$, thus reducing the marginal cost associated with making a more efficacious vaccine. Finally, on the third region, for producing a marginally more efficacious vaccine, the manufacturer receives a marginal performance-based payment of $\widetilde{D}_3 = p_2 Q$ and incurs marginal R&D costs $2rt$; thus the marginal profit curve is given by $\widetilde{D}_3 - 2rt$.

Figure 3.7: Marginal costs of the manufacturer's problem as a function of the target efficacy under the linear contract.



$\widetilde{D}_1 = \frac{(p_1 - c)Q + p_2 Q u}{2u}$, $\widetilde{M} = \frac{p_2 Q}{2u}$, and $\widetilde{D}_3 = p_2 Q$. The slope on $(0, \eta_1 - u)$ and $(\eta_1 + u)$ is $-2r$, while the slope on $\eta_1 - u, \eta_1 + u$ is $\frac{p_2 Q}{2u} - 2r$.

Given the prices p_1 and p_2, the manufacturer's optimal target $t(p_1, p_2)$ can take one of four possible values. Proposition 9 presents the targets along with sufficient conditions under which each target is optimal for the manufacturer.

Proposition 9. *The manufacturer's best response $t(p_1, p_2)$ under the linear contract is given as follows:*

(i) $t(p_1,p_2)=0$ *if* $\widetilde{M}<\min\{2r,\frac{r}{u}(\eta_1+u),\frac{2r}{\eta_1}(\eta_1-u)-\frac{(p_1-c)Q}{2u\eta_1}\}$

(ii) $t(p_1,p_2)=\frac{\widetilde{D}_1}{2r-\widetilde{D}_2}$ *if* $\frac{2r(\eta_1-u)}{\eta_1}-\frac{(p_1-c)Q}{2u\eta_1}<\widetilde{M}<\min\{2r,\frac{r}{u}(\eta_1+u),\frac{2r(\eta_1+u)}{2u+\eta_1}-\frac{(p_1-c)Q}{2u(2u+\eta_1)}\}$

(iii) $t(p_1,p_1)=\eta_1+u$ *if* $\frac{2r(\eta_1+u)}{2u+\eta_1}-\frac{(p_1-c)Q}{2u(2u+\eta_1)}<\widetilde{M}<\min\{2r,\frac{r}{u}(\eta_1+u)\}$ *or* $2r<\widetilde{M}<\frac{r}{u}(\eta_1+u)$

(iv) $t(p_1,p_2)=\frac{\widetilde{D}_3}{2r}$ *if* $\widetilde{M}>\max\{2r,\frac{r}{u}(\eta_1+u)\}$

Given the manufacturer's best response $t(p_1,p_2)$, the GHO selects optimal prices $\widetilde{p}_1$ and $\widetilde{p}_2$ to minimize their costs, subject to ensuring that the manufacturer earns a non-negative expected profit. We find that there are a total of five equilibrium targets $\widetilde{t}$ that can be obtained, three of which agree with the first-best targets. Proposition 10 details the equilibrium targets and prices. All additional conditions needed are provided in Appendix B.2.

Proposition 10. *The equilibrium target efficacy* $\widetilde{t}$ *and prices* $\widetilde{p}_1$ *and* $\widetilde{p}_2$ *under the linear contract are given as follows:*

1. $\widetilde{t}_{(i)}=0$; $\widetilde{p}_{1(i)}<\frac{(4ru-\widetilde{p}_{2(i)}Q)(\eta_1-u)-\widetilde{p}_{2(i)}Qu}{Q}+c$; $\widetilde{p}_{2(i)}<\min\{\frac{4ru}{Q},\frac{2r(\eta_1+u)}{Q}\}$
2. $\widetilde{t}_{(ii)}=\frac{D_1}{2r}$; $\widetilde{p}_{1(ii)}=c+\frac{4ru\widetilde{t}_{(ii)}}{Q(\widetilde{t}_{(ii)}+u-\eta_1)^2}(\eta_1^2-\widetilde{t}_{(ii)}u-u^2)$; $\widetilde{p}_{2(ii)}=\frac{4ru\widetilde{t}_{(ii)}(\widetilde{t}_{(ii)}-2(\eta_1-u))}{Q(\widetilde{t}_{(ii)}+u-\eta_1)^2}$
3. $\widetilde{t}_{(iii)}=\frac{D_2}{2r}$; $\widetilde{p}_{1(iii)}=c+\frac{4rut_{(iii)}}{Q(\widetilde{t}_{(iii)}+u-\eta_1)^2}(\eta_1^2-\widetilde{t}_{(iii)}u-u^2)$; $\widetilde{p}_{2(iii)}=\frac{4ru\widetilde{t}_{(iii)}(\widetilde{t}_{(iii)}-2(\eta_1-u))}{Q(\widetilde{t}_{(iii)}+u-\eta_1)^2}$
4. $\widetilde{t}_{(iv)}=\eta_1+u$; $\widetilde{p}_{1(iv)}=\frac{r(\eta_1+u)^2}{Q}-\widetilde{p}_{2(iv)}(\eta_1+u)+c$; $\frac{r(\eta_1+u)}{Qu}(3u-\eta_1)<\widetilde{p}_{2(iv)}<\min\{\frac{4ru}{Q},\frac{2r(\eta_1+u)}{Q}\}$
5. $\widetilde{t}_{(v)}=\frac{D_3}{2u}$; $\widetilde{p}_{1(v)}=c-\frac{(K_2-K_3)^2}{16ru^2Q}$; $\widetilde{p}_{2(v)}=\frac{K_2-K_3}{2Qu}$

From Proposition 10, we see that the linear contract is able to achieve every first-best target except for the highest one, η_2+u. The target η_2+u fails to be an equilibrium of this contract because, provided that the manufacturer sets this target and guarantees the production of a vaccine that can eliminate the disease, the GHO has no incentive to set a high price. Unlike lower targets, where the GHO has an opportunity to lower their costs by encouraging the manufacturer to develop

a more efficacious vaccine, at this target, the GHO's efficacy-related costs are at their lowest, and they set the price just high enough to ensure the manufacturer's participation.

While the target $\eta_2 + u$ cannot be achieved as an equilibrium of the linear contract, the central planner can select prices p_1 and p_2 to coordinate the manufacturer's best response target $t(p_1, p_2) = \frac{\widetilde{D}_3}{2r}$ to the first-best target $\eta_2 + u$. Proposition 11 provides the coordinating prices.

Proposition 11. *The linear contract with* $p_1 \geq c - \frac{r(\eta_2+u)^2}{Q}$ *and* $p_2 = \frac{2r(\eta_2+u)}{Q}$ *coordinates the manufacturer's target efficacy level* $\frac{\widetilde{D}_3}{2r}$ *to the first-best value* $\eta_2 + u$.

3.4 Case Study

To illustrate our joint game-theoretic and epidemic model, we conduct a numerical study for two NTDs: Chagas and Ebola. We compute the equilibrium vaccine prices and resulting efficacy targets for each disease under the lump sum and linear contracts. The goal of this analysis is to (i) compare the behavior of the two performance-based contracts for different diseases, and (ii) examine how differences in infectiousness and cost of disease treatment may require different payment contracts to incentivize manufacturers to produce high-efficacy vaccines.

For each disease, we introduce a deterministic compartmental model – represented by a system of nonlinear differential equations – with homogeneous mixing to describe the epidemic's progression over time. In epidemiology, partially effective vaccines are typically modeled in one of three manners: (i) *failure in take* assumes a vaccine provides perfect immunity to a fraction of those vaccinated, but provides no protection to the remaining portion, (ii) *failure in degree* assumes a vaccine reduces the probability of infection upon exposure in all vaccinated individuals, and (iii) *failure in duration* assumes a vaccine offers perfect protection from infection for a period of time, but subsequently wanes (McLean and Blower, 1993). For tractability, we consider a vaccine with failure in take (also known as an *all-or-nothing* vaccine).

The purpose of formulating epidemic models for each disease is to compute the *basic reproduction number with vaccination*, denoted by R_v, an analogue of the basic reproduction number R_0 in the presence of vaccination. This computation is performed using the next generation method, and the resulting expressions for R_v characterize the relationship between the vaccine efficacy e and the state of the epidemic (Van den Driessche and Watmough, 2008). If $R_v < 1$, the disease is eliminated in the long run, while if $R_v > 1$ the disease is mitigated but remains endemic (i.e., continues to persist in the population). Computations of R_0 and R_v are provided in Appendix B.3.

3.4.1 Chagas

An estimated 7.2 million people are infected with Chagas disease worldwide, primarily in rural areas of Latin America. The disease, responsible for more than 7,000 annual deaths, is caused by the parasite *trypanosoma cruzi*, which is transmitted to animals and humans by insects known as triatominae, or kissing bugs (Vos et al., 2016). Kissing bugs acquire the infection by biting an infected human or other animal. Among humans, transmission can also occur via blood transfusion, organ transplantation, or from mother to child, though contracting the disease by these means is unlikely; for example, the risk of a pregnant or breast-feeding mother transmitting Chagas to her child is 1-5% (Centers for Disease Control and Prevention, 2018).

Symptoms of Chagas occur in two phases: an acute phase, lasting 8 to 12 weeks, and a chronic phase, lasting until the infection is cured or the host dies. During the acute phase, symptoms tend to be absent or mild, and include fever, headaches, and swollen lymph nodes. In 60-70% of individuals, no further symptoms occur. In the remaining 30-40% of infections, life-threatening symptoms such as enlargement of the heart ventricles, colon, or esophagus can develop 10-30 years after the acute phase (Centers for Disease Control and Prevention, 2017a).

To describe the transmission and progression of Chagas disease, we introduce a compartmental

epidemic model, summarized in Figure 3.8, consisting of a population of N_H humans, who are either susceptible (S_H), in the acute phase of infection (A_H), in the chronic phase of infection (I_H), or vaccinated (V_H), and a population of N_V disease vectors (kissing bugs) that are either susceptible (S_V) or infected (I_V). The corresponding system of differential equations is given by (3.2).

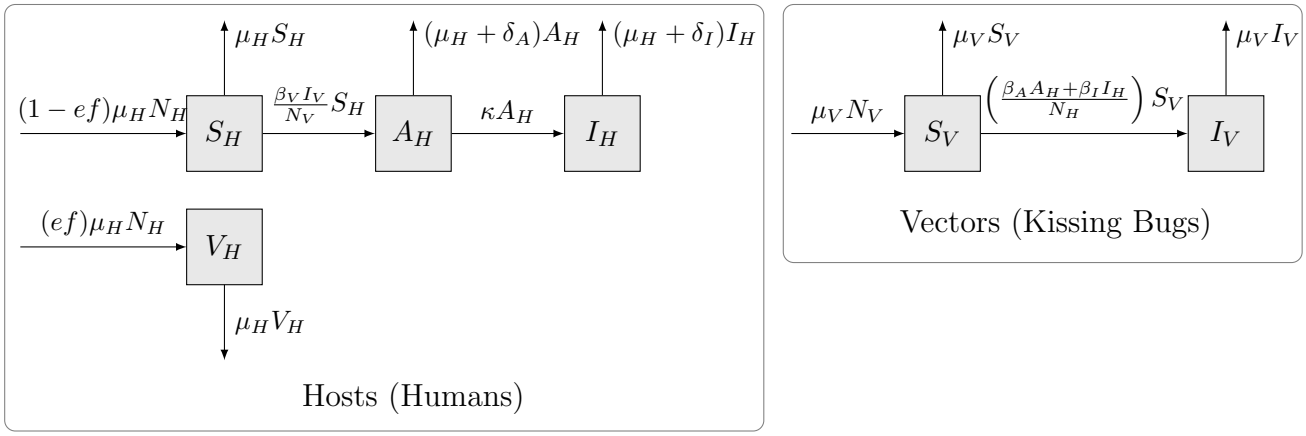
$$\begin{aligned}
\frac{dS_H}{dt} &= (1-ef)\mu_H N_H - \frac{\beta_V I_V}{N_V} S_H - \mu_H S_H & \frac{dS_V}{dt} &= \mu_V N_V - \left(\frac{\beta_A A_H + \beta_I I_H}{N_H}\right) S_V \mu_V S_V \\
\frac{dA_H}{dt} &= \frac{\beta_V I_V}{N_V} S_H - (\mu_H + \delta_A) A_H - \kappa A_H & \frac{dI_V}{dt} &= \left(\frac{\beta_A A_H + \beta_I I_H}{N_H}\right) S_V - \mu_V I_V \\
\frac{dI_H}{dt} &= \kappa A_H - (\mu_H + \delta_I) I_H & \frac{dN_H}{dt} &= -\delta_A A_H - \delta_I I_H \\
\frac{dV_H}{dt} &= (ef)\mu_H N_H - \mu_H V_H
\end{aligned} \tag{3.2}$$

We assume a per-capita birth rate μ_H that is equal to the (non-Chagas related) death rate, a common assumption in the epidemiological literature (Anderson and May, 1991). Of the $\mu_H N_H$ babies born per period, a fraction f are vaccinated with an all-or-nothing vaccine with efficacy e. Remaining newborns either do not receive a vaccine, or receive a vaccine that fails to provide protection and thus remain susceptible to the disease. Infected vectors bite susceptible humans and transmit Chagas at rate β_V; under homogeneous mixing, the rate at which susceptible humans become acutely infected is $\frac{\beta_V I_V}{N_V} S_H$. Humans remain in the acute phase for an exponentially distributed amount of time with mean $1/\kappa$, after which they enter the chronic phase. Acutely and chronically infected humans die from the disease at rates δ_A and δ_I, respectively.

For vectors, we also assume equal birth and death rates μ_V. Susceptible vectors can contract Chagas from biting acutely or chronically infected humans, and thus under homogenous mixing, the rate at which susceptible vectors become infected is $\left(\frac{\beta_A A_H + \beta_I I_H}{N_H}\right) S_V$, where β_A and β_I are the transmission rates for acutely and chronically infected humans, respectively.

Proposition 12. *The basic reproduction number R_0 and the basic reproduction number with vac-*

Figure 3.8: Compartmental epidemic model for Chagas.



cination R_v for Chagas are given as follows:

$$R_0 = \sqrt{\frac{\beta_V \beta_A}{(\mu_H + \delta_A + \kappa)\mu_V} + \frac{\beta_V \kappa \beta_I}{(\mu_H + \delta_A + \kappa)(\mu_H + \delta_I)\mu_V}} \qquad R_v = \sqrt{(1-ef)}R_0$$

The square root in R_0 and R_v arises because it takes two *generations* – waves of secondary infection that flow from each previous infection – for an infected human to cause infection in another human, as the first human must transmit the disease to the vector, which subsequently bites and infects another human. The first term in R_0 is the ratio of the *force of infection* – the rate at which susceptibles acquire an infectious disease (β_V and β_A for humans and vectors, respectively) – for the acute phase and the rate of removal due to natural death, death from acute infection, or transition to the chronic phase ($\mu_H + \delta_A + \kappa$) and μ_V for humans and vectors, respectively). The second term is the ratio of the force of infection ($\frac{\beta_V \kappa}{\mu_H + \delta_A + \kappa}$ for humans, where $\frac{\kappa}{\mu_H + \delta_A + \kappa}$ is the probability of transitioning from the acute to chronic phase, and β_I for vectors) and the rate of removal ($\mu_H + \delta_I$ and μ_V for humans and vectors, respectively) for the chronic phase.

3.4.2 Ebola

Ebola virus disease (EVD) is a hemorrhagic fever caused by infection with the Ebola virus that occurs among humans and other primates. The disease has a high risk of death; since its first

recorded outbreak in 1976, there have been 31,099 cases, of which 12,962 resulted in death (WHO, 2018c). Ebola virus spreads through human-to-human transmission via direct contact with bodily fluids of infected individuals. Symptoms of Ebola typically begin two to three weeks after the onset of infection, and individuals are not infectious until they develop symptoms. Early indicators of infection include fever, muscle pain, headache, a sore throat, and general fatigue, while later symptoms include vomiting, diarrhea, and internal and external bleeding.

To describe the progression of Ebola, we introduce a compartmental epidemic model, summarized in Figure 3.9, comprising a population of N humans, who are either susceptible (S), exposed but not yet infectious (E), infected and infectious (I), and recovered (R). The corresponding system of differential equations is given by (3.3).

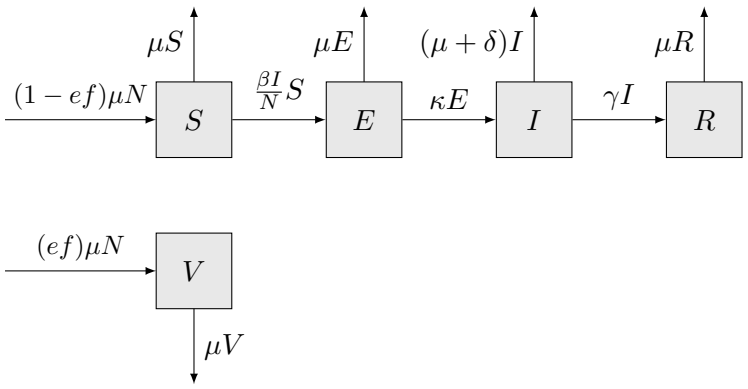
$$\begin{aligned} \frac{dS}{dt} &= (1-ef)\mu N - \mu S - \frac{\beta I}{N}S & \qquad \frac{dR}{dt} &= \gamma I - \mu R \\ \frac{dE}{dt} &= \frac{\beta I}{N}S - (\mu+\kappa)E & \qquad \frac{dV}{dt} &= (ef)\mu N - \mu V \\ \frac{dI}{dt} &= \kappa E - (\mu+\delta+\gamma)I & \qquad \frac{dN}{dt} &= -\delta I \end{aligned} \tag{3.3}$$

As in our previous epidemic models, we assume (i) equal birth and death rates μ and (ii) vaccination of a fraction f of the μN babies born per period with an all-or-nothing vaccine with efficacy e. Assuming a homogeneously mixing population, infected individuals transmit the disease to susceptibles at rate β; thus, the rate of new infections is $\frac{\beta I}{N}S$. These exposed individuals are asymptomatic and cannot transmit the disease during an incubation period that is exponentially distributed with mean $\frac{1}{\kappa}$, after which they become infectious. Infectious individuals either recover (at rate γ) or die from the disease (at rate δ).

Proposition 13. *The basic reproduction number R_0 and the basic reproduction number with vaccination R_v for Ebola are given as follows:*

$$R_0 = \frac{\beta\kappa}{(\mu+\kappa)(\mu+\delta+\gamma)} \qquad\qquad R_v = (1-ef)R_0$$

Figure 3.9: Compartmental epidemic model for Ebola.



The basic reproduction number R_0 is the ratio of the force of infection, which consists of the rate of direct transmission β multiplied by the fraction $\frac{\kappa}{\mu+\kappa}$ of individuals that transition from the exposed to infectious compartments, and the average duration of infectivity $\frac{1}{(\mu+\delta+\gamma)}$ before dying or recovering from the disease.

3.4.3 Parameter Values

We focus our analysis on the geographic regions that have previously experienced an Ebola epidemic, which is predominantly in west Africa, and the South American countries where Chagas is endemic. We provide a brief overview of our parameter estimation process.

Epidemic Parameters. The basic reproduction number R_0 for each disease is estimated by collecting R_0 values from the epidemiology literature; these values and their sources are summarized in Appendix Table B.3 . For Chagas, we only use sources that study the disease in South America. As these values are slightly skewed to the right, we use the median R_0 value for each disease.

Market size Q is estimated as the sum of the expected number of infants immunized in each country in our analysis, given as the product of the births per year and the country's DTP3 coverage, a common measure of the strength of a nation's immunization system (see Appendix Tables B.1 and B.2). The overall vaccination coverage f is computed as the market size Q divided by the

aggregate number of births.

We set $\eta_1 = 1 - (\frac{1}{R_0})^2$ and $1 - \frac{1}{R_0}$, for Chagas and Ebola, respectively, reflecting the minimum efficacy needed to eliminate the epidemic (i.e., the critical threshold for herd immunity $R_v < 1$), assuming all infants are vaccinated (i.e., $f = 1$). We define η_1 this way under the assumption that the WHO would not authorize the use of vaccines that cannot eliminate an epidemic, even with full vaccination coverage. We set $\eta_2 = \frac{\eta_1}{f}$ as the efficacy threshold required for elimination if only the fraction $f < 1$ of infants are vaccinated.

Manufacturing Cost and Efficacy Variability. We set the manufacturing cost c at \$1 per unit, which is comparable to the range of \$1.5 to \$3 used in the influenza vaccine literature (Chick et al., 2008). In order for Assumption 1 to hold, the variability in efficacy u must satisfy $u > \frac{\eta_2 - \eta_1}{2}$. Accordingly, we set $u = 0.06$ for Chagas and $u = 0.07$ for Ebola.

Epidemic and R&D Costs. The cost K_1 of having no vaccine is estimated as the product of the number of cases of each disease in the absence of a vaccine and the treatment cost per case. For Chagas, the number of cases is calculated using estimates from the WHO, and the range of values for the treatment cost per case are taken from Castillo-Riquelme et al. (2008) (WHO, 2015). For Ebola, the number of cases is calculated by extrapolating the number of cases from the 2014 epidemic, which reflects a very severe, wide-ranging epidemic, to the countries we study, and the range of treatment costs per case are taken from Bartsch et al. (2015). The cost K_3 of adding the vaccine the the country's routine immunization program is calculated as the product of the number of doses Q and the per-person vaccine distribution cost, estimated by Portnoy et al. (2015b). In the case that the disease is mitigated, the cost K_3 of vaccinating individuals is incurred, and we assume there is a reduction in the cost of treating infected individuals. Accordingly, we estimate K_2 as $K_3 + \theta K_1$, and we vary θ from 0.10 (a major reduction in infection costs) to 0.90 (a minor reduction in infection costs). We vary the R&D cost from \$100 million to \$800 million.

Table 3.3: Parameter estimates for Chagas and Ebola.

Parameter	Chagas	Ebola	Sources
R_0	2.19	1.79	See Appendix Table B.3
Q	5,935,378	5,944,018	See Appendix Tables B.1 and B.2
f	0.88	0.77	See Appendix Tables B.1 and B.2
η_1	0.79	0.44	See Propositions 9 and 10
η_2	0.90	0.57	See Propositions 9 and 10
c (\$)	1	1	Assumption
u	0.06	0.07	Assumption 1
K_1 (\$ million)	225-1238	866-1732	WHO (2015), Castillo-Riquelme et al. (2008) and Bartsch et al. (2015)
K_2 (\$ million)	28-1173	93-1618	Assumption
K_3 (\$ million)	6-59	6-59	Portnoy et al. (2015b)
r (\$ million)	100-800	100-800	Assumption

Table 3.3 summarizes our estimated parameter values for both diseases. Chagas has a higher basic reproduction number R_0, driven by the fact that infected individuals infected often live with the disease for years and have ample opportunities to spread the disease, while Ebola tends to kill its hosts before they are able to infect others. Although the market size Q for the two diseases is quite similar, Chagas-affected countries have a higher vaccination coverage f, in part because these nations tend to be wealthier than Ebola-affected nations. The mitigation and elimination thresholds η_1 and η_2 are substantially higher for Chagas as compared to Ebola. This disparity is driven by the fact that Ebola is transmitted from human to human, meaning that vaccination directly reduces transmission by preventing individuals from becoming infected and spreading the disease. In contrast, Chagas is vector-borne, and thus vaccination only reduces transmission indirectly, as infected kissing bugs are still able to spread the disease. Although Chagas has a larger number of cases than Ebola (4.5 million vs 216,500), treatment costs per case are significantly cheaper (\$50-\$275 vs \$4000-\$8000), resulting in lower epidemic costs K_1 and K_2 compared to Ebola.

3.4.4 Numerical Results

We generate cost scenarios by choosing 50 points uniformly from each interval of costs for K_1, K_2, K_3, and r, for a total of $50^4 = 6.25$ million scenarios. In our analysis, we only consider scenarios in which the cost of having no vaccine exceeds the cost of mitigation, which exceeds the cost of elimination (i.e., $K_1 > K_2 > K_3$). After removing scenarios that do not satisfy this condition, we have 4,119,984 cost scenarios remaining for Chagas and 5,451,696 for Ebola.

For each cost scenario, we compute the first-best targets and compare them to the optimal targets of the lump sum and linear contracts for both diseases. For a given set of parameters, Table 3.4 summarizes how often the first-best and optimal targets for each contract fall into each one of the five target efficacy regions.

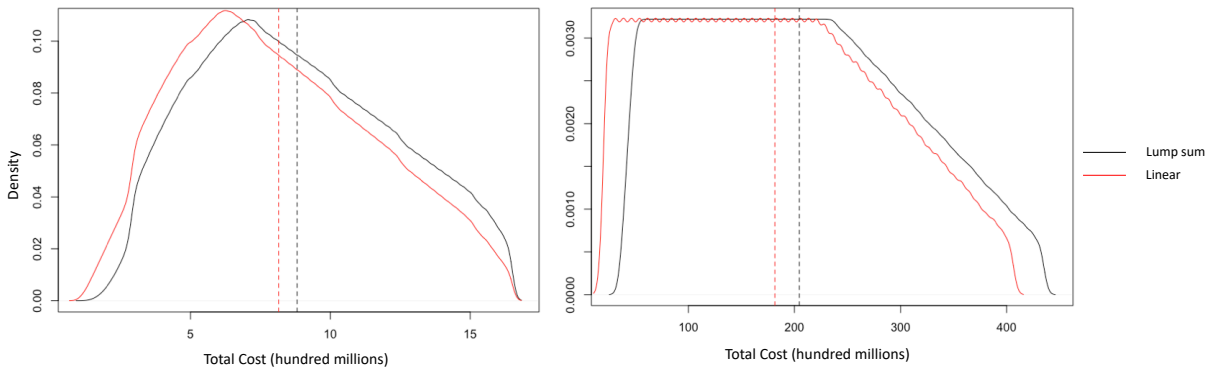
Table 3.4: Percent of cost scenarios in which the optimal target falls into each target efficacy region by contract and disease.

Disease	Contract	Region I	Region II	Region III	Region IV	Region V
Chagas	First-Best	6.26%	0%	0%	1.03%	92.71%
	Lump Sum	36.61%	0%	63.39%	0%	0%
	Linear	28.29%	0%	0%	71.71%	0%
Ebola	First-Best	0%	0%	0%	0%	100%
	Lump Sum	0.32%	0%	99.68%	0%	0%
	Linear	0%	0%	0%	100%	0%

Each region includes its left-most efficacy value and excludes its right-most value. For example, Region I is defined as $t \in [0, \eta_1 - u)$.

First, we observe that for the majority (all) of cost scenarios, the first-best targets for Chagas (Ebola) fall into Region V, in which elimination is guaranteed, though for Chagas we also observe scenarios in which the central planner does not produce a vaccine (Region I), and in which mitigation is guaranteed and elimination is possible (Region IV). Compared to first-best, both the lump sum and linear contracts for both diseases are more likely to result in lower targets over the scenarios we examined. Specifically, the lump sum contract is more likely to result in having no vaccine or in

Figure 3.10: Total non-procurement costs (R&D, manufacturing, and treatment) under the two price contract (black) and the performance-based contract (red) for Chagas (left) and Ebola (right).



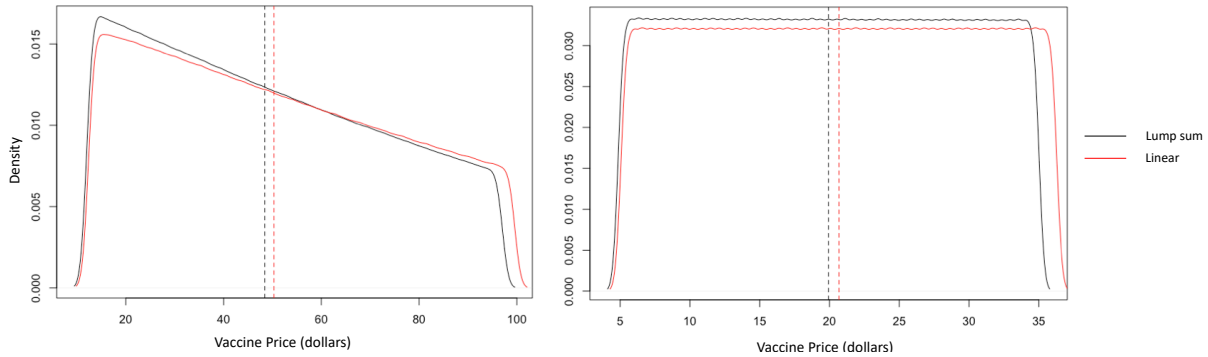
The dotted line marks the average (with respect to the imposed uniform distribution) total non-procurement cost under each contract.

making a vaccine where both mitigation and elimination are possible (Region III), while the linear contract either results in no vaccine (for Chagas only) or in a vaccine that is guaranteed to mitigate and possibly eliminate (Region IV).

Figures 3.10 and 3.11 are created by imposing a discrete uniform distribution over the cost scenarios in our analysis. Figure 3.10 displays the resulting distribution of total non-procurement costs (R&D, manufacturing, and treatment) across all cost scenarios under each contract. For both diseases, we find that, for a given cost scenario, the linear contract always results in lower total non-procurement costs as compared to the lump sum contract. Across all scenarios, the performance-based contract results in an average cost reduction of \$66 million (7.5%) for Chagas and \$2.3 billion (11.3%) for Ebola as compared to the lump sum contract. Per individual immunized, this is a savings of \$11.13 for Chagas and \$390.19 for Ebola.

Although the linear contract results in an average reduction in non-procurement costs, vaccines purchased under this contract tend to be more expensive per unit (\$4.36 (17.5%) for Chagas and \$1.78 (4.1%) for Ebola) than under the lump sum contract. However, as shown in Figure 3.11, the potential range of prices under both contracts is comparable to that of many routine vaccines such as Hib, which the CDC lists for \$9.48 and Varicella, listed for \$104.09 (CDC, 2019a).

Figure 3.11: Total per-unit price under the lump sum contract (black) and the linear contract (red) for Chagas (left) and Ebola (right)

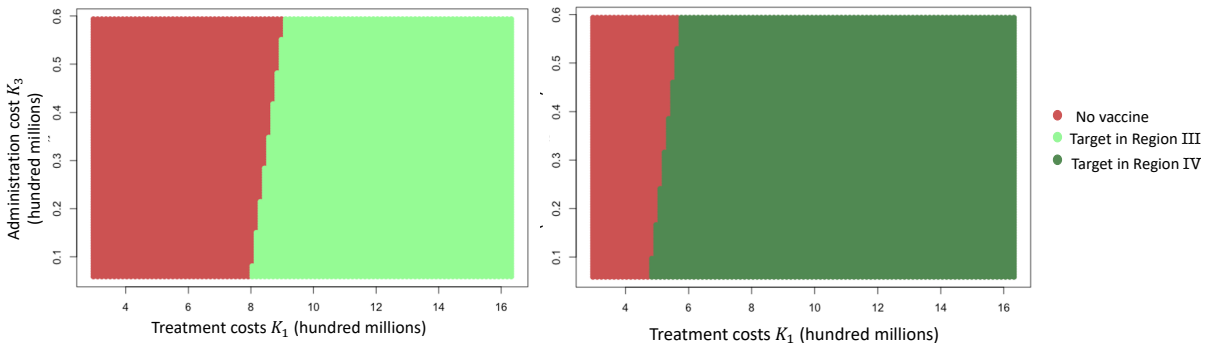


The dotted line marks the average (with respect to the imposed uniform distribution) total vaccine price under each contract.

As illustrated in Table 3.4, the lump sum and linear contracts result in optimal targets that either result in no vaccine (Region I), a vaccine that possibly mitigates and possibly eliminates (Region III), or (under the linear contract only) a vaccine that is guaranteed to mitigate and possibly eliminate (Region IV). Figures 3.12 and 3.13 illustrate the sensitivity of the optimal target under each contract to the cost of having no vaccine K_1 and the vaccine administration cost K_3. As in Section 3.4, K_2 is set so that $K_2 = \theta K_1 + K_3$; we choose a value of $\theta = 0.5$ to illustrate a situation in which a mitigating vaccine results in a moderate reduction in infection costs.

For both Chagas and Ebola, Figures 3.12 and 3.13 show that low values of K_1 are associated with producing no vaccine, which is line with the notion that if the cost of treating the disease is sufficiently low, then investing in vaccine development may be prohibitively expensive. For a given value of K_1, increasing the vaccine administration costs K_3 eventually causes the costs associated with developing and distributing a vaccine to outweigh the savings in treatment costs, leading to no investment in the vaccine. Comparing the left-hand and right-hand plots in both figures, we see that, over the range of costs examined, the linear contract invests in a vaccine for lower values of K_1 as compared to the lump sum contract, suggesting that this contract may be more successful at incentivizing manufacturers to invest in diseases with lower treatment costs.

Figure 3.12: Comparison of the optimal target for Chagas under the lump sum (left) and linear (right) contracts for different values of K_1 and K_3.

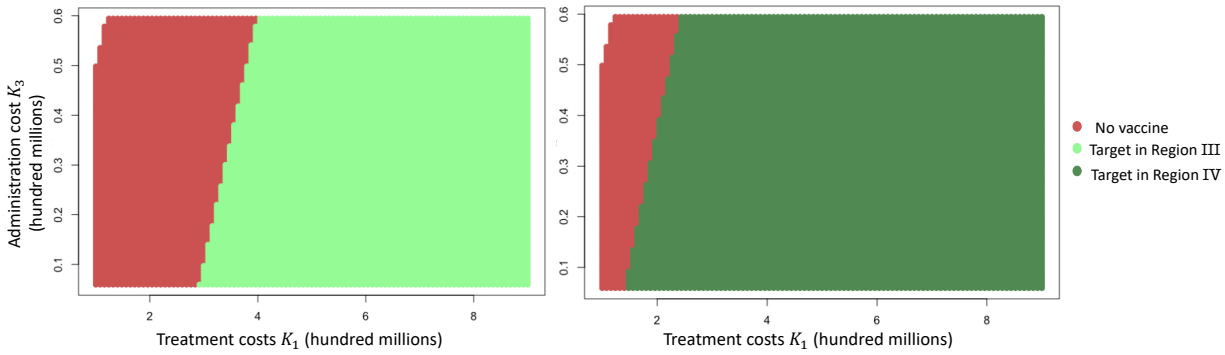


$K_2 = \theta K_1 + K_3$, where $\theta = 0.5$.

For Ebola, our estimated disease treatment costs K_1 (given in Table 3.3) are such that we only observe optimal targets in Region IV because of the high cost of treating this disease. To more easily explore the relationship between the optimal target and the treatment and administration costs, Figure 3.13 varies K_1 from \$100 million to \$900 million, which consists of cost scenarios under which producing no vaccine is optimal. We note that the white regions in upper left-hand corner of each plot correspond to cost scenarios that violate the assumption that $K_1 > K_2 > K_3$ and are thus excluded from our analysis. Figure 3.13 indicates that the optimal targets for Ebola respond to changes in treatment and administration costs in a similar manner as the targets for Chagas, and we similarly find that the linear contract invests in a vaccine for lower values of K_1 than the lump sum vaccine.

Comparing the right-hand plots in Figures 3.12 and 3.13, we note that both contracts for Ebola invest in a vaccine for lower values of the treatment cost K_1 as compared to Chagas. As the administration costs K_3 are similar for the two diseases, this is not the source of this difference. Rather, Ebola vaccines can be developed for lower values of K_1 because a lower vaccine efficacy is needed to mitigate/eliminate the disease – and thus the manufacturer incurs lower R&D costs – due to the fact that Ebola is spread directly between humans instead of indirectly via kissing bugs.

Figure 3.13: Comparison of the optimal target for Ebola under the lump sum (left) and linear (right) contracts for different values of K_1 and K_3.



$K_2 = \theta K_1 + K_3$, where $\theta = 0.5$.

3.5 Discussion

Although our work is among the first to study performance-based pricing to encourage R&D investment by vaccine manufacturers in developing more efficacious vaccines, performance-based contracting has been widely used in other healthcare settings. In the United States, the Centers for Medicare & Medicaid Services has implemented several performance-based programs designed to improve the quality of healthcare; perhaps their best-known program is the Hospital Readmissions Reduction Program, which reduces payments to hospitals that have high rates of avoidable readmissions for patients experiencing heart attacks, heart failure, or pneumonia. Additionally, pharmaceutical companies have implemented outcome-based pricing for drugs based on adverse patient outcomes. For example, in 2017, Amgen agreed to provide health services company Harvard Pilgrim with a rebate for the full cost of their cardiovascular drug Repatha in the event that a patient experiences a heart attack or stoke while using the product (Amgen, 2019). These examples provide payment to different stakeholders based on the outcomes of a single patient or single hospital. In contrast, performance-based contracting for vaccine development has the potential to benefit millions of susceptible individuals and to provide additional indirect protection to others

via herd immunity.

Our case study of Chagas and Ebola highlights the key role that the dynamics of the epidemic play in shaping the optimal target efficacy. In particular, the relationship between the realized efficacy and the basic reproduction number with vaccination depends on the mode of transmission. Our results suggests that manufacturers may be more likely to invest in diseases that are spread directly between humans (such as Ebola and Trachoma, the leading cause of blindness) due to the fact that, holding all other aspects of the disease constant, lower efficacy levels are needed to ensure mitigation/elimination as compared to a vector-transmitted disease. As illustrated in Table 3.1, many prevalent NTDs are transmitted via parasitic worms; our model could be used to analyze how this mode of transmission impacts the performance of different payment contracts.

We consider vaccine development for NTDs, but our model could be extended to analyze dynamic vaccines such as the flu vaccine whose composition (and thus efficacy) changes from year to year due to genetic drift. Between 2004 and 2018, the vaccine's efficacy has varied between a low of 10% during the 2004-2005 season to a high of 60% during the 2010-2011 season. Such an analysis could consider the annual interaction between governments and vaccine manufacturers as a repeated game (CDC, 2019b), and contracts that seek to minimize the variability in efficacy or to raise the expected efficacy over a given time period could be studied.

3.5.1 Limitations

Our work has several limitations. First, we consider a single manufacturer, rather than analyzing a model with competition among several manufacturers. Additionally, we assume that the manufacturer has enough capacity to fulfill all demand. The assumption of sufficient capacity could easily be relaxed, but incorporating multiple manufacturers would significantly increase the complexity of our model, as we would have to model the equilibrium market share resulting from competition.

Furthermore, unlike other infectious diseases with large global markets that attract multiple pharmaceutical companies, NTDs have smaller markets and generally suffer from a lack of investment, meaning that a single manufacturer is likely realistic for our setting.

We also make several assumptions regarding vaccine efficacy. First, we assume that efficacy follows a uniform distribution, although several other distributions (such as normal or beta) are possible, and we consider the mitigation cost K_2 to be fixed cost rather than a function of the realized vaccine efficacy. Relaxing these assumptions would render our model analytically intractable, but different assumptions could be explored numerically. Finally, in our numerical analysis, we consider vaccines that exhibit failure in take, but depending on the disease under consideration, failure in degree or duration may be more appropriate.

3.5.2 Future Work

Our work prompts several directions for future studies. One extension would involve comparing performance-based contracts to an AMC, with the goal of identifying conditions under which one mechanism dominates the other. Under an AMC, a GHO must select (i) an initial high price to offer for the first Q doses of a vaccine, and (ii) a lower tail price to offer for additional doses, while manufacturers select their target vaccine efficacy.

There are also additional settings within vaccine markets that may benefit from the use of performance-based contracts. For example, in an effort to raise immunization rates, Gavi, the Vaccine Alliance pays healthcare workers a flat price per individual vaccinated during a campaign; the costs and benefits of alternative payment schemes such as performance-based payment could be analyzed.

3.5.3 Conclusions

Vaccines have revolutionized global health, eradicating diseases that were once commonplace and preventing millions of premature deaths. Existing funding mechanisms have succeeded in incentivizing the development of vaccines for diseases with large markets in wealthy nations, but different approaches are needed to encourage the development of products for diseases affecting the world's poorest individuals. Innovative payment schemes such as performance-based contracts can help better align incentives between GHOs and manufacturers and increase the effort exerted by pharma companies to develop more efficacious vaccines.

Appendices

Appendix B Contracts to Increase the Effectiveness and Availability of Vaccines

B.1 Notation

General Model Parameters

R_0	basic reproduction number
R_v	basic reproduction number with vaccination
f	fraction of newborn infants immunized
Q	quantity of vaccines purchased from the manufacturer
$p(e)$	per-unit price for a vaccine with efficacy e
e	realized vaccine efficacy
η_1	minimum efficacy threshold
t	target efficacy level selected by the manufacturer
r	manufacturer research and development cost rt^2
ϵ	uncertainty in vaccine efficacy
u	variability in vaccine efficacy
c	per-unit manufacturing cost
K_1	lump sum cost of treating the disease with no vaccine
η_2	efficacy threshold for disease elimination
K_2	lump sum cost of administering a vaccine and treating infected individuals in the case of mitigation
K_3	lump sum cost of administering a vaccine in the case of elimination

Centralized System Parameters

$\Pi(t)$	total costs for the immunization supply chain
D_1	marginal expected savings to central planner on Region II
D_2	marginal expected savings to central planner on Region III
D_3	marginal expected savings to central planner on Region IV
t^*	first-best target efficacy level

Lump Sum Contract Parameters

p_1	per-unit price for a mitigating vaccine
p_2	per-unit price for an eliminating vaccine
$\widehat{\Pi}_G$	expected GHO costs
$t(p_1, p_2)$	manufacturer's best response as a function of contract prices
$\widehat{\Pi}_M$	expected manufacturer profit
$\widehat{D}_1$	manufacturer's marginal expected revenue on Region II
$\widehat{D}_2$	manufacturer's marginal expected revenue on Region III
$\widehat{D}_3$	manufacturer's marginal expected revenue on Region IV
$\widehat{t}$	optimal target efficacy
$\widehat{p}_1$	optimal per-unit price for a mitigating vaccine
$\widehat{p}_2$	optimal per-unit price for an eliminating vaccine

Linear Contract Parameters

p_1	per-unit base price
p_2	per-unit marginal efficacy price
$\widetilde{\Pi}_G$	expected GHO costs
$\widetilde{\Pi}_M$	expected manufacturer profit
$\widetilde{D}_1$	vertical shift in manufacturer's marginal expected revenue on Regions II and III
$\widetilde{M}$	change in slope of the manufacturer's marginal expected revenue on Regions II and III
$\widetilde{D}_2$	vertical shift in manufacturer's marginal expected revenue on Regions IV and V
$\widetilde{t}$	optimal target efficacy
$\widetilde{p}_1$	optimal per-unit base price
$\widetilde{p}_2$	optimal marginal efficacy price

B.2 Proofs

Proof of Proposition 4 The objective function for the centralized system can be written as follows:

$$\Pi(t) = \begin{cases} rt^2 + K_1 & \text{if } t < \eta_1 - u \\ rt^2 + K_1\frac{(\eta_1 - t + u)}{2u} + (cQ + K_2)\frac{(u - \eta_1 + t)}{2u} & \text{if } \eta_1 - u \le t < \eta_2 - u \\ rt^2 + K_1\frac{(\eta_1 - t + u)}{2u} + (cQ + K_2)\frac{(\eta_2 - \eta_1)}{2u} + cQ\frac{(u - \eta_2 + t)}{2u} + K_3\left(\frac{u - \eta_2 + t}{2u}\right) & \text{if } \eta_2 - u \le t < \eta_1 + u \\ rt^2 + cQ + K_2\frac{\eta_2 - t + u}{2u} + K_3\left(\frac{u - \eta_2 + t}{2u}\right) & \text{if } \eta_1 + u \le t < \eta_2 + u \\ rt^2 + cQ + K_3 & \text{if } t \ge \eta_2 + u \end{cases}$$

Taking derivatives, we have

$$\Pi'(t) = \begin{cases} 2rt & \text{if } t < \eta_1 - u \\ 2rt + \frac{cQ+K_2-K_1}{2u} & \text{if } \eta_1 - u \le t < \eta_2 - u \\ 2rt + \frac{cQ+K_3-K_1}{2u} & \text{if } \eta_2 - u \le t < \eta_1 + u \\ 2rt + \frac{K_3-K_2}{2u} & \text{if } \eta_1 + u \le t < \eta_2 + u \\ 2rt & \text{if } t \ge \eta_2 + u \end{cases}$$

The marginal cost on all intervals is linearly increasing in t, and thus the objective function can either be (i) always decreasing, (ii) decreasing then increasing or (iii) always increasing. A sufficient condition for (i) is that the marginal cost is negative at the right endpoint of an interval. Sufficient conditions for (ii) are that the marginal cost is negative at the left endpoint and positive at the right endpoint, while a sufficient condition for (iii) is that the marginal cost is positive at the left endpoint. The objective is increasing on $(0, \eta_1 - u)$ and on $(\eta_2 + u, 1)$ but the behavior on the remaining intervals depends on the problem parameters.

There are eight candidate optimal solutions, which occur either at the boundary of an interval or when the marginal cost is zero: $t = 0$, $\eta_1 - u$, $\frac{D_1}{2r}$, $\eta_2 - u$, $\frac{D_2}{2r}$, $\eta_1 + u$, $\frac{D_3}{2r}$, and $\eta_2 + u$.

We begin by imposing sufficient conditions that ensure the objective is unimodular and thus has a unique optimum. We note that all of our candidate solutions may be possible optima, with the exception of $\eta_1 - u$ and $\eta_2 - u$. To see that $\eta_1 - u$ cannot be optimal, note that the objective is strictly increasing on $(0, \eta_1 - u)$. In order for $\eta_2 - u$ to be optimal (and the objective be monotonic), we would need the objective to be decreasing on $(\eta_1 - u, \eta_2 - u)$ and increasing on $(\eta_2 - u, \eta_1 + u)$. A sufficient condition for the first behavior is given by $2r(\eta_2 - u) + \frac{cQ+K_2-K_1}{2u} < 0$, while a sufficient condition for the second behavior is given by $2r(\eta_2 - u) + \frac{cQ+K_3-K_1}{2u} > 0$. Jointly, these conditions imply that $K_3 > K_2$, which contradicts our assumption that $K_1 > K_2 > K_3$.

The remaining six solutions and the sufficient conditions needed to ensure the objective is unimodular are given below:

1. $t^* = 0$ if $2r(\eta_1 - u) > D_1$, $2r(\eta_2 - u) > D_2$, $2r(\eta_1 + u) > D_2 - D_1$
2. $t^* = \frac{D_1}{2r}$ if $2r(\eta_1 - u) < D_1 < 2r(\eta_2 - u)$, $2r(\eta_2 - u) > D_2$, and $2r(\eta_1 + u) > D_2 - D_1$
3. $t^* = \frac{D_2}{2r}$ if $2r(\eta_1 - u) > D_1$, $2r(\eta_2 - u) < D_2 < 2r(\eta_1 + u)$, and $2r(\eta_1 + u) > D_2 - D_1$
4. $t^* = \eta_1 + u$ if $2r(\eta_2 - u) > D_1$, $2r(\eta_1 + u) < D_2$, and $2r(\eta_1 + u) > D_2 - D_1$
5. $t^* = \frac{D_3}{2r}$ if . $2r(\eta_1 - u) > D_1$, $2r(\eta_2 - u) > D_2$, and $2r(\eta_1 + u) < D_2 - D_1 < 2r(\eta_2 + u)$
6. $t^* = \eta_2 + u$ if $2r(\eta_1 - u) > D_1$, $2r(\eta_2 - u) > D_2$, and $2r(\eta_2 + u) < D_2 - D_1$

Noting that we must have $D_2 > D_1$ to ensure that $K_1 > K_2 > K_3$, we see that if we impose the condition $D_2 < 2r(\eta_2 - u)$, then we are able to fully characterize the optimal solution (see Figure 3.3). In imposing this condition, we rule out solutions (3) and (4). The remaining four solutions and the regions on which they are optimal are presented in Figure 3.3. ■

Proof of Proposition 2 The manufacturer's profit function can be written as follows:

$$\widehat{\Pi}_M(t) = \begin{cases} -rt^2 & \text{if } t < \eta_1 - u \\ -rt^2 + (p_1 - c)Q\left(\frac{u-\eta_1+t}{2u}\right) & \text{if } \eta_1 - u \le t < \eta_2 - u \\ -rt^2 + (p_1 - c)Q\left(\frac{\eta_2-\eta_1}{2u}\right) + (p_2 - c)Q\left(\frac{u-\eta_2+t}{2u}\right) & \text{if } \eta_2 - u \le t < \eta_1 + u \\ -rt^2 + (p_1 - c)Q\left(\frac{\eta_2-t+u}{2u}\right) + (p_2 - c)Q\left(\frac{u-\eta_2+t}{2u}\right) & \text{if } \eta_1 + u \le t < \eta_2 + u \\ -rt^2 + (p_2 - c)Q & \text{if } t \ge \eta_2 + u \end{cases}$$

Taking derivatives, we have

$$\widehat{\Pi}'_M(t) = \begin{cases} -2rt & \text{if } t < \eta_1 - u \\ -2rt + \frac{(p_1-c)Q}{2u} & \text{if } \eta_1 - u \le t < \eta_2 - u \\ -2rt + \frac{(p_2-c)Q}{2u} & \text{if } \eta_2 - u \le t < \eta_1 + u \\ -2rt + \frac{(p_2-p_1)Q}{2u} & \text{if } \eta_1 + u \le t < \eta_2 + u \\ -2rt & \text{if } t \ge \eta_2 + u \end{cases}$$

Similar to the centralized problem, we see that the marginal cost on all intervals is linearly decreasing in t, and so the objective is either (i) always decreasing, (ii) increasing then decreasing, or (iii) always increasing. A sufficient condition for (i) is that the marginal cost is negative at the left endpoint of an interval. Sufficient conditions for (ii) are that the marginal cost is positive at the left endpoint and negative at the right endpoint, while a sufficient condition for (iii) is that the marginal cost is positive at the right endpoint. The objective is strictly decreasing on $(0, \eta_1 - u)$ and $(\eta_2 + u, 1)$, but the behavior on the other intervals depends on the problem parameters.

There are eight candidate optimal soultions, which occur either at the boundary of an interval or when the marginal cost is zero: $t = 0$, $\eta_1 - u$, $\frac{\widehat{D}_1}{2r}$, $\eta_2 - u$, $\frac{\widehat{D}_2}{2r}$, $\eta_1 + u$, $\frac{\widehat{D}_3}{2r}$, $\eta_2 + u$.

We begin by imposing sufficient conditions that ensure the manufacturer's profit is unimodular and thus has a unique optimum. We note that all of our candidate solutions may be possible optima, with the exception of $\eta_1 - u$, which cannot be optimal because the objective is strictly decreasing on $(0, \eta_1 - u)$.

The remaining seven solutions and the sufficient conditions needed to ensure the objective is unimodular for each solution are given below:

1. $t(p_1, p_2) = 0$ if $\widehat{D}_1 < 2r(\eta_1 - u)$, $\widehat{D}_2 < 2r(\eta_2 - u)$, and $\widehat{D}_2 - \widehat{D}_1 < 2r(\eta_1 + u)$
2. $t(p_1, p_2) = \frac{\widehat{D}_1}{2r}$ if $2r(\eta_1 - u) < \widehat{D}_1 < 2r(\eta_2 - u)$, $\widehat{D}_2 < 2r(\eta_2 - u)$, and $\widehat{D}_2 - \widehat{D}_1 < 2r(\eta_1 + u)$
3. $t(p_1, p_2) = \eta_2 - u$ if $\widehat{D}_1 > 2r(\eta_2 - u)$, $\widehat{D}_2 < 2r(\eta_2 - u)$, and $\widehat{D}_2 - \widehat{D}_1 < 2r(\eta_1 + u)$
4. $t(p_1, p_2) = \frac{\widehat{D}_2}{2r}$ if $\widehat{D}_1 < 2r(\eta_1 - u)$, $2r(\eta_2 - u) < \widehat{D}_2 < 2r(\eta_1 + u)$, and $\widehat{D}_2 - \widehat{D}_1 < 2r(\eta_1 + u)$
5. $t(p_1, p_2) = \eta_1 + u$ if $\widehat{D}_1 < 2r(\eta_1 - u)$, $\widehat{D}_2 > 2r(\eta_1 + u)$, and $\widehat{D}_2 - \widehat{D}_1 < 2r(\eta_1 + u)$

6. $t(p_1,p_2)=\frac{\widehat{D}_3}{2r}$ if $\widehat{D}_1<2r(\eta_1-u)$, $\widehat{D}_2<2r(\eta_2-u)$, and $2r(\eta_1+u)<\widehat{D}_2-\widehat{D}_1<2r(\eta_2+u)$

7. $t(p_1,p_2)=\eta_2+u$ if $\widehat{D}_1<2r(\eta_1-u)$, $\widehat{D}_2<2r(\eta_2-u)$, and $\widehat{D}_2-\widehat{D}_1>2r(\eta_2+u)$

We note that if we impose the condition $\widehat{D}_2<2r(\eta_2-u)$, then we are able to fully characterize the optimal solution (see Figure 3.5. By imposing this condition, we rule out solutions (4) and (5). The remaining five solutions and the regions on which they are selected by the manufacturer are presented in Figure 3.5. ■

Proof of Proposition 3 For each of the five possible values of the manufacturer's best response function, we solve the GHO's problem to find the five possible equilibria $t_{(i)}-t_{(v)}$. We provide the optimal prices $\widehat{p}_1$ and $\widehat{p}_2$, as well as feasibility conditions and individual rationality (IR) and participation constraints. The feasibility conditions ensure that the value of the optimal target $\widehat{t}$ lies in the desired range. The IR constraints ensure that $\widehat{t}$ maximizes the manufacturer's profit and are obtained by ensuring the unimodularity conditions given in Proposition 2 hold. $\widehat{t}_{(i)}$: If $t(p_1,p_2)=0$, then the GHO's objective becomes K_1, and the participation constraint is satisfied. The IR constraints give $\widehat{p}_{1(i)}<\frac{4ru(\eta_1-u)}{Q}+c$, $\widehat{p}_{2(i)}<\frac{4ru(\eta_2-u)}{Q}+c$, and $\widehat{p}_{2(i)}-\widehat{p}_{1(i)}<\frac{4ru(\eta_1+u)}{Q}$.

$\widehat{t}_{(ii)},\widehat{t}_{(iii)}$: If $t(p_1,p_2)=\frac{\widehat{D}_1}{2ru}$, then the GHO's problem becomes

$$\min_{p_1,p_2} p_1^2\frac{Q^2}{8ru^2}+p_1Q\left(\frac{K_2-cQ}{8ru^2}-\frac{(\eta_1-u)}{2u}-\frac{K_1}{8ru^2}\right)+\frac{K_1(\eta_1+u)}{2u}-\frac{K_2(\eta_1-u)}{2u}+\frac{(K_1-K_2)cQ}{8ru^2}$$

$$\text{s.t. } p_1\geq\frac{8ru(\eta_1-u)}{Q}+c$$

We see that the objective is a quadratic in p_1, subject to a lower bound constraint. Thus we get

$$p_1=\max\left\{\frac{8ru(\eta_1-u)}{Q}+c,\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_2}{2Q}\right\}$$

If $\frac{8ru(\eta_1-u)}{Q}+c\geq\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_2}{2Q}$, then $p_1=\widehat{p}_{1(ii)}=\frac{8ru(\eta_1-u)}{Q}+c$ and $t=\widehat{t}_{(ii)}=2(\eta_1-u)$. In order for $\widehat{t}_{(ii)}$ to be in the range (η_1-u,η_2-u), we need $\eta_1-u<2(\eta_1-u)<\eta_2-u$. This gives the two conditions $\eta_1-u<\eta_2-\eta_1$ and $\eta_1<3u$. In order for $\frac{8ru(\eta_1-u)}{Q}+c>\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_2}{2Q}$, we need $3(\eta_1-u)>\frac{K_1-K_2-cQ}{4ru}$. The IR constraints give $\widehat{p}_{2(ii)}<\min\{\frac{8ru(\eta_1-u)}{Q}+\frac{4ru(\eta_1+u)}{Q}+c,\frac{4ru(\eta_2-u)}{Q}+c\}$.

If $\frac{8ru(\eta_1-u)}{Q}+c\leq\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_2}{2Q}$ then $p_1=\widehat{p}_{1(iii)}=\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_2}{2Q}$ and $\widehat{t}_{(iii)}=\frac{K_1-K_2-cQ}{8ru}+\frac{\eta_1-u}{2}$. In order for $\widehat{t}_{(iii)}$ to be in the range (η_1-u,η_2-u), we need $\eta_1-u<\frac{K_1-K_2-cQ}{8ru}+\frac{\eta_1-u}{2}<\eta_2-u$. To have $\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_2}{2Q}>\frac{8ru(\eta_1-u)}{Q}+c$, we need $\frac{K_1-K_2-cQ}{4ru}>3(\eta_1-u)$. The IR constraints give $\widehat{p}_{2(iii)}<\min\{\frac{4ru(\eta_2-u)Q}{+}c,\frac{4ru(\eta_1+u)}{Q}+\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_2}{Q}\}$.

$\widehat{t}_{(iv)}$: If $t(p_1,p_2)=\eta_2-u$, then the GHO's problem becomes

$$\min_{p_1,p_2} K_1\left(\frac{\eta_1-\eta_2+2u}{2u}\right)+(K_2+p_1Q)\frac{(\eta_2-\eta_1)}{2u}$$

$$\text{s.t.}p_1\geq c+\frac{2ru(\eta_2-u)^2}{Q(\eta_2-\eta_1)}$$

We see that $\widehat{p}_{1(iv)}=c+\frac{2ru(\eta_2-u)^2}{Q(\eta_2-\eta_1)}$, and that this price makes the participation constraint binding. One IR constraint gives $\widehat{p}_{1(iv)}>\frac{4ru(\eta_2-u)}{Q}+c$, which simplifies to $2\eta_1>\eta_2+u$. The remaining IR constraints give $\widehat{p}_{2(iv)}<\min\left\{\frac{4ru(\eta_2-u)}{Q}+c,\frac{4ru(\eta_1+u)}{Q}+c+\frac{2ru(\eta_2-u)^2}{Q(\eta_2-\eta_1)}\right\}$.

$\widehat{t}_{(v)}$: If $t(p_1,p_2)=\frac{\widehat{D}_3}{2r}$, then the GHO problem becomes

$$\min_{p_1,p_2} \frac{p_1^2Q^2}{8ru^2}+\frac{p_2^2Q^2}{8ru^2}-\frac{2p_1p_2Q^2}{8ru^2}+p_1Q\left(\frac{\eta_2+u}{2u}+\frac{K_2}{8ru^2}-\frac{K_3}{8ru^2}\right)+p_2Q\left(\frac{K_3}{8ru^2}-\frac{K_2}{8ru^2}-\frac{\eta_2-u}{2u}\right)$$
$$+\frac{K_2(\eta_2+u)}{2u}-\frac{K_3}{2u}(\eta_2-u)$$
$$\text{s.t. } \frac{8ru(p_1-c)Q(\eta_2+u)}{16ru^2}-\frac{8ruQ(p_1-c)(\eta_2-u)}{16ru^2}+\frac{(p_2-p_1)^2Q^2}{16ru^2}\geq 0$$

From the KKT conditions, we find that $\widehat{p}_{2(v)}-\widehat{p}_{1(v)}=\frac{K_2-K_3}{Q}$ and that the participation constraint is tight. Substituting p_2 into the participation constraint and solving for p_1 gives $\widehat{p}_{1(v)}=c+\frac{(\eta_2-u)(K_2-K_3)}{2Qu}-\frac{(K_2-K_3)^2}{16ru^2Q}$. Using the previous relationship, we get $\widehat{p}_{2(v)}=c+\frac{(\eta_2-u)(K_2-K_3)}{2Qu}-\frac{(K_2-K_3)^2}{16ru^2Q}+\frac{K_2-K_3}{Q}$.

In order to ensure that $\widehat{t}_{(v)}\in(\eta_1+u,\eta_2+u)$, we need $\eta_1+u<\frac{K_2-K_3}{4ru}<\eta_2+u$. From the IR constraints, we need $\frac{(\widehat{p}_{1(v)}-c)Q}{4ru}<\eta_1-u$ and $\frac{(\widehat{p}_{2(v)}-c)Q}{4ru}<\eta_2-u$. Substituting in our expressions for $\widehat{p}_{1(v)}$ and $\widehat{p}_{2(v)}$ gives $\frac{K_2-K_3}{8ru^2}\left(\frac{8ru(\eta_2-u)-K_2-K_3}{8ru}\right)<\eta_1-u$ and $\frac{K_2-K_3}{8ru^2}\left(\frac{(\eta_2+u)8ru-K_2-K_3}{8ru}\right)<\eta_2-u$.

In the case that $t(p_1,p_2)=\eta_2+u$, the GHO's problem becomes

$$\min_{p_1,p_2} K_3+p_2Q$$
$$\text{s.t. } -r(\eta_2+u)^2+(p_2-c)Q\geq 0$$

which has solution $\widehat{p}_2=\frac{r(\eta_2+u)^2}{Q}+c$. However, one of the IR constraints dictates that $\frac{(\widehat{p}_2-c)Q}{4ru}<\eta_2-u$. Substituting in for $\widehat{p}_2$ and rearranging gives $(\eta_2-u)^2<-4u^2$, indicating that $t=\eta_2+u$ is not an equilibrium of the lump sum contract. ■

Proof of Proposition 4 In order to coordinate the manufacturer's target efficacy to the first-best value $\frac{D_1}{2r}=\frac{K_1-K_2-cQ}{4ru}\in(\eta_1-u,\eta_2-u)$, we note that the manufacturer's best response function on this region is given by $\frac{\widehat{D}_1}{2r}=\frac{(p_1-c)Q}{4ru}$. Thus we can choose $p_1=\frac{K_1-K_2}{Q}$ in order to align the manufacturer's best response to the first-best target. For the IR constraints to hold, we need $p_2<\frac{4ru(\eta_2-u)}{Q}+c$ and $p_2<\frac{4ru(\eta_1+u)}{Q}+p_1$. Finally, in order for the manufacturer's participation constraint to hold, we need $\frac{D_1}{2r}\geq 2(\eta_1-u)$. However, as the first-best target takes the value $\frac{D_1}{2r}$ only if $2r(\eta_1-u)\leq D_1\leq 2r(\eta_2-u)$, we see that we need $4r(\eta_1-u)\leq 2r(\eta_2-u)$, which simplifies to $\eta_1\leq\frac{\eta_2+u}{2}$.

To see that there are no prices that incentivize the manufacturer to select the target η_2+u, recall that the manufacturer's participation constraint under this target becomes $-r(\eta_2+u)^2+(p_2-c)Q\geq 0$, meaning that the central planner must select p_2 so that $p_2\geq\frac{r(\eta_2+u)^2}{Q}+c$. However, in order for this target to be optimal for the manufacturer, we need $p_2<\frac{4ru(\eta_2-u)}{Q}+c$. Together, these conditions require $\frac{r(\eta_2+u)^2}{Q}+c<\frac{4ru(\eta_2-u)}{Q}+c$, which gives $(\eta_2-u)^2<-4u^2$, a contradiction. Thus no prices exist that can incentivize the manufacturer to select the target $t=\eta_2+u$. ■

Proof of Proposition 5 Under the wholesale price contract, the manufacturer's problem is

$$\max_{t\in[0,1]} \overline{\Pi}_M(t)=(p_1-c)Q\mathbb{P}(e>\eta_1)-rt^2$$

which can be rewritten as

$$\overline{\Pi}_M(t) = \begin{cases} -rt^2 & \text{if } t < \eta_1 - u \\ (p_1 - c)Q\left(\frac{u-\eta_1+t}{2u}\right) - rt^2 & \text{if } \eta_1 - u < t < \eta_1 + u \\ (p_1 - c)Q - rt^2 & \text{if } t > \eta_1 + u \end{cases}$$

Taking derivatives, we have

$$\overline{\Pi}'_M(t) = \begin{cases} -2rt & \text{if } t < \eta_1 - u \\ \frac{(p_1-c)Q}{2u} - 2rt & \text{if } \eta_1 - u < t < \eta_1 + u \\ -2rt & \text{if } t > \eta_1 + u \end{cases}$$

so we see that the manufacturer's profit is decreasing on $(0, \eta_1 - u)$ and on $(\eta_1 + u, 1)$. Solving for the manufacturer's best response function gives

$$t(p_1) = \begin{cases} 0 & \text{if } \frac{(p_1-c)Q}{4ru} < \eta_1 - u \\ \frac{(p_1-c)Q}{4ru} & \text{if } \eta_1 - u < \frac{(p_1-c)Q}{4ru} < \eta_1 + u \\ \eta_1 + u & \text{if } \frac{(p_1-c)Q}{4ru} > \eta_1 + u \end{cases}$$

Under the wholesale price contract, the GHO's problem is given as

$$\min_{p_1} \overline{\Pi}_G(p_1) = K_1\mathbb{P}(e < \eta_1) + \mathbb{P}(\eta_1 < e < \eta_2)(K_2 + p_1Q) + (K_3 + p_1Q)\mathbb{P}(e > \eta_2)$$

$$\text{s.t. } (p_1 - c)Q\mathbb{P}(e > \eta_1) - rt^2 \geq 0$$

The analysis of the GHO's problem for $t(p_1) = 0$ and part of the analysis for $t(p_1) = \frac{(p_1-c)Q}{4ru}$ (when $t(p_1) < \eta_2 - u$) is identical to cases (i), (ii), (iii) in the proof of proposition 3 because these equilibria occur when the target falls below $\eta_2 - u$ and the lump sum contract reduces to the wholesale price contract. We denote the three equilibria that are shared by these two contracts as (i), (ii), and (iii). We analyze the remaining cases where the manufacturer's best response falls above $\eta_2 - u$.

(iv) and (v): If $t(p_1) = \frac{(p_1-c)Q}{4ru}$ and $\eta_2 - u < t(p_1) < \eta_1 + u$, then the GHO's problem becomes

$$\min_{p_1} \frac{p_1^2Q^2}{8ru^2} + p_1Q\left(\frac{K_3}{8ru^2} - \frac{cQ}{8ru^2} - \frac{\eta_1 - u}{2u} - \frac{K_1}{8ru^2}\right)$$
$$+ \frac{K_1cQ}{8ru^2} + \frac{K_1(\eta_1 + u)}{2u} + \frac{K_2(\eta_2 - \eta_1)}{2u} - (\eta_2 - u)\frac{K_3}{2u} - \frac{cQ}{8ru^2}$$
$$\text{s.t. } p_1 \geq \frac{8ru(\eta_1 - u)}{Q} + c$$

The objective is quadratic in p_1, with a lower bound constraint. Thus

$$p_1 = \max\left\{\frac{8ru(\eta_1 - u)}{Q} + c, \frac{c}{2} + \frac{2ru(\eta_1 - u)}{Q} + \frac{K_1 - K_3}{2Q}\right\}$$

If $\frac{8ru(\eta_1-u)}{Q}+c \geq \frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_3}{2Q}$, then $\overline{p}_{1(iv)}=\frac{8ru(\eta_1-u)}{Q}+c$ and $\bar{t}_{(iv)}=2(\eta_1-u)$. To have $\frac{8ru(\eta_1-u)}{Q}+c > \frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_3}{2Q}$ we need $3(\eta_1-u) > \frac{K_1-K_3-cQ}{4ru}$. The IR constraints give $\eta_2-\eta_1 < \eta_1-u$ and $\eta_1 < 3u$.

If $\frac{8ru(\eta_1-u)}{Q}+c \leq \frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_3}{2Q}$, then $\overline{p}_{1(v)}=\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_3}{2Q}$ and $\bar{t}_{(v)}=\frac{K_1-K_3-cQ}{8ru}+\frac{\eta_1-u}{2}$. The IR constraint gives $2\eta_2-\eta_1-u < \frac{K_1-K_3-cQ}{4ru} < \eta_1+3u$. In order for $\frac{c}{2}+\frac{2ru(\eta_1-u)}{Q}+\frac{K_1-K_3}{2Q} > c+\frac{8ru(\eta_1-u)}{Q}$ we need $3(\eta_1-u) < \frac{K_1-K_3-cQ}{4ru}$. Combining this constraint with the IR constraint, we see that we need $\eta_1 < 3u$.

(vi): If $t(p_1)=\eta_1+u$, then the GHO's problem becomes

$$\min_{p_1} p_1Q+K_2\left(\frac{\eta_2-\eta_1}{2u}\right)+K_3-\frac{K_3}{2u}(\eta_2-\eta_1)$$

$$\text{s.t. } p_1 \geq \frac{r(\eta_1+u)^2}{Q}+c$$

Thus the GHO's optimal decision is $\overline{p}_{1(vi)}=\frac{r(\eta_1+u)^2}{Q}+c$. The IR condition is $\frac{(p_1-c)Q}{4ru} > \eta_1+u$, which requires $\eta_1 > 3u$.

From the manufacturer's best response function, it is clear that there is no price p_1 that can coordinate the vaccine efficacy target to a first-best level greater than η_1+u. ■

Proof of Proposition 6 Under the linear contract, the manufacturer's profit function can be written as follows:

$$\widetilde{\Pi}_M(t)=\begin{cases} -rt^2 & \text{if } t < \eta_1-u \\ (p_1-c)Q\left(\frac{t+u-\eta_1}{2u}\right)+p_2Q\left(\frac{1}{4u}(t+u+\eta_1)(t+u-\eta_1)\right)-rt^2 & \text{if } \eta_1-u \leq t < \eta_1+u \\ (p_1-c)Q+p_2Qt-rt^2 & \text{if } t \geq \eta_1+u \end{cases}$$

Taking derivatives gives

$$\widetilde{\Pi}'_M(t)=\begin{cases} -2rt & \text{if } t < \eta_1-u \\ \frac{1}{2u}(p_1-c)Q+\frac{p_2Q}{2u}(t+u)-2rt & \text{if } \eta_1-u \leq t < \eta_1+u \\ p_2Q-2rt & \text{if } t \geq \eta_1+u \end{cases}$$

We note that the marginal profit is piecewise linear in the target efficacy. There are five candidate optimal solutions, which either occur at the boundary of an interval or when the marginal cost is zero: $t=0, \eta_1-u, \frac{(p_1-c)Q+p_2Qu}{4ru-p_2Q}, \eta_1+u, \frac{p_2Q}{2r}$. By imposing the sufficient conditions given in the proposition, one can show that it is possible to achieve all candidate solutions, with the exception of η_1-u, which cannot be optimal because the profit function is strictly decreasing on the interval $(0, \eta_1-u)$. ■

Proof of Proposition 7 For each of the four possible values of the manufacturer's best response function, we solve the GHO's problem to find the five possible equilibria (i)-(v). We provide the optimal prices $\widetilde{p}_1$ and $\widetilde{p}_2$, as well as feasibility conditions and IR and participation constraints.

(i): If $t(p_1,p_2)=0$, then the GHO's objective becomes K_1, and the participation constraint is satisfied. The IR constraints give $\widetilde{p}_{1(i)} < \frac{(4ru-\widetilde{p}_{2(i)}Q)(\eta_1-u)-\widetilde{p}_{2(i)}Qu}{Q}+c$ and $\widetilde{p}_{2(i)} < \min\left\{\frac{4ru}{Q}, \frac{2r(\eta_1+u)}{Q}\right\}$.

(ii) and (iii): If $t(p_1,p_2)=\frac{(p_1-c)Q+p_2Qu}{4ru-p_2Q}$ then we have two cases. If $\eta_1-u < t(p_1,p_2) < \eta_2-u$ then we have solution (ii), while if $\eta_2-u < t(p_1,p_2) < \eta_1+u$ we have solution (iii). Under solution

(ii), the GHO's problem becomes

$$\min_{p_1,p_2} K_1\left(\frac{\eta_1+u-t(p_1,p_2)}{2u}\right)+K_2\left(\frac{u-\eta_1+t(p_1,p_2)}{2u}\right)+p_1Q\left(\frac{u-\eta_1+t(p_1,p_2)}{2u}\right)$$

$$+\frac{p_2Q}{4u}(t(p_1,p_2)+u-\eta_1)(t(p_1,p_2)+u+\eta_1)$$

$$\text{s.t. } (p_1-c)Q\left(\frac{u-\eta_1+t(p_1,p_2)}{2u}\right)+\frac{p_2Q}{4u}(t(p_1,p_2)+u-\eta_1)(t(p_1,p_2)+u+\eta_1)-r(t(p_1,p_2))^2\geq 0$$

where $t(p_1,p_2)=\frac{(p_1-c)Q+p_2Qu}{4ru-p_2Q}$. Examining the KKT conditions, we find that the participation constraint is binding and that $\widetilde{t}_{(ii)}=\frac{D_1}{2r}$. Given this, we can solve a system of linear equations to find $\widetilde{p}_{1(ii)}$ and $\widetilde{p}_{2(ii)}$: $p_{1(ii)}=c+\frac{4ru\widetilde{t}_{(ii)}}{Q(t_{(ii)}+u-\eta_1)^2}(\eta_1^2-\widetilde{t}_{(ii)}u-u^2)$; $\widetilde{p}_{2(ii)}=\frac{4ru\widetilde{t}_{(ii)}(\widetilde{t}_{(ii)}-2(\eta_1-u))}{Q(\widetilde{t}_{(ii)}+u-\eta_1)^2}$. Checking the IR conditions, we need $\widetilde{p}_{2(ii)}<\min\{\frac{4ru}{Q},\frac{2r(\eta_1+u)}{Q}\}$.

Under solution (iii), the GHO's problem becomes

$$\min_{p_1,p_2} K_1\left(\frac{\eta_1+u-t(p_1,p_2)}{2u}\right)+K_2\left(\frac{\eta_2-\eta_1}{2u}\right)+K_3\left(\frac{u-\eta_2+t(p_1,p_2)}{2u}\right)+p_1Q\left(\frac{u-\eta_1+t(p_1,p_2)}{2u}\right)$$

$$+\frac{p_2Q}{4u}(t(p_1,p_2)+u-\eta_1)(t(p_1,p_2)+u+\eta_1)$$

$$\text{s.t. } (p_1-c)Q\left(\frac{u-\eta_1+t(p_1,p_2)}{2u}\right)+\frac{p_2Q}{4u}(t(p_1,p_2)+u-\eta_1)(t(p_1,p_2)+u+\eta_1)-r(t(p_1,p_2))^2\geq 0$$

where $t(p_1,p_2)=\frac{(p_1-c)Q+p_2Qu}{4ru-p_2Q}$. Examining the KKT conditions, we find that the participation constraint is binding and that $\widetilde{t}_{(iii)}=\frac{D_2}{2r}$. Given this, we find $\widetilde{p}_{1(iii)}$ and $\widetilde{p}_{2(iii)}$ by solving a system of linear equations. We find $\widetilde{p}_{1(iii)}=c+\frac{4ru\widetilde{t}_{(iii)}}{Q(\widetilde{t}_{(iii)}+u-\eta_1)^2}(\eta_1^2-\widetilde{t}_{(iii)}u-u^2)$; $\widetilde{p}_{2(iii)}=\frac{4ru\widetilde{t}_{(iii)}(\widetilde{t}_{(iii)}-2(\eta_1-u))}{Q(\widetilde{t}_{(iii)}+u-\eta_1)^2}$. Checking the IR constraints, we need $\widetilde{p}_{2(iii)}<\min\left\{\frac{4ru}{Q},\frac{2r(\eta_1+u)}{Q}\right\}$.

(iv): If $t(p_1,p_2)=\eta_1+u$, the GHO's problem becomes

$$\min_{p_1,p_2}\frac{K_2(\eta_2-\eta_1)}{2u}+K_3\left(\frac{\eta_1-\eta_2+2u}{2u}\right)+p_1Q+p_2Q(\eta_1+u)$$

$$\text{s.t. } (p_1-c)Q+p_2Q(\eta_1+u)-r(\eta_1+u)^2\geq 0$$

From the KKT conditions, we find that the participation constraint is tight, so $\widetilde{p}_{1(iv)}$ and $\widetilde{p}_{2(iv)}$ must be set so that

$$(\widetilde{p}_{1(iv)}-c)Q+\widetilde{p}_{2(iv)}Q(\eta_1+u)=r(\eta_1+u)^2$$

. Checking the IR constraints, we either need $\widetilde{p}_{2(iii)}<\min\left\{\frac{4ru}{Q},\frac{2r(\eta_1+u)}{Q}\right\}$ and $\frac{(\widetilde{p}_{1(iii)}-c)Q+\widetilde{p}_{2(iii)}Qu}{4ru-\widetilde{p}_{2(iii)}Q}>\eta_1+u$ or $\widetilde{p}_{2(iii)}>\frac{4ru}{Q}$ and $\widetilde{p}_{2(iii)}<\frac{2r(\eta_1+u)}{Q}$.

(v): If $t(p_1,p_2)=\frac{p_2Q}{2r}$ then we have two cases. If $\eta_1+u<t(p_1,p_2)<\eta_2+u$ then we can write the GHO problem as

$$\min_{p_1,p_2}\frac{K_2}{2u}(\eta_2+u)-\frac{p_2QK_2}{4ru}+\frac{K_3}{2u}(u-\eta_2)+\frac{K_3p_2Q}{4ru}+p_1Q+\frac{p_2^2Q^2}{2r}$$

$$\text{s.t. } (p_1-c)Q+\frac{p_2^2Q^2}{4r}\geq 0$$

From the KKT conditions, we find that $\widetilde{p}_{2(v)}=\frac{K_2-K_3}{2Qu}$ and that the participation constraint

binds. From this value of $\widetilde{p}_{2(v)}$, we have $\widetilde{t}_{(v)} = \frac{K_2-K_3}{4ru}$. Plugging in $\widetilde{p}_{2(v)}$ to the participation constraint and solving for $\widetilde{p}_{1(v)}$ gives $\widetilde{p}_{1(v)} = c - \frac{(K_2-K_3)^2}{16ru^2Q}$. Checking the IR constraints, we need $\widetilde{p}_{2(v)} > \max\left\{\frac{4ru}{Q}, \frac{2r(\eta_1+u)}{Q}\right\}$, which reduces to $\frac{K_2}{4ru} > 2u$ and $\frac{K_2-K_3}{4ru} > \eta_1 + u$.

If $t(p_1, p_2) > \eta_2 + u$, then we can write the GHO's problem as

$$\min_{p_1,p_2} K_3 + p_1 Q + \frac{p_2^2 Q^2}{2r}$$

$$\text{s.t. } (p_1 - c)Q + \frac{p_2^2 Q^2}{4r} \geq 0$$

From the KKT conditions, we find that the participation constraint is binding and that $p_2 = 0$. Using p_2 in the participation constraint gives $p_1 = c$. However, the IR constraints give $p_2 > \frac{4ru}{Q}$, so we see that this cannot be an equilibrium. ■

Proof of Proposition 8 The only central target that is not already achieved by the linear contract is $t = \eta_2 + u$. In order to achieve this, we note that the manufacturer's best response in this region is given by $t(p_1, p_2) = \frac{p_2 Q}{2r}$. Thus if we set $p_2 = \frac{2r(\eta_2+u)}{Q}$ then the manufacturer's target becomes $\eta_2 + u$. Note that with this choice of p_2, the IR constraint $p_2 > \max\left\{\frac{4ru}{Q}, \frac{2r(\eta_1+u)}{Q}\right\}$ is satisfied. Furthermore, to ensure the manufacturer's participation we simply need to choose p_1 so that $p_1 \geq c - \frac{r(\eta_2+u)^2}{Q}$. ■

B.3 Numerical Study

Proof of Proposition 9 To compute R_0 and R_v, we use the next generation method, as detailed in Van den Driessche and Watmough (2008). We first compute R_v using our compartmental model with vaccination, then we obtain R_0 by considering the special case of this system when either the vaccine efficacy $e = 0$ or when the fraction vaccinated $f = 0$. Following Van den Driessche and Watmough (2008), we identify 3 disease compartments for Chagas (A_H, I_H, and I_V), and we let $x \in \mathbb{R}^3$ be the subpopulations in each of these compartments. We denote by F_i the rate secondary infections increase the ith disease compartment and by V_i the rate disease progression, death, and recovery decrease the ith compartment. We thus have

$$\mathcal{F} = \begin{bmatrix} \frac{\beta_V S_H I_V}{N_V} \\ 0 \\ \frac{\beta_A S_V A_H}{N_H} + \frac{\beta_I S_V I_H}{N_H} \end{bmatrix} \qquad \begin{bmatrix} (\mu_H + \delta_A + \kappa)A_H \\ -\kappa A_H + (\mu_H + \delta_I)I_H \\ \mu_V I_V \end{bmatrix}$$

Next, we define F and V to be the 3×3 matrices with entries $F = \frac{\partial \mathcal{F}_i}{\partial x_j}(y_0)$ and $V = \frac{\partial \mathcal{V}_i}{x_j}(y_0)$ where y_0 is the *disease free equilibrium*, obtained by setting the disease compartments equal to zero in (3.2) and solving for the resulting equilibria. For Chagas, the disease free equilibrium is given by $(S_H^0, A_H^0, I_H^0, V_H^0, N_H^0, S_V^0, I_V^0, N_V^0) = (N_H(1-ef), 0, 0, efN_H, N_H, N_V, 0, N_V)$. This gives

$$F = \begin{bmatrix} 0 & 0 & \beta_V(1-ef) \\ 0 & 0 & 0 \\ \frac{\beta_A N_V^0}{N_H^0} & \frac{\beta_I N_V^0}{N_H^0} & 0 \end{bmatrix} \qquad V = \begin{bmatrix} \mu_H + \delta_A + \kappa & 0 & 0 \\ -\kappa & \mu_H + \delta_I & 0 \\ 0 & 0 & \mu_V \end{bmatrix}$$

The basic reproduction number with vaccination R_v is the largest eigenvalue of FV^{-1}, and thus

we have

$$R_v = \sqrt{\frac{\beta_V \beta_A (1-ef)}{(\mu_H + \delta_A + \kappa)\mu_V} + \frac{\beta_V \kappa \beta_I (1-ef)}{(\mu_H + \delta_A + \kappa)(\mu_H + \delta_I)\mu_V}}$$

To obtain the basic reproduction number in the absence of vaccination R_0, we set $e = 0$ (or, equivalently, $f = 0$):

$$R_0 = \sqrt{\frac{\beta_V \beta_A}{(\mu_H + \delta_A + \kappa)\mu_V} + \frac{\beta_V \kappa \beta_I}{(\mu_H + \delta_A + \kappa)(\mu_H + \delta_I)\mu_V}}$$

■

Proof of Proposition 10 The computation of R_0 and R_v for Ebola closely follows the derivation of these values for Chagas, as described in the proof of Proposition 9; see this proof for more detail.

For Ebola, there are two disease compartments, E and I. Following the proof of Proposition 2, we define $\mathcal{F} \in \mathbb{R}^2$ and $\mathcal{V} \in \mathbb{R}^2$ as follows:

$$\mathcal{F} = \begin{bmatrix} \frac{\beta SI}{N} \\ \\ 0 \end{bmatrix} \qquad \mathcal{V} = \begin{bmatrix} (\mu + \kappa)E \\ \\ -\kappa E + (\mu + \delta + \gamma)I \end{bmatrix}$$

Next, we define F and V to be the 2×2 matrices with entries $F = \frac{\partial \mathcal{F}_i}{\partial x_j}(y_0)$ and $V = \frac{\partial \mathcal{V}_i}{x_j}(y_0)$ where y_0 is the disease free equilibrium, given by $(S^0, E^0, I^0, R^0, V^0, N^0) = ((1-ef)N, 0, 0, 0, efN, N)$.

$$F = \begin{bmatrix} 0 & \beta(1-ef) \\ \\ 0 & 0 \end{bmatrix} \qquad V = \begin{bmatrix} \mu + \kappa & 0 \\ \\ -\kappa & \mu + \delta + \gamma \end{bmatrix}$$

R_v is the largest eigenvalue of FV^{-1}, and is given by

$$R_v = \frac{\beta\kappa(1-ef)}{(\mu + \kappa)(\mu + \delta + \gamma)}$$

and R_0 is obtained by setting $e = 0$ or $f = 0$ in the expression for R_v:

$$R_0 = \frac{\beta\kappa}{(\mu + \kappa)(\mu + \delta + \gamma)}$$

■

Table B.1: Market size estimation for Chagas disease.

Country	**Births/Year**	**DTP3 Coverage**
Argentina	760,222	86%
Bolivia	256,971	84%
Brazil	2,964,149	89%
Chile	239,784	93%
Colombia	745,699	92%
Ecuador	335,406	85%
French Guiana	7,039	91%*
Guyana	16,005	97%
Paraguay	142,676	92%
Peru	620,182	83%
Suriname	10,262	81%
Uruguay	48,512	95%
Venezuela	608,523	84%

*regional average was used due to lack of country data.
Sources: Chagas Coalitiion (2018); World Bank Group (2019),WHO (2017a)

Table B.2: Market size estimation for Ebola.

Country	**Births/Year**	**DTP3 Coverage**
Congo	182,174	69%
Democratic Republic of the Congo	3,439,054	81%
Gabon	59,765	75%
Guinea	456,686	45%
Ivory Coast	894,824	84%
Liberia	162,389	86%
Sierra Leone	264,547	90%
South Sudan	451,920	26%
Uganda	1,806,416	85%

Sources: Centers for Disease Control and Prevention (2017b); World Bank Group (2019); WHO (2017a)

Table B.3: Basic reproduction numbers from literature.

Disease	**Country/Region**	R_0	**Source**
Chagas	Brazil	1.25	Massad (2008)
	Chile	1.52	Canals et al. (2017)
		2.86	Canals and Cattan (1992)
	Columbia	7	Cordovez et al. (2014)
Ebola	Democratic Republic of the Congo	1.83	Chowell et al. (2004)
		1.36	Lekone and Finkenstädt (2006)
		3.65	Ferrari et al. (2005)
	Guinea	1.2552	Shen et al. (2015)
		1.51	Althaus (2014)
		1.71	Team (2014)
	Liberia	1.54	Webb et al. (2015)
		1.59	Althaus (2014)
		1.757	Khan et al. (2015)
		1.7994	Shen et al. (2015)
		1.83	Team (2014)
		1.84	Merler et al. (2015)
		2.012	Xia et al. (2015)
		2.49	Lewnard et al. (2014)
	Liberia and Sierra Leone	1.80	Meltzer et al. (2014)
		2.22	Rivers et al. (2014)
	Multiple Regions, 2014 Outbreak	1.78	Fisman et al. (2014)
		1.80	Gomes et al. (2014)
	Sierra Leone	1.26	Webb et al. (2015)
		1.492	Khan et al. (2015)
		1.6093	Shen et al. (2015)
		1.78	Rivers et al. (2014)
		2.02	Team (2014)
		2.53	Althaus (2014)
	Uganda	1.34	Chowell et al. (2004)
		1.79	Ferrari et al. (2005)

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