Flexible Drug Approval Policies

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Problem Definition: 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.

Practical Relevance: New drug approval requires weighing the risks of committing 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.

Methodology: 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.

Results: 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 intensity. 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.

Managerial Implications: 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.

Key words: Drug Approval, FDA, Queuing Model, Healthcare Policy

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 total expected net benefits are sensitive to some modeling assumptions, the significance level that maximizes the simulated objective function is largely 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. 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 only on trial duration and the rate of new drug discovery. By incorporating these elements of the R&D pipeline together with attrition rates of clinical trials, as well as post-approval considerations including substitution between drugs within a therapeutic class and obsolescence of older therapies, our approach captures key aspects of the drug development process 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.

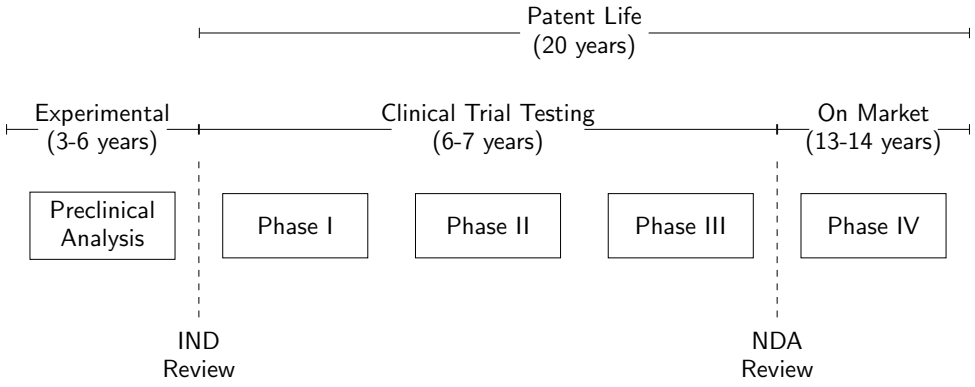
New Product Development. The journey of a candidate drug from conception through R&D, testing, regulatory approval, and post-approval market penetration relates to new product development (NPD), the process of transforming product concepts into commodities. See Krishnan and Ulrich (2001) and Killen et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

Using a queueing network model, Adler et al. (1995) identify bottlenecks and find opportunities to reduce time to market for new products, taking the perspective of a single firm seeking to maximize profits. Our work similarly models drug development as a sequence of queues, but also captures post-development features such as drug obsolescence, and assumes the role of a social planner seeking to maximize societal benefits. Other research examines how new products compete for market share. Ding and Eliashberg (2002) employ dynamic programming to optimize a portfolio of projects to maximize expected profit, when the final products target the same market and compete for revenue. Whereas they define the number of projects pursued by a firm as a decision variable, R&D intensity is exogenous in our work. Rather than focus on strict market competition, we allow for substitution among FDA-approved drugs targeting the same condition, and for obsolescence as newer drugs replace older therapies.

3. Drug Development Overview

The drug approval process in the U.S. consists of a series of stages, beginning with the discovery of a new pharmaceutical compound and ending with the FDA deciding whether to grant marketing approval. See Figure 1 for a summary and average duration of each stage (PhRMA 2015a).

Figure 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).

New drug development begins with identification of a novel chemical compound intended to treat a target disease. Promising candidates are subjected to preclinical analysis, involving laboratory (*in vitro*) and animal (*in vivo*) testing, to screen for for potential safety issues and study how the human body metabolizes the drug at specific doses (*pharmacokinetics*). If a drug candidate raises no safety concerns, the sponsoring firm can file an Investigational New Drug (IND) application to the FDA presenting a plan for clinical trial testing, which may begin after 30 days provided the FDA does not respond with objections.

Clinical trials typically consist of three phases, designed to test safety and efficacy in humans. Phase I entails testing in healthy volunteers to observe any potential side effects and pharmacokinetics. If the drug is well-tolerated, it can advance to Phase II, where it is administered to volunteers diagnosed with the target illness to establish 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 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 ultimately gaining 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 filing, which usually occurs before the 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 drug-related adverse events 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).

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 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.

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. We obtain the following joint probability expressions:

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

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 α because, in practice, trial enrollment is decided by the pharmaceutical company, taking into account the costs and feasibility of patient recruitment.

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) followed by an analysis of the optimal approval policy and its respective comparative statics. A summary of model parameters is provided in Table 1.

4.1. Queueing Network Model

Assume that candidate drugs begin clinical trials according to a Poisson process with arrival rate λ. Combining the three clinical trial phases into a single queue simplifies the analyses and does not change key insights, as shown in the numerical simulation. Drugs either complete clinical trial assessment, or the sponsoring firm halts the trials early. We model clinical trial duration as an exponential race between trial completion and abandonment with rates μ_{CT} and μ_{AB}, supported by data from `clinicaltrials.gov` (see Appendix B for details). Drugs advance to FDA review with probability $\frac{\mu_{CT}}{\mu_{CT}+\mu_{AB}}$ or exit the system with probability $\frac{\mu_{AB}}{\mu_{CT}+\mu_{AB}}$. Thus, drugs enter FDA review at net rate $\tilde{\lambda} = \lambda \frac{\mu_{CT}}{\mu_{CT}+\mu_{AB}}$ and abandon trials at rate $\tilde{\mu} = \lambda \frac{\mu_{AB}}{\mu_{CT}+\mu_{AB}}$. For simplicity, we assume trial completion and abandonment rates are identical across drug classes; a model extension could include parallel queues with class-specific rates. Modelling the clinical trial sequence as an $M/M/\infty$ queue captures three key elements, the initiation rate (λ), total duration ($1/\mu_{CT}$), and abandonment rate (μ_{AB}), an advantage over using a single event for trial completion.

Following 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, although in reality, review lasts between six months and two years. Accounting for this delay would entail 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:

$$\lambda_{AE}(\alpha) = \tilde{\lambda}\pi_{AE}(\alpha), \quad \lambda_{AI}(\alpha) = \tilde{\lambda}\pi_{AI}(\alpha), \quad \lambda_{RE}(\alpha) = \tilde{\lambda}\pi_{RE}(\alpha), \quad \lambda_{RI}(\alpha) = \tilde{\lambda}\pi_{RI}(\alpha). \tag{2}$$

After undergoing FDA review, rejected drugs depart the system. Approved *effective* drugs enter the market, where they remain, often for decades, and may eventually become obsolete as newer drugs gain approval. Approved *ineffective* drugs spend relatively little time on the market as patients discontinue taking them or they are withdrawn by the FDA or manufacturer. 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 as a collection of K parallel preemptive $M/M/1/1$ queues with mean service time $1/\mu_E$, each representing a unique therapeutic class for a particular disease. An FDA-approved effective drug falls into a single class with probability $1/K$, an assumption required for analytical tractability that we relax in the numerical simulation. Preemption is designed to account for older drugs becoming obsolete as newer therapies gain approval.

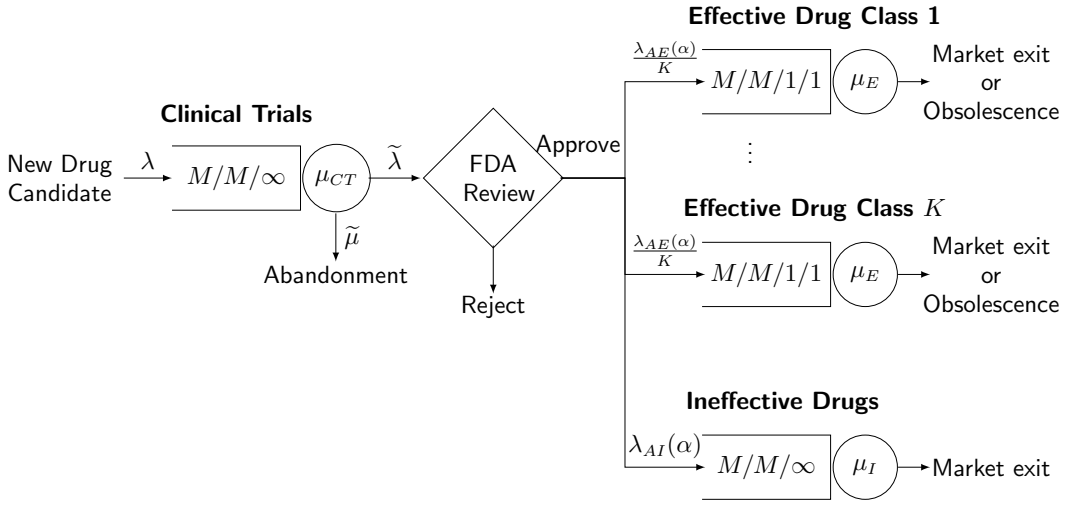
Table 1 Summary of key model parameters.

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

Due to the high market concentration within a class—a handful of drugs typically account for the majority of prescriptions—we consider the case where at most one drug in 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 tractability, we analyze the system in steady state with time invariant parameters. We consider two criteria in the FDA's decision to approve or reject candidate drugs: health benefits and monetary value. Health benefits are explicitly outlined in the FDA's mission statement, which establishes the agency's role in protecting and advancing public health (FDA 2018j). Accounting for monetary value accords 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).

Figure 2 Queueing network representing the drug development and approval process.



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

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 rejecting 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 $V(\alpha)$:

$$\alpha^* = \underset{\alpha\in[0,1]}{\arg\max}\ V(\alpha) \tag{3}$$

where

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

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 write these terms as:

$$\mathbb{E}[N_E(\alpha)] = \frac{K\psi_E(\alpha)}{1+\psi_E(\alpha)}, \qquad \mathbb{E}[N_I(\alpha)] = \psi_I(\alpha). \tag{4}$$

Each monetary value is multiplied by the corresponding approval or rejection rate, reflecting the market value gains (or losses) 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).

4.2. Model Analysis

We first examine the structure of the optimal approval policy to gain insights into how the pre- and post-review drug characteristics 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:*

$$\alpha^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}}\log\left(\frac{1-p}{p}\frac{C_{AI} + WTP\cdot Q_I/\mu_I}{WTP\cdot Q_E/(\mu_E(1+\psi_E(\alpha^*))^2) + C_{RE} + C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right). \tag{5}$$

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 obtain the comparative statics of α^* using first order analysis.

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

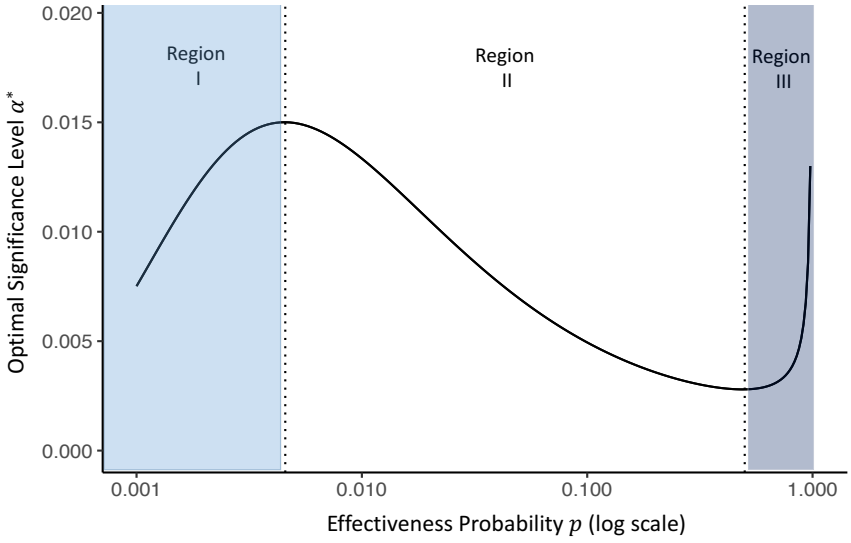
(a) increasing in Q_E, C_{AE}, C_{RE}, μ_I, and μ_{AB},

(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 those with high attrition rates (large μ_{AB}). As expected, drugs with greater health benefits Q_E or higher rejection costs C_{RE} (a type II error) have easier approval policies compared to those with higher approval costs C_{AI} (a type I error) and health costs Q_I. Prolonging the time that ineffective drugs 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 spent on the market $1/\mu_E$ increases, one might expect that approving *more* drugs is optimal. However, this intuition only holds if $\psi_E(\alpha^*) = \lambda_{AE}(\alpha^*)/(K\mu_E) < 1$, as stated in Proposition 1. In other words, the approval rate of effective drugs in a given class $\lambda_{AE}(\alpha^*)/K$ is less than the market exit rate μ_E. Since we model the 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.

Figure 3 Sensitivity of the optimal approval policy level α^* 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 $0 \le p \le 0.005$, Region II to $0.005 < p \le 0.5$, and Region III to $0.5 < p \le 1$.

The relationship between market crowding and non-monotonicity of the optimal policy (holding all other parameters constant) is illustrated by the following example (Figure 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. $C_{AE} = C_{AI} = C_{RE} = 0$. Drugs with a low effectiveness probability ($p < 0.5$) are defined as *long shots*, and those with high effectiveness probability ($p \geq 0.5$) are *safe bets*. A market is considered *crowded* if many available therapies are available ($\mathbb{E}[N_E(\alpha)] \approx K$) and *neglected* if few are available ($\mathbb{E}[N_E(\alpha)] << K$).

We divide Figure 3 into three regions, where 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 gaining an additional effective drug, as many alternative therapies 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. Increasing K—interpreted as approving a *first-in-class* drug with a new mechanism of action for disease treatment—changes the optimal policy (Proposition 2) and expected net societal benefits (Proposition 3).

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

$$\alpha_0^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}} \log\left(\frac{1-p}{p}\frac{C_{AI} + WTP \cdot Q_I/\mu_I}{C_{RE} + C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right) \tag{6}$$

and

$$\alpha_\infty^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}} \log\left(\frac{1-p}{p}\frac{C_{AI} + WTP \cdot Q_I/\mu_I}{WTP \cdot Q_E/\mu_E + C_{RE} + C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right). \tag{7}$$

The optimal approval policy is non-decreasing in the number of drug classes K, an intuitive result. As K increases, there is less substitution and obsolescence among drug classes, i.e., more opportunities exist for different therapy classes to be on the market, and thus the optimal policy is to ease approval standards to fill the market and obtain all the associated benefits. 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.

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*,*

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

First, increasing the number of drug classes K intuitively generates greater expected benefits due to additional effective drugs on the market. Second, among diseases with few available therapy 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). In other words, spurring innovation in drug development by easing approval standards is particularly beneficial for diseases with few available treatments.

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 offers insights for disease-specific approval recommendations.

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, $\mathbb{P}(\text{Complete clinical trials})$. The trial abandonment rate is calculated as $\mu_{AB} = \frac{\mu_{CT}[1-\mathbb{P}(\text{Complete clinical trials})]}{\mathbb{P}(\text{Complete clinical trials})}$. 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 C2-C4) and estimates for the NDA approval probability from Thomas et al. (2016). The clinical trial initiation rate λ is estimated using $\tilde{\lambda}$ and $\mathbb{P}(\text{Complete clinical trials})$.

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 disease-specific 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 C1.

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 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 C5.

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, 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

Table 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 C1
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	0.040	`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 (2017, 2019); National Cancer Institute (2018a); FDA (2018a).

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 R&D pipeline across diseases (Table 2). Many candidate drugs for breast cancer enter clinical trials each year ($\lambda = 9.99$), but these trials have long durations ($1/\mu_{CT} = 12.5$ years over Phases I-III) and high attrition stemming from a difficulty in establishing efficacy for oncology drugs (Arrowsmith and Miller 2013), resulting in a modest NDA submission rate of $\tilde{\lambda} = 1.48$ drugs per year. At the other extreme, fewer drugs for hypertension initiate clinical trials each year ($\lambda = 3.85$), but these candidate drugs also have the lowest attrition rate and the shortest average trial duration ($1/\mu_{CT} = 3.2$ years), leading to a higher NDA submission rate of $\tilde{\lambda} = 2.34$ drugs per year. Candidate drugs for HIV fall in the middle with average trial durations ($1/\mu_{CT} = 7.1$ years), moderate attrition, and a net NDA rate of $\tilde{\lambda} = 1.60$ drugs per year. The estimated probability p that a drug is effective, conditional on undergoing FDA review, is similar across the examined conditions, with estimated values exceeding 0.90.

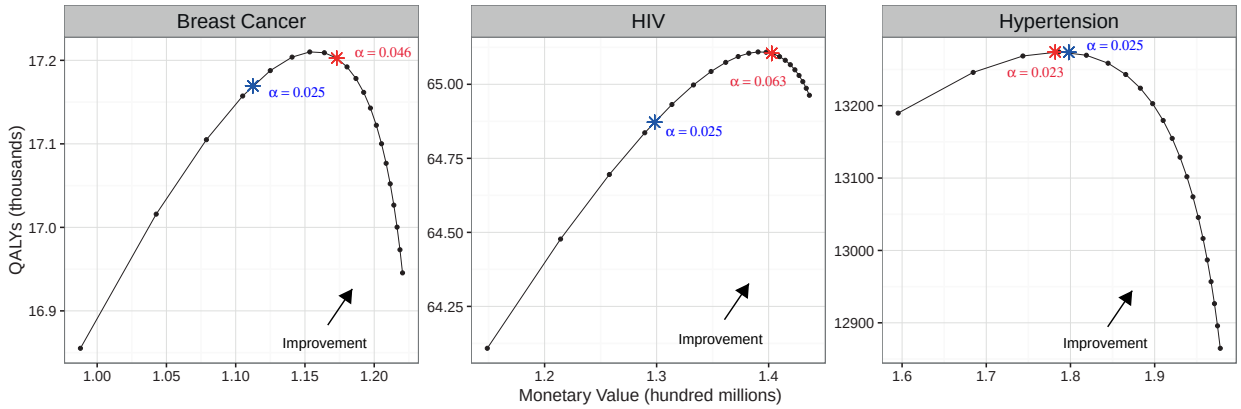
Substantial variation also exists in the population-level health benefits of treating these three diseases. Driven by differences in both market size and potential life-saving benefits, hypertension has the greatest societal per-drug health benefit Q_E, while breast cancer medications have the least. Hypertension drugs retain longer patent protection on the market due to shorter average trial duration, 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 HIV virus was only recently identified in 1981, possibly explaining its lack of unique drug classes compared to hypertension and breast cancer, which have had established therapies since the 1950s (Department of Health and Human Services 2016).

We compute the optimal approval policies α^* for each disease (Table 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 dearth of available treatment alternatives.

Table 3 Optimal FDA-approval policies for selected diseases.

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

Figure 4 Comparison of the monetary value and QALYs achieved by different approval policies.



Note. Each point on a curve represents a different approval policy α, ranging from 1% (far left) to 10% (far right).

Figure 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 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 of approving effective drugs outweigh any potential monetary losses. Increasing α generates more QALYs initially as more (effective) drugs enter the market, but eventually reduces net QALYs because the health costs associated with potentially approving ineffective drugs dominate.

For breast cancer and HIV, the optimal policy α^* strictly dominates—offering 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.

5.3. Sensitivity Analysis

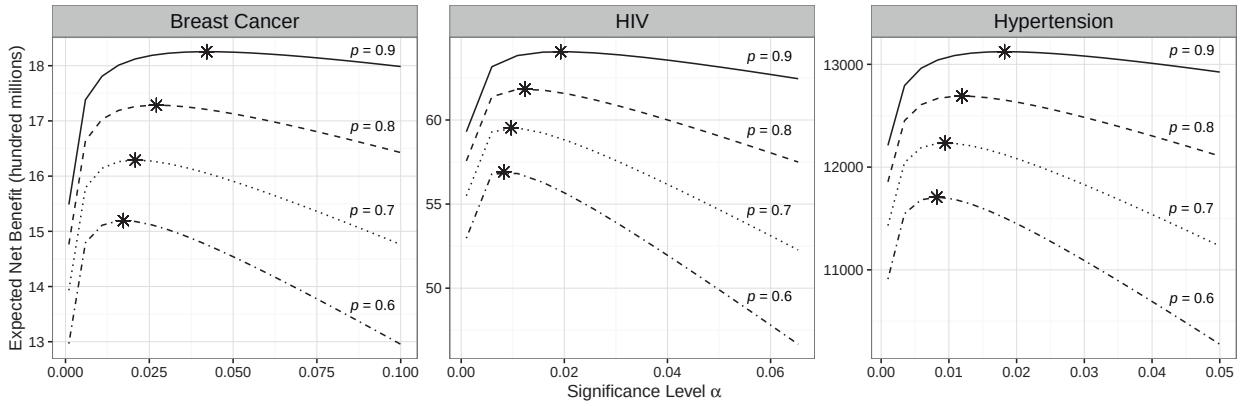
We conduct sensitivity analysis of the optimal approval policies and expected net benefit with respect to the nominal parameter values (Table 2), focusing on three key parameters: the prior probability p of effectiveness, NDA intensity $\tilde{\lambda}$ (which comprises the pre-review parameters λ, μ_{CT}, and μ_{AB}), and the average time effective drugs spend on the market $1/\mu_E$. For each parameter, we plot the expected net benefit as a function of α. Each curve corresponds to a different parameter value and the optimal significance level α^* is highlighted on each curve.

Sensitivity to effectiveness probability. We vary the prior effectiveness probability $p \in \{0.6, 0.7, 0.8, 0.9\}$, assuming that the FDA is unlikely to approve drugs with a lower probability. The optimal approval policy α^* is increasing in p for all diseases, but expected net benefits are sensitive

to p (Figure 5). For high values of p, as is currently estimated for breast cancer ($p = 0.912$), HIV ($p = 0.985$), and hypertension ($p = 0.933$), deviating from the optimal α^* only modestly changes net benefits, because the risk of approving an ineffective drug is so low, and approving more effective drugs will push older drugs off the market, leaving net benefits largely unchanged.

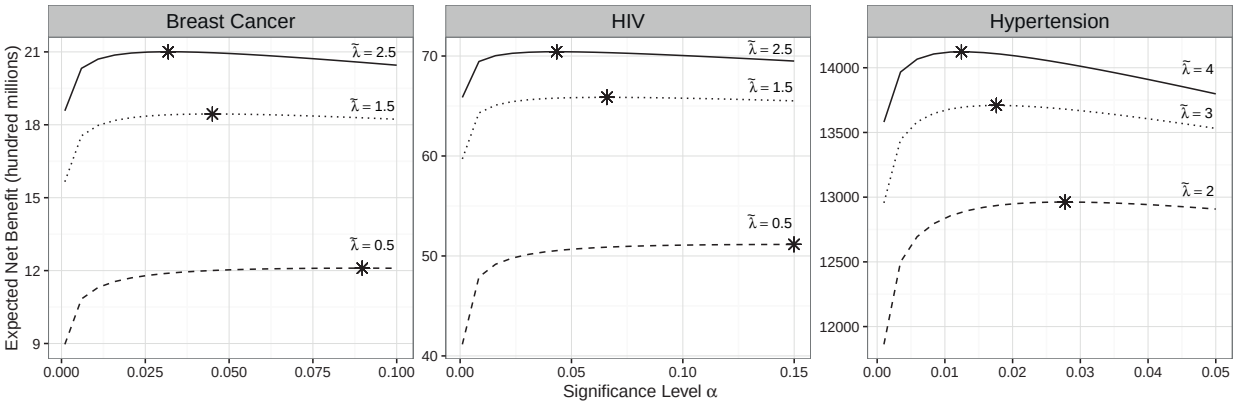
For low values of p, however, the objective function has high curvature, as net benefits are more sensitive to α because of the non-negligible risk of approving an ineffective drug. This might occur when developing a novel drug class, which requires a paradigm shift in understanding the underlying biological mechanism, leading to a low probability that a new therapy proves to be effective. In these settings, diverging from the optimal significance level α^* can be quite costly, as ineffective or even harmful drugs make it to the market. For example, nucleoside reverse transcriptase inhibitors (NRTIs) were approved as monotherapy for HIV in the 1990s, but some drugs (e.g., zalcitabine) were subsequently shown to be less effective than initially thought, especially in patients with prior treatment history, illustrating that a more stringent approval policy was warranted.

Figure 5 **Sensitivity of the expected net benefit and α^* to the effectiveness probability p.**



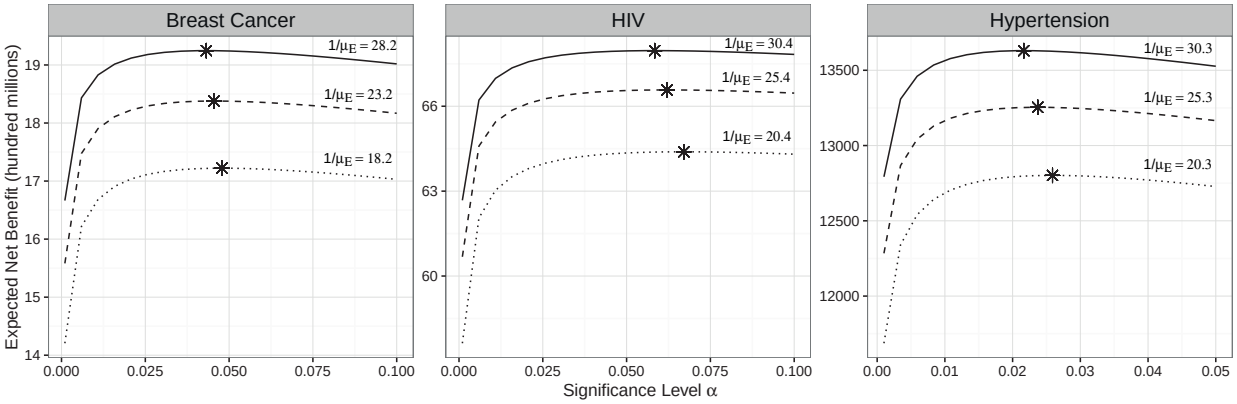
Sensitivity to NDA intensity. We consider three values for the NDA submission rate: a value similar to the nominal $\tilde{\lambda}$ given in Table 2, a value that reflects one fewer NDA submission each year, and a value that reflects one additional submission. As indicated by Proposition 1, the optimal approval policy α^* is decreasing in $\tilde{\lambda}$ (Figure 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. NDA intensity also affects the curvature of the expected net benefits. For instance, in the case of hypertension, an increase in the NDA intensity $\tilde{\lambda}$ increases the curvature of the objective function. The more pronounced curvature implies that, intuitively, when many NDAs are being submitted (high $\tilde{\lambda}$), a small change in the approval policy α substantially affects the resulting number of approved and rejected drugs.

Figure 6 **Sensitivity of the expected net benefit and α^* to the NDA intensity $\tilde{\lambda}$.**



Sensitivity to market duration. Post-approval market duration $1/\mu_E$ is comprised of the time a drug spends on patent and time as a generic. In addition to the base values given in Table 2, we consider durations that are both five years longer and shorter, reflecting potential future legislation changes. If drugs spend more time on the market under patent-protection, the optimal approval policy α^* only slightly decreases, as existing therapies obviate the need for new drugs. Even with a five-year difference, however, α^* changes minimally because the expected net benefit function does not significantly change in curvature, highlighting the robustness of our results to this model assumption (Figure 7).

Figure 7 **Sensitivity of the expected net benefit and α^* to the average time on the market $1/\mu_E$.**



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 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 durations, 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). Fast Track is estimated to reduce total clinical trial and review time by 5% across all drugs (Tufts Center for the Study of Drug Development 2008), but does not affect other aspects of the drug development and approval process (FDA 2014a).

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. Under the no Fast Track scenario, the clinical trial completion rate μ_{CT} decreases, while the per drug monetary gains and losses, health benefits and costs, post-approval market durations, and effectiveness probability remain unchanged. Although Fast Track may seem like an obvious improvement, its potential downsides include approving more ineffective drugs and increasing drug obsolescence post-approval.

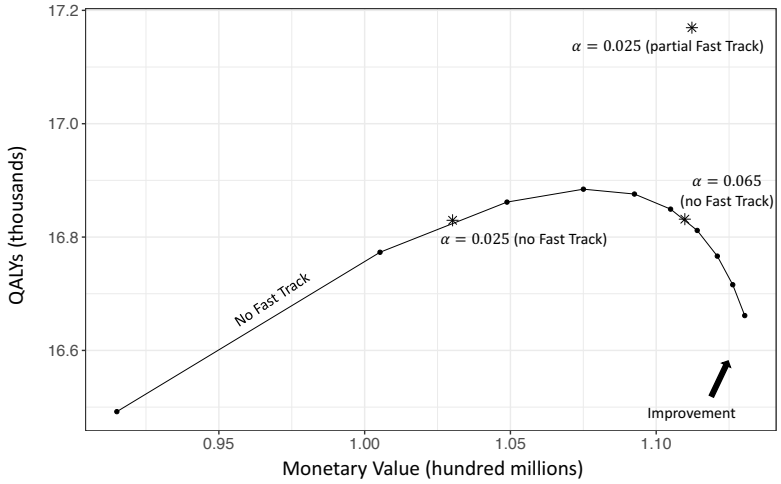
Figure 8 depicts the trade-off between monetary value and QALYs of varying α between 1% and 10% assuming no Fast Track exists, versus the current fixed policy $\alpha = 2.5\%$ with partial Fast Track. The current system offers greater monetary value and QALYs, *dominating* the approval process without Fast Track. In the absence of this program, 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.

Table 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 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 no Fast Track system varies from 1% (far left point) to 10% (far right point).

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.

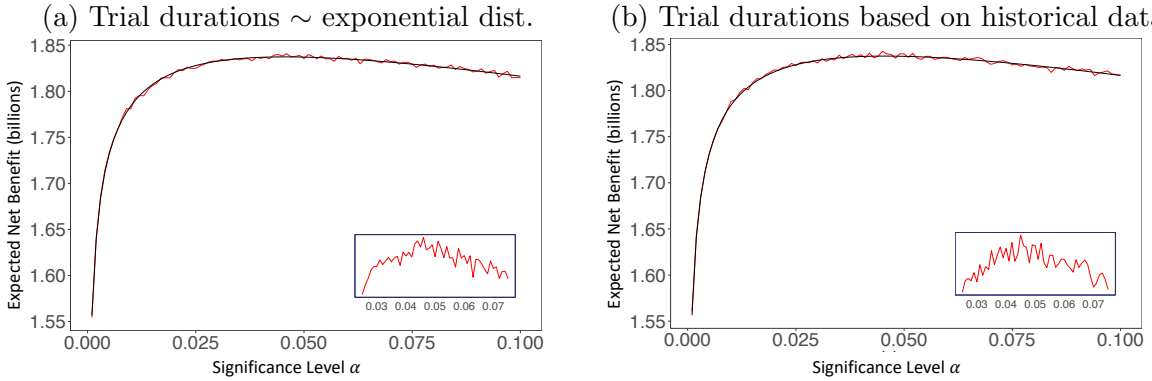
5.5. Simulation

To test our model's robustness, we simulate the R&D and drug approval process, focusing on breast cancer. We relax several key 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. We consider a long time horizon in order to achieve steady-state behavior because of how infrequently approving an ineffective drug occurs.

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. The significance level maximizing the simulated objective function is (i) $\alpha = 4.6\%$ and (ii) $\alpha = 4.5\%$, virtually identical

to the original optimal policy $\alpha^* = 4.6\%$ (Figure 9), suggesting that our earlier analysis is robust to structural variations in the pre-review queueing model.

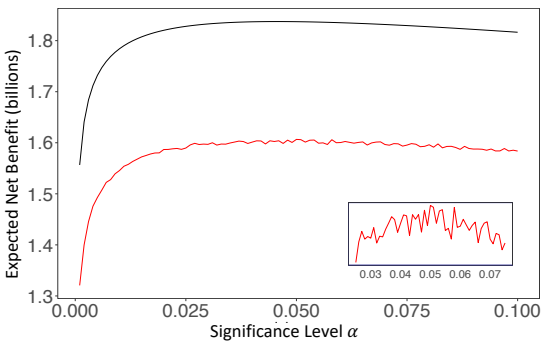
Figure 9 **Expected net benefit from simulation (red line) and base model (black line) if clinical trials are modeled as three separate phases.**



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

Drug Class Distribution. In the base model, effective drugs that gain FDA approval belong to any of K drug classes, with equal probability. We relax this assumption by setting the probability distribution across drug classes using historical data on breast cancer drug approvals (Appendix table C2). 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 more likely to become obsolete—as newer therapies gain FDA approval—and thus removed from the market prematurely, before patent expiry. The remaining eight classes consequently receive fewer new drugs, decreasing the expected total number of approved effective drugs and, hence, decreasing expected net benefits (Figure 10). Compensating for this reduction in available therapies on the market, the significance level that maximizes simulated net benefits increases slightly to $\alpha = 5.0\%$.

Figure 10 **Expected net benefit from simulation (red line) and base model (black line) with post-market drug class distribution based on historical data.**

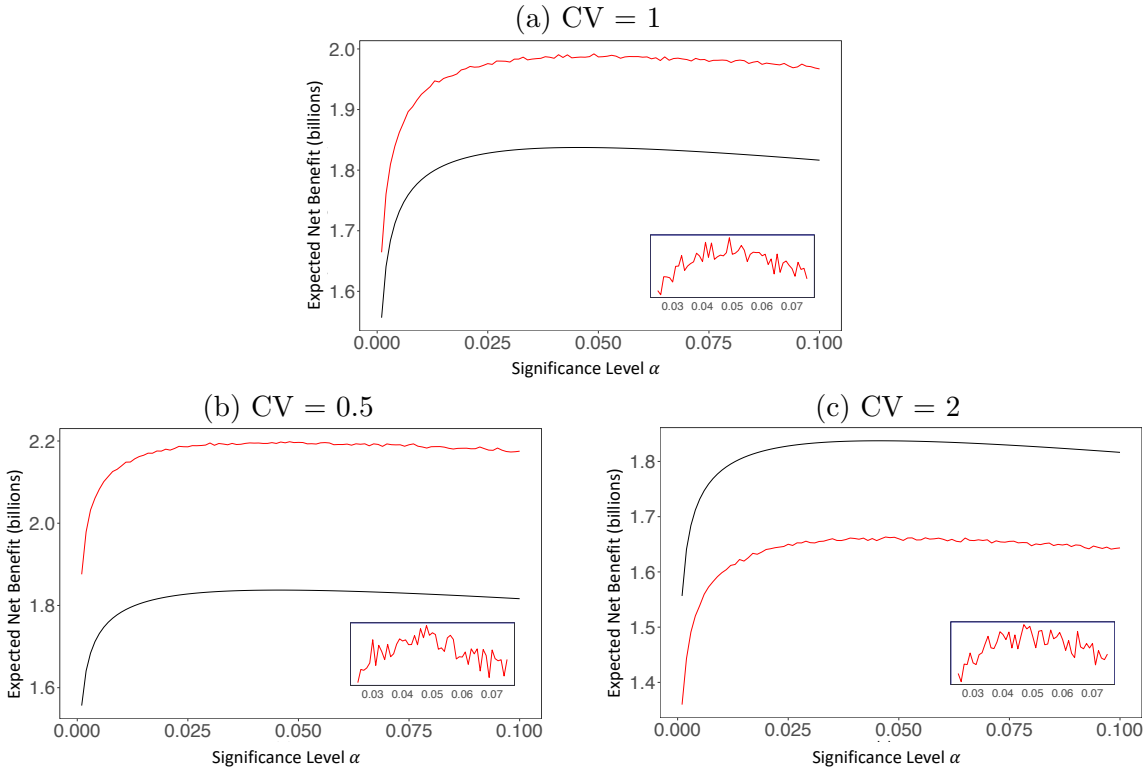


Note. The inset plot shows the simulated expected net benefit function for $\alpha = 2.5\%$ to $\alpha = 7.5\%$.

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. Using a $M/G/1/1$ queue with log-normally distributed time on the market and the same mean as before, we now vary the coefficient of variation (CV) $= \frac{\sigma}{\mu}$ in the simulated queue, where CV$= 0.5$, CV$= 1$, or CV$= 2$.

If CV$= 0.5$ or CV$= 1$, expected health benefits significantly increase, as more probability mass is placed on longer market durations, compared to the exponential distribution (Figure 11). Conversely, if CV$= 2$, fewer health benefits accrue. The preferred significance levels based on these simulations fall between $\alpha = 4.7\%$ and $\alpha = 4.9\%$, close to the optimal policy for breast cancer, $\alpha^* = 4.6\%$ using the base model.

Figure 11 **Expected net benefit from simulation (red line) and base model (black line) assuming lognormally distributed time on market with varying coefficient of variation.**



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

6. Discussion

Our queueing framework presents a novel scheme for analyzing a disease-specific FDA-approval policy, accounting for both the pre-review drug pipeline and post-approval market characteristics. Our model considers three drivers of the shortfall of therapies available to treat some diseases: (i) a 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. The FDA's existing *Orphan Drug Designation* program, for example, 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 approach for mitigating low R&D investment is to ease approval standards for diseases with few drugs in the early stages of development (i.e., a low clinical trial arrival rate), encouraging pharmaceutical companies to divert resources from diseases with many competitor drugs to therapies more likely to gain approval.

Our work relates to Montazerhodjat et al. (2017), who apply Bayesian Decision Analysis to find the significance levels that minimize the expected type I and type II error costs for oncology drugs. Their optimal level of 17.6% for breast cancer is 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 include approve ineffective drugs and, in an attempt to incorporate obsolescence, we model effective drugs using 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. We account for obsolescence within each drug class, whereas Montazerhodjat et al. (2017) ignore these effects and model effective and ineffective drugs identically, resulting in more lenient policies. Furthermore, the authors focus solely on the health costs of approval decisions, while we additionally consider monetary gains or losses, based on stock price movements of the sponsoring pharmaceutical company, following public news of a new drug approval, rejection, or market-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.

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 structural 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.

6.2. Future Work

Our study motivates several directions for future work. Currently, we assume drugs are either effective or ineffective, and confer the same health benefits across patients. Possible extensions include modeling drug effectiveness as a continuous (or random) variable, and modeling the health effects as random variables, to account for heterogeneous responses to a given treatment.

Another extension 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 developed.

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.

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Appendix A: 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

$$\frac{\partial \alpha^*}{\partial x} = -\frac{\frac{\partial V'(\alpha^*)}{\partial x}}{\frac{\partial V'(\alpha^*)}{\partial \alpha}} \tag{A.8}$$

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

$$\begin{aligned} V'(\alpha) = &\left(Q_E \frac{\partial \mathbb{E}[N_E(\alpha)]}{\partial \psi_E}\frac{\partial \psi_E(\alpha)}{\partial \alpha} - Q_I \frac{\partial \mathbb{E}[N_I(\alpha)]}{\partial \psi_I}\frac{\partial \psi_I(\alpha)}{\partial \alpha}\right) WTP \\ &+ \left(C_{AE}\frac{\partial \lambda_{AE}(\alpha)}{\partial \alpha} - C_{AI}\frac{\partial \lambda_{AI}(\alpha)}{\partial \alpha} - C_{RE}\frac{\partial \lambda_{RE}(\alpha)}{\partial \alpha}\right) \end{aligned} \tag{A.9}$$

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

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial Q_E}\right) = \operatorname{sgn}\left(\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E}\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\right) \geq 0 \tag{A.10}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial Q_I}\right) = \operatorname{sgn}\left(-\frac{\partial \mathbb{E}[N_I(\alpha^*)]}{\partial \psi_I}\frac{\partial \psi_I(\alpha^*)}{\partial \alpha}\right) \leq 0 \tag{A.11}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial C_{AE}}\right) = \operatorname{sgn}\left(\frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha}\right) \geq 0 \tag{A.12}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial C_{AI}}\right) = \operatorname{sgn}\left(-\frac{\partial \lambda_{AI}(\alpha^*)}{\partial \alpha}\right) \leq 0 \tag{A.13}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial C_{RE}}\right) = \operatorname{sgn}\left(-\frac{\partial \lambda_{RE}(\alpha^*)}{\partial \alpha}\right) \geq 0 \tag{A.14}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \mu_I}\right) = \operatorname{sgn}\left(-Q_I\frac{\partial^2 \psi_I(\alpha^*)}{\partial \alpha \partial \mu_I}\right) \geq 0 \tag{A.15}$$

$$\begin{aligned} \bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \tilde{\lambda}}\right) = \operatorname{sgn}\Bigg(&\mathrm{WTP}\cdot Q_E\left(\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E}\frac{\partial^2 \psi_E(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} + \frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E^2}\frac{\partial \psi_E(\alpha^*)}{\partial \tilde{\lambda}}\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\right) \\ &-\mathrm{WTP}\cdot Q_I\frac{\partial^2 \psi_I(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} + C_{AE}\frac{\partial^2 \lambda_{AE}(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} - C_{AI}\frac{\partial^2 \lambda_{AI}(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}} - C_{RE}\frac{\partial^2 \lambda_{RE}(\alpha^*)}{\partial \alpha \partial \tilde{\lambda}}\Bigg) \end{aligned} \tag{A.16}$$

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

$$\begin{aligned} \operatorname{sgn}\left(\tilde{\lambda}\frac{\partial \alpha^*}{\partial \tilde{\lambda}}\right) &= \operatorname{sgn}\Bigg(\mathrm{WTP}\cdot Q_E\frac{\partial \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E}\frac{\partial \psi_E(\alpha^*)}{\partial \alpha} - \mathrm{WTP}\cdot Q_I\frac{\partial \psi_I(\alpha^*)}{\partial \alpha} + C_{AE}\frac{\partial \lambda_{AE}(\alpha^*)}{\partial \alpha} \\ &\quad - C_{AI}\frac{\partial \lambda_{AI}(\alpha^*)}{\partial \alpha} - C_{RE}\frac{\partial \lambda_{RE}(\alpha^*)}{\partial \alpha} + \mathrm{WTP}\cdot Q_E\frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E^2}\psi_E(\alpha^*)\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\Bigg) \end{aligned} \tag{A.17}$$

$$= \operatorname{sgn}\left(\mathrm{WTP}\cdot Q_E\frac{\partial^2 \mathbb{E}[N_E(\alpha^*)]}{\partial \psi_E^2}\psi_E(\alpha^*)\frac{\partial \psi_E(\alpha^*)}{\partial \alpha}\right) \leq 0 \tag{A.18}$$

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:

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial \mu_E}\right) = \operatorname{sgn}\left(-\frac{\tilde{\lambda}}{\mu_E^2}pe^{\Phi^{-1}(1-\alpha^*)\delta\sqrt{I_n}-\frac{\delta^2 I_n}{2}}\left(\frac{1-\psi_E(\alpha^*)}{(1+\psi_E(\alpha^*))^3}\right)\right) \tag{A.19}$$

$$\bullet \operatorname{sgn}\left(\frac{\partial \alpha^*}{\partial p}\right) = \operatorname{sgn}\left(\tilde{\lambda} e^{\Phi^{-1}(1-\alpha^*)\delta\sqrt{I_n} - \frac{\delta^2 I_n}{2}} \left(\mathrm{WTP} \cdot Q_E \left(1-\psi_E(\alpha^*)\right) + C_{AE} + C_{RE}\right) + \mathrm{WTP} \cdot Q_I \frac{\tilde{\lambda}}{\mu_I} + C_{AI}\tilde{\lambda}\right) \tag{A.20}$$

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:

$$V_K'(\alpha_{K+1}^*) - V_{K+1}'(\alpha_{K+1}^*) = WTP \cdot Q_E \left(\frac{\partial \mathbb{E}[N_E^K(\alpha_{K+1}^*)]}{\partial \psi_E^K}\frac{\partial \psi_E^K}{\partial \alpha} - \frac{\partial \mathbb{E}[N_E^{K+1}(\alpha_{K+1}^*)]}{\partial \psi_E^{K+1}}\frac{\partial \psi_E^{K+1}}{\partial \alpha}\right) \tag{A.21}$$

$$= -\frac{Q_E}{\mu_E}\frac{\partial \lambda_{AE}}{\partial \alpha}\frac{WTP}{(1+\psi_E^K)^2(1+\psi_E^{K+1})^2}\left(\frac{2\psi_E^K}{K+1} + \frac{(\psi_E^K)^2(2K+1)}{(K+1)^2}\right) \tag{A.22}$$

From the optimality of α_{K+1}^*, we know that $V_{K+1}'(\alpha_{K+1}^*) = 0$, and thus noting that (A.22) 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

$$V_0'(\alpha_1^*) - V_1'(\alpha_1^*) = -WTP \cdot \frac{Q_E}{\mu_E}\frac{\partial \lambda_{AE}}{\partial \alpha}\frac{1}{(1+\psi_E^1)^2} \tag{A.23}$$

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

$$\alpha_0^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}}\log\left(\frac{1-p}{p}\frac{C_{AI} + WTP \cdot Q_I/\mu_I}{C_{RE}+C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right) \leq \alpha_1^* \tag{A.24}$$

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:

$$V_K'(\alpha_\infty^*) - V_\infty'(\alpha_\infty^*) = WTP \cdot Q_E \left(\frac{\partial \mathbb{E}[N_E^K(\alpha_\infty^*)]}{\partial \psi_E^K}\frac{\partial \psi_E^K}{\partial \alpha} - \frac{\partial \mathbb{E}[N_E^\infty(\alpha_\infty^*)]}{\partial \alpha}\right) \tag{A.25}$$

$$= -WTP \cdot \frac{Q_E}{\mu_E}\frac{\lambda_{AE}}{\partial \alpha}\left(2\psi_E^K + (\psi_E^K)^2\right) \tag{A.26}$$

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

$$\alpha_K^* \leq \alpha_\infty^* = 1 - \Phi\left(\frac{1}{\delta\sqrt{I_n}}\log\left(\frac{1-p}{p}\frac{C_{AI} + WTP \cdot Q_I/\mu_I}{WTP \cdot Q_E/\mu_E + C_{RE} + C_{AE}}\right) + \frac{\delta\sqrt{I_n}}{2}\right) \tag{A.27}$$

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:

$$V_K(\alpha) - V_{K+1}(\alpha) = WTP \cdot Q_E \left(\frac{K\lambda_{AE}}{K\mu_E + \lambda_{AE}} - \frac{(K+1)\lambda_{AE}}{(K+1)\mu_E + \lambda_{AE}}\right) \tag{A.28}$$

$$= \frac{-WTP \cdot Q_E \cdot \lambda_{AE}^2}{(K\mu_E + \lambda_{AE})((K+1)\mu_E + \lambda_{AE})} \tag{A.29}$$

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:

$$V_K(\alpha) - V_\infty(\alpha) = WTP \cdot Q_E \left(\frac{K\lambda_{AE}}{K\mu_E + \lambda_{AE}} - \frac{\lambda_{AE}}{\mu_E}\right) \tag{A.30}$$

$$= -\frac{WTP \cdot Q_E \cdot \lambda_{AE}^2}{\mu_E(K\mu_E + \lambda_{AE})} \tag{A.31}$$

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:

$$V_{K+1}(\alpha) - V_K(\alpha) - (V_{K+2}(\alpha) - V_{K+1}(\alpha)) \tag{A.32}$$

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

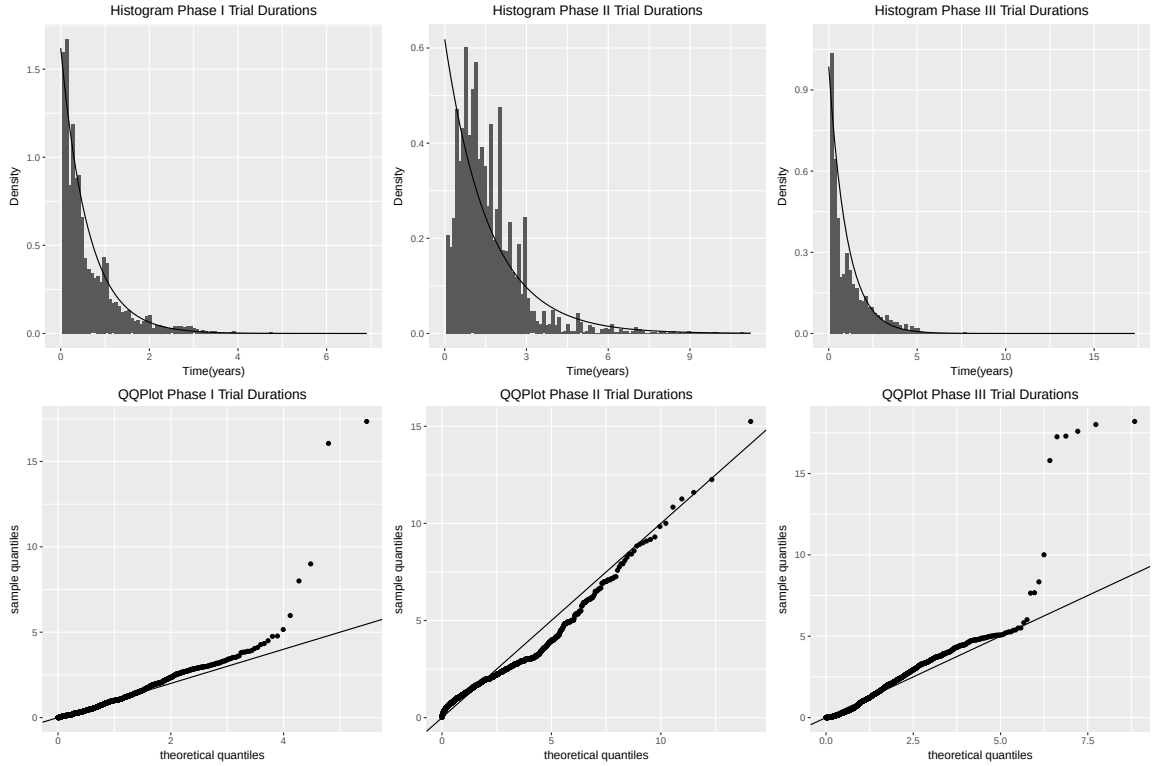
$$= \frac{2 \cdot WTP \cdot Q_E \cdot \mu_E}{((K+1)\mu_E + \lambda_{AE})\,((K+2)\mu_E + \lambda_{AE})\,(K\mu_E + \lambda_{AE})} \quad \blacksquare \tag{A.33}$$

Appendix B: 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 B1 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 B1 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 B1 Histograms and qqplots of the duration of phase I, phase II, and phase III clinical trials.



Appendix C: 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

$$\mathbb{P}(\text{complete clinical trials}) = \frac{\mu_{CT}}{\mu_{CT} + \mu_{AB}} \tag{C.34}$$

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 C.34 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 C2 - C4), 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 $\tilde{\lambda} = (\lambda_{AE} + \lambda_{AI})/\mathbb{P}(\text{Approve NDA})$. The rate at which drugs begin clinical trials λ is then estimated as $\lambda = \tilde{\lambda}/\mathbb{P}(\text{Complete clinical trials})$.
- **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 withdrawal $r_{withdrawal}$. We combine these values with the median pharmaceutical market capitalization to obtain the following monetary value estimates:

$$C_{AE} = (r_{initial} + r_{approvable} + r_{approval\ day} + r_{day\ after\ approval}) \cdot Market\ Cap \tag{C.35}$$

$$C_{AI} = C_{AE} - (r_{withdrawal}) \cdot Market\ Cap \tag{C.36}$$

$$C_{RE} = (r_{initial} + r_{approvable} - r_{rejection}) \cdot Market\ Cap \cdot p. \tag{C.37}$$

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 C1 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 C2 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	

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

Table C2 FDA-approved breast cancer drugs (continued).

Drug (Brand Name)	Approval	Drug Class
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	
Doxorubicin & Cyclophosphamide	N/A	
Doxorubicin, Cyclophosphamide & Paclitaxel	N/A	
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 C3 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	

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

Table C3 FDA-approved HIV drugs (continued).

Drug (Brand Name)	Approval	Drug Class
Abacavir, Dolutegravir & Lamivudine (Triumeq)	Aug 2014	Combination Medications
Atazanavir & Cobicistat (Evotaz)	Jan 2015	(Continued)
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 C4 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 C4 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 C5 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)