1 Introduction

Since its establishment in 1906, the U.S. Food and Drug Administration (FDA) has approved over 1,500 novel drugs, with total sales of approved drugs exceeding $310 billion each year (Kinch et al. 2014, IMS Health 2016). Despite undergoing rigorous evaluation, some FDA-approved drugs were subsequently shown to be ineffective or even harmful to patients. In September 2004, for example, the anti-inflammatory drug Vioxx was withdrawn from world markets due to safety concerns over increased risks of heart attack and stroke, after more than 160,000 patients suffered adverse events and 38,000 patients died (DrugWatch 2017). The struggle between providing sick patients with potentially beneficial remedies, while protecting consumers from harmful adverse events plays a significant role in the FDA’s decision-making. In this work, we develop a novel queueing model of the drug approval process, starting from development through evaluation, FDA approval or rejection, and obsolescence or market expiry. Our modeling framework can proffer insights for the FDA’s approval policy, 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) in a patient population, prevalence—the number of individuals afflicted with a disease, intensity of research and development (R&D), and the number of alternative treatments available for a target condition.

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. Safety and efficacy of candidate drugs are usually established by conducting a series of clinical trials, allowing policymakers to weigh the risk of approving an ineffective drug (type I error) against the chance 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, \( \alpha \), 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 for drug approval recommend a constant threshold of \( \alpha = 2.5\% \) for all diseases (Food and Drug Administration 2017b). By controlling only for the probability of a type I error, this policy ignores the asymmetric costs of type I and type II errors across diseases. Rejecting an effective medication for mild pain management, which has many other effective treatment options, for example, is less costly than rejecting an effective drug for Alzheimer’s disease, for which few treatments exist. A fixed threshold ignores the nuances of clinical trial design (e.g., rate of new molecule discovery, trial duration, rate of attrition), characteristics of the target patient population (e.g., disease prevalence and severity), and the post-approval market (e.g., availability of alternative drugs).
In recognition of the limitations of a fixed threshold, the FDA has introduced the Fast Track, Accelerated Approval, Breakthrough Therapy, and Priority Review programs to provide the agency with regulatory discretion to address some aspects of disease prevalence, disease severity, and the duration of the drug development and approval process (Food and Drug Administration 2015). The Fast Track program facilitates development and review of candidate drugs that treat serious conditions and fill an unmet medical need. Accelerated Approval allows the FDA to base approval decisions for expedited drugs on surrogate endpoints believed to reasonably predict clinical benefit, but are not themselves measures of clinical benefit. For example, a surrogate endpoint for heart disease is cholesterol level. A Breakthrough Therapy designation aims to hasten the development and review of drugs that demonstrate a 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. In this paper, we explore a different regulatory policy: vary the FDA’s choice of significance level based on characteristics of the drug development process for each disease.

The decision making process of whether to approve or reject a drug is complex. The FDA considers a variety of factors when judging whether to grant marketing approval, including performing a risk-benefit assessment of the drug under consideration, but these factors are weighed qualitatively, making it difficult to ascertain the relative importance of each factor (Food and Drug Administration 2017a). By developing a model in which the significance level required for approval explicitly depends on the characteristics of the drug development process, one can discern the quantitative effect of a given factor on the likelihood of approval. Furthermore, the FDA is often accused of fostering opaque approval policies, and a more objective approach to drug approval could improve the transparency of this process.

2 Contributions and Results

- We develop a queueing approach to analyze the drug development and approval process, accounting for characteristics such as disease severity and prevalence, R&D intensity, clinical trial duration, and the availability of alternative treatments. We model the drug development process using a series of $M/M/\infty$ queues, and the market for approved drugs as a collection 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 determine the optimal significance level that maximizes the societal expected net benefits from approving and rejecting drugs, which include the health impact of drugs on the market, as well as monetary values for the correct decision of approving effective drugs and for the incorrect decisions of approving ineffective (type I error) and rejecting
effective (type II error) drugs. We interpret health impacts as the incremental gain in QALYs associated with novel drugs and monetary values as the change in the market capitalization of publicly traded pharmaceutical companies following news of successful drug approval, rejection, or withdrawal. We show that the optimal significance level is higher (easier to approve) for diseases with lengthy clinical trials, high rates of attrition, and low R&D intensity.

- Using publicly available datasets encompassing all registered clinical trials and FDA drug approvals, we estimate model parameters and determine the optimal significance levels for three high-burden diseases: breast cancer, HIV, and hypertension. We test model robustness and 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 future research on this topic should consider both pre- and post-approval drug characteristics.

- We perform a counterfactual analysis to evaluate the effect of the Fast Track program on health impacts and monetary values. Using published studies on the observed effects of Fast Track on clinical trial duration and NDA review, we estimate parameters for a hypothetical approval process without this program. Our results indicate that, by bringing drugs to the 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 only changing the significance level for drug approval.

References


