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ABSTRACT

Regulators of new products confront a tradeoff between speeding a new product to market and collecting additional product quality information. The FDA's Breakthrough Therapy Designation (BTD) provides an opportunity to understand if a regulator can use new policy to innovate around this tradeoff—i.e., whether it improved regulator productivity by allowing products to come to market more quickly without compromising quality. We find that the BTD program shortened clinical development times by 23 percent and did not impact the ex post safety profile of drugs with the designation. In exploring mechanisms, we find that the BTD program had the greatest impact on less experienced firms and was associated with reduced BTD clinical trial design complexity. The results suggest that targeted regulatory innovation can shorten R&D periods without compromising the quality of new products.

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1. INTRODUCTION

In markets with entry regulation, regulatory authorities play an important role in shaping new product development. Prior to reaching market authorization decisions, a regulator must strike a balance between which products to prioritize and gathering additional information about their quality, which can delay approval. Such information deficiencies have important consequences: in the extreme, a dearth of information about a product's quality can lead to consumer harm and damages to both a firm's reputation and shareholder value (Jarrell and Peltzman 1985; Rhee and Haunschild 2006; Shah et al. 2017).

Nowhere is this tradeoff starker than in health care, where regulators such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approve new therapies, such as drugs and vaccines against COVID-19 (Philipson and Sun 2008; Califf 2017; Miller and Woodcock 2017; U.S. Food and Drug Administration 2019; Lackey, Thompson, and Eggers 2021).[1] For new medicines, the costs of new product development are considerable, and have been estimated to be as high as $2.6 billion (DiMasi et al. 2003; DiMasi et al. 2016). A large literature documents the decline in R&D productivity, driven by increasing drug development and review times (see, e.g., Pammolli, Magazzini, and Riccaboni 2011; Schuhmacher, Gassmann, and Hinder 2016). While patients are typi-

[1] Discussions of regulatory priorities and the tradeoff between speed and additional information have been central in the context of COVID-19 vaccine development: the much-visited *New York Times Coronavirus Vaccine Tracker* (Zimmer, Corum, and Wee 2021) website leads with the text: "Vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists embarked on a race to produce safe and effective coronavirus vaccines in record time." Additionally, headlines such as " 'Are they safe ... and how have they been developed so quickly?': an expert answers nine frequently asked questions about Covid-19 vaccines" (Thomas 2020) hint at the tension between speed and information gathering in the development of new medical products.

cally eager to have faster access to valuable medicines, such high R&D costs serve to further underscore drug developers' interest in faster approvals. Against this backdrop, regulatory priorities become particularly salient as patients, regulators and policy-makers grapple with considering whether new products can be brought to market faster in ways that do *not* compromise information about product quality.

We examine this tradeoff in the context of a recent policy change that impacted incentives for new drug development in the United States, the FDA's *Breakthrough Therapy Designation* (BTD). The BTD program was created in 2012 to make the clinical development and regulatory approval processes faster by providing a number of benefits – chiefly "intensive guidance on an efficient drug development program" from "senior managers" at the FDA. The FDA did not receive any additional funds to support this program (Woodcock 2014). As a result, the program could have had a variety of effects on R&D times and drug quality. To the extent that development times were shortened, the key question is whether less safe medicines were approved, or whether the increased interaction between senior regulators and drug developers facilitated by the BTD program allowed the FDA to increase its productivity by more quickly approving medicines without a safety-tradeoff (Sherman et al. 2013; U.S. Food and Drug Administration 2014; Daniel et al. 2015).

The existing literature provides mixed evidence as to how regulatory incentives shape new product development and regulatory approval. For example, observational studies have suggested that medicines that experience shorter regulatory review may be linked with higher adverse events levels (Olson 2008; Darrow et al. 2014) but other researchers have failed to find evidence for this relationship (Philipson et al. 2008; Schick et al. 2017).

Similarly, the existing literature on the effects of the BTD is mixed and largely relies on anecdotal or cross-sectional evidence. Anecdotal reports on the BTD program suggest that the program shortened drug development and review times.[2] Shaywitz (2017) documents the success of Merck's drug pembrolizumab (Keytruda), describing how the BTD designation "fundamentally changes the relationship between the FDA and the company developing the drug." Moreover, survey evidence suggests that the BTD is poorly understood by clinician prescribers. Kesselheim et al. (2016) find that physicians frequently overestimate a "breakthrough" drug's clinical effectiveness, raising concerns that they might prescribe that drug inappropriately once it is approved for marketing. In the medical literature, Hwang et al. (2018) examines the subset of cancer drugs and documents that BTD and non-BTD drugs experience similar levels of adverse events among clinical trial patients. However, in this study concerns about the limited sample size, unobservable factors, and adverse event measures may limit the causal interpretation and external validity of the estimates.[3] In particular, drugs that are eligible for the BTD are likely to be quite different than those that did not receive the designation. Indeed, one reason for the sparse empirical literature on the BTD program is likely due to the challenge of identifying an appropriate control group for BTD drugs.

Using a combination of algorithmic matching and a difference-in-difference design, we overcome these challenges to provide the first comprehensive, econometrically-driven analysis of the impact of the BTD program on (1) time-to-market for new drugs and (2) product quality. In particular, we construct a treatment (respectively, control) group includes all BTD (non-BTD) medicines and medicines

[2] See, for example, https://www.statnews.com/2018/04/27/breakthrough-therapy-designation-helps-cancer-patients/ and https://www.nytimes.com/2015/05/02/upshot/speedy-drug-approvals-have-become-the-rule-not-the-exception.html

in the pre-BTD era that shared the key features of BTD (non-BTD) drugs, as determined by a multivariate statistical matching procedure.

With this design, we find that products receiving the BTD spent, on average, 23 percent less time in clinical development. A shortening of the development process of this magnitude is economically meaningful: in our comprehensive dataset, BTD drugs spent an average of 2.74 years (32.9 months) in the last phase of pre-approval clinical trials. Martin et al. (2017) find that "each additional month for phase III trials translates into a median $671,000 spent," suggesting that the BTD program may be worth over $5 million for a developer at this stage of research alone. This estimate is conservative, as it does not take into account the shortening of the development process in earlier clinical trial phases, health benefits to patients of faster access to medicines, the additional profits associated with a longer period of on-patent drug sales for the drug maker.

The benefits of faster product development are most compelling and unambiguous when product quality is not compromised. We explore quality directly by examining whether faster clinical development among BTD products is associated with higher rates of drug adverse events reported by patients, physicians, and drug developers. Unlike the previous literature, which primarily focuses on the impact of a review program on subsequent adverse event *levels*—e.g., reported events per month—we account for the fact that innovative products may have different diffusion *rates*—i.e., the *per-patient* risks associated with a product. Focusing on *rates* of adverse events (i.e., per user) is crucial if BTD drugs are prescribed more frequently by physicians and/or in higher demand by patients. We find that on a per-patient basis, BTD products are no more likely than an algorithmically matched set of drugs to be associated with adverse events.

Taken together, these findings suggest that the BTD program has provided a mechanism for accelerating new medicines to market, without evidence of a compromise to those products' safety profiles. These issues are salient in the context of COVID-19 vaccines where the speed-safety tradeoff has been central; we return to this setting in the last section of this paper.

The remainder of the paper proceeds as follows. Section 2 describes the setting. Section 3 introduces the conceptual framework. Section 4 describes the data and Section 5 presents the main results. Section 6 probes the robustness of our findings and examines mechanisms, and Section 7 concludes.

2. Background

2.1 Drug Regulation in the United States

In most countries, drug developers must first seek formal regulatory approval before they can legally market pharmaceutical products (Scott Morton and Kyle 2011). In the United States, a drug developer typically files an Investigational New Drug (IND) application with the FDA in order to begin testing in humans (Jin 2014). With an approved IND, developers typically proceed chronologically through three stages of clinical research, each with varying objectives and cost: *Phase I* trials are principally meant to test drug candidate safety and dosage; *Phase II* trials are larger and are meant to test drug candidate efficacy and side effects; *Phase III* trials usually test the efficacy and safety of drug candidates among a larger group of patients.[4] Drug developers often perform multiple trials in each clinical development stage. For example, Zhang et al. (2020) note that the share of drug approvals typically supported by at least two so-called "pivotal" efficacy trials (usually Phase III trials) ranged from approximately 50 to 60 percent. Upon successful completion of clinical trials, developers file a New Drug Application (NDA) or Biologics License Application (BLA) for FDA marketing approval.

[4] There are exceptions to these statements. In particular in recent years, there has been increased interest in conducting trials that cover multiple phases concurrently (e.g., phase I/II and phase II/III trials).

The clinical development process takes years to complete: each *Phase II* trial lasts several months to two years, each *Phase III* trial typically lasts 1-4 years, and the FDA's standard review period for new drugs is 10 months.

2.2 The BTD Program

In response to rising concerns about the length of the drug development process for important new drugs, Congress passed the *Advancing Breakthrough Therapies for Patients Act of 2012* (U.S. Food and Drug Administration 2014), which created the Breakthrough Therapy Designation (BTD) with the intention of shortening this timeline for important new drugs that treat serious conditions and fill unmet medical needs (Bennett 2012; U.S. Food and Drug Administration 2014).

According to the FDA, "unmet need" exists for a serious or life-threatening disease unless there is a cure for every person with the disease (U.S. Food and Drug Administration 2014). For example, in diseases where various genetic mutations are present (such as in a viral infection like HIV or an inborn error disease like Cystic Fibrosis), a curative treatment may be developed for only certain mutations of the disease. Products that treat those subsets of patients already addressed by therapeutics may no longer be eligible for a BTD, but the remaining subgroups would still have unmet need and as such, treatments for these subgroups would remain eligible for a BTD.

The BTD program requires substantial preliminary evidence of efficacy over existing therapies, and in return, offers significant engagement on drug development planning by senior regulators (U.S. Food and Drug Administration 2014). Firms are expected to submit a BTD request along with or soon after completing their Phase I or II trials, such that that the effect of the BTD on clinical development times would surface in the later stage(s) of clinical trials (Conrad et al. 2017).

Firms that successfully obtain a BTD receive information from regulators and access to alternative review procedures, which are aimed at reducing the time between the start of clinical development and final approval for a (breakthrough) drug. These benefits include intensive regulatory guidance on

efficient drug development on all aspects of the development program (e.g., which primary and secondary endpoints to measure in trials, defining the target population, necessary inclusion/exclusion criteria, appropriate selection of the control group (e.g., historical, placebo), and which patients to study), organizational commitment by FDA senior managers, and the ability to request a rolling regulatory review, during which the FDA may consider reviewing portions of a marketing application before the sponsor submits a complete application (U.S. Food and Drug Administration 2014; Daniel et al. 2015).

The BTD program therefore allows regulators to inform clinical trial design and other aspects of drug development and to expedite information evaluation. While industry scientists are experts at drug development, FDA scientists are experts in the "regulatory science" aspects. This includes an understanding of historical precedent, by knowing what selections were successful in other studies, where issues may arise (e.g., manufacturing), and the full gamut of regulatory requirements. As such, intensive regulatory guidance could meaningfully improve the efficiency of arriving at late-stage clinical trial designs as well as selecting those designs that are most efficient for the products in development.

Importantly, the level of evidence required by the FDA for approval does not differ between BTD and non-BTD drugs. This is also true for the trial designs used in confirmatory studies, which are based on characteristics of the drug and disease, not a drug's BTD status. Thus, the regulatory "goal posts" haven't been moved, but rather the speed with which a manufacturer can arrive at the designs for and subsequently execute late-stage trials may be significantly improved.[5]

[5] For certain diseases, more regulatory communication may result in the conclusion that the use of historical controls or "open label" (non-blinded) assignment of an experimental drug to patients would be sufficient for regulatory decision making. We note further that the level of evidence that is necessary and appropriate for a regulator to make a decision about the safety and efficacy of a new drug for a disease with unmet need may well differ from the level of evidence that

2.3 Other FDA Expedited Programs

Against this backdrop, it is interesting to compare the BTD with other expedited programs and considering how they interact (for additional details, see Appendix A). As noted above, the creation of the BTD program followed several FDA "expedited programs" aimed at providing special benefits for certain novel drug candidates before, during, and after regulatory approval. Key programs make provisions for "Priority Review," "Accelerated Approval," and "Fast-Track Designation."

The *Priority Review* designation was created in 1992 and is given to drug candidates that are expected to provide a significant improvement in safety and efficacy relative to existing therapies.[6] Products receiving Priority Review benefit from a shortened period of regulatory review, receiving a decision regarding market approval in six months rather than the standard ten months allocated for FDA review otherwise (U.S. Food and Drug Administration 2014).

Also dating back to 1992, the *Accelerated Approval Pathway* allows drug candidates that provide a meaningful advantage over available therapies to be approved based on demonstration of an effect on an intermediate clinical endpoint—i.e., "surrogate endpoints", such as a laboratory measurement, a radiographic image, or a physical sign—that predicts clinical benefit, but is not by itself a measure of benefit (U.S. Food and Drug Administration 2014). For example, in HIV drug development, viral load can be used as a surrogate endpoint for product approval (i.e., drugs can be approved based on their impact on HIV viral load rather than waiting to observe patient death or severe disease progression as a study endpoint). The use of surrogate endpoints can meaningfully reduce the size and/or duration

is considered most rigorous by systematic reviewers. To say it another way: there are settings in which the FDA may not require evidence from RCTs, even if such evidence is considered to be of higher quality than other types. We revisit this discussion in the context of our results in the final section below.

[6] https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review

of clinical trials and lower the costs associated with clinical development (Naci et al., 2017; Liu and Kesselheim, 2019).

Created in 1997, the *Fast Track Designation* provides benefits for drugs that are intended to treat serious or life-threatening conditions and demonstrate the potential to address unmet medical needs. Because the program allows products to receive expedited development and review, most sponsors request the designation during the IND phase of drug development (U.S. Food and Drug Administration 2014, 2020).

3. Regulatory Priorities and Trade-offs

We describe the decisions and trade-offs faced by regulators in markets with entry regulation. First, regulators must determine the *types* of activities to prioritize (e.g., activities related new drug development and product review vs. activities related to manufacturing and guidance development) and when such prioritization might take place. Second, regulators face a key trade-off that require striking a balance between moving a new product to market quickly and gathering additional information about its quality. This trade-off is captured explicitly in the FDA's dual mandate to protect both public health and ensure access to new therapies. Quoting directly from the FDA's mission statement,[7] we are reminded that:

> "The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices…[and] FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health."

[7] https://www.fda.gov/about-fda/what-we-do

With respect to the prioritization decision, regulators must determine how best to allocate a fixed set of resources across different regulatory activities. Prioritization decisions are potentially affected by a variety of stakeholders, such as Congress, public interest groups, regulated firms, and consumers (Carpenter 2002). Regulators may opt to reallocate resources towards speeding the development of products that are more effective than available products or address an unmet need (Dranove and Meltzer 1994) and such prioritization could happen at different points in time. For example, the Fast Track Designation and Priority Review Designation described above provide benefits at different times during the drug development process.

Many regulatory programs are designed to reallocate regulatory resources towards products that treat serious unmet needs. As noted earlier, the BTD program was not accompanied by additional user fees, nor were an new funds appropriated (Woodcock 2014), however responsibility for communication with manufacturers of products with a BTD was made explicit in a way that was not true for non-BTD products. A key feature of the BTD program was that "high-level regulator" time committed to BTD drugs were not being drawn away from non-BTD drugs, but rather from activities that were outside of the set of approved medicines (which may include generic drugs and biosimilars, post-marketing requirements, over the counter drugs, and manufacturing issues to name a few).

Looking next to the trade-off between speed and information gathering, regulators must consider the benefits and costs of prioritizing timely approval against (requisite) information gathering to ensure product quality. Too little information before approving a product for marketing may lead to unforeseen negative outcomes, whereas overly burdensome information requirements may delay users' access to new products and deter innovation (Peltzman 1973). Examples of the pitfalls of speeding a product to market without sufficient information gathering can be seen in nearly every industry: launching a new software application without sufficient testing will get the tool to consumers faster, but it may have "bugs." Similarly, launching a new medical device without sufficient assessment of the

biocompatibility of the materials used may lead to urgent medical device recalls (e.g., as seen in 2014 with the Hulka Clip, a surgical occlusion device).

In such settings, regulators implicitly determine the point along a trade-off curve between speed and information that maximizes public welfare. Such a curve is presented in Figure 1, where point A is a policy choice of the regulator. Revealed in the choice of point A are the regulator's preferences: the regulator believes this is the combination of information (regulatory requirements in the form of clinical evidence) and the speed of commercialization that maximizes public welfare. Notably, the absence of therapies for a severe illness may mean that point A' (which corresponds to faster time-to-market coupled with less information at the time) may still lead to greater welfare (Isakov et al. 2018).

In most instances, regulators face resource constraints and must therefore move along a fixed speed-information trade-off curve. Given additional resources or more efficient allocation of existing resources, the possible combinations of information and speed of commercialization expand: it may be possible to move to a higher "regulatory isoquant"— in other words, if innovative regulatory policy can shift out the regulatory frontier presented in Figure 1, one could imagine bringing products to market more quickly in ways that do not compromise information about product quality. This possibility would be tantamount to a shift outward of the trade-off curve to point B.

4. DATA

We collect data on all New Molecular Entities (NMEs) approved by the FDA from 2006 through 2018. For each NME, we obtain the date of U.S. approval, its approved indication(s) at the time, flags for expedited review programs (BTD, Priority Review, Accelerated Approval, Fast Track), Orphan Drug Designation status, and whether the drug was initially approved with a boxed warning, an indicator of more severe risk. We focus only on primary approvals – i.e., the initial approval decision and its associated medical condition (indication) – and classify all drug indications into 14 mutually-exclu-

sive categories using the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system (see Appendix B for details). This results in a final sample of 396 NMEs (Appendix Table B1).[8] [9]

Our measures of time-to-market come from identifying, for each NME, the amount of time spent in discrete periods of regulatory review and clinical testing. As shown in Figure 2, we calculate regulatory review times by measuring the number of days between the date on which the developer (sponsor) submitted its completed NDA (the submission date) to the date on which the FDA officially approved the drug (the approval date). The regulatory review period may also include time that a sponsor spends responding to FDA questions and additional requests for data.[10] To measure time spent in late-stage clinical testing, we focus on two time periods: (1) the elapsed time between the start of Phase II trials and NDA submission and (2) the elapsed time between the start of Phase III trials and NDA submission. Of course, the BTD can only have an impact on clinical development if it has been granted.

In order to assess the changes in the observed safety information of newly approved NMEs, we collect data on reported adverse events from the FDA's Adverse Event Reporting System (FAERS),

[8] In the remainder of the paper, we use the terms "drug-indication," "drug approval," and "NME" interchangeably (U.S. Food and Drug Administration 2012).

[9] Our final sample includes eight combination drugs with BTD status. We keep these drugs in our primary analysis since it is precisely the *combination* of molecules that was the basis for "preliminary clinical evidence indicat[ing] that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)" (U.S. Food and Drug Administration 2018). However, a separate robustness test (not shown) that excludes the combination drugs documents results that are highly similar to the main results.

[10] Notably, the FDA may begin its review process prior submission of the entire NDA. For example, under the Fast Track program, regulators may begin to review sections of the NDA on a rolling basis. However, anecdotal evidence suggests that rolling review is infrequently used.

which we use as a proxy for such information.[11] FAERS is used for post-marketing drug safety surveillance and relies on reports submitted by developers, doctors, lawyers, and consumers. Adverse events range from headaches and nausea to hospitalizations and death. We generate monthly measures of pharmacy sales at the drug level using drug claims records from the Optum Labs Data Warehouse (henceforth OLDW) which allows us to measure the use of drugs overall and across indications. This database includes comprehensive medical and pharmacy claims, laboratory results, and enrollment records for both commercially insured and Medicare Advantage (MA) enrollees. The database contains deidentified longitudinal health information on enrollees and patients, representing a mixture of ages and geographical regions across the United States; we had data from 1993 through 2019. From this database we use only the pharmacy claims data—in particular, counts of prescriptions filled for each of the drugs in our sample.

Combined with contemporaneous FAERS data we generate adverse event rates at monthly increments within windows of two to six months from the date of approval for each NME. The rationale for using these windows of observation is twofold: (1) the five windows considered provide products sufficient time to launch in a market (whereas take-up may be difficult to see in the first month after launch) and (2) such windows of time are typically before any subsequent indications for a NME are

[11] In addition to safety, we can examine real-world differences in efficacy among BTD and non-BTD drugs by focusing on phase IV trials. For ongoing regulatory surveillance, many firms are also required to pursue phase IV trials. These post-market surveillance studies usually include several thousand diseased volunteers and are meant to monitor drug safety and efficacy in an ongoing way. In Appendix Table C1, we document that there is no significant difference in the likelihood of phase IV trial data existing for BTD vs. non-BTD drugs.

approved, which typically happens half a year or more after an initial approval. As such, we can reasonably confidently attribute adverse events observed to the first approved indication, rather than other drug uses such as later-approved indications or later "discovered" off-label uses.[12]

Table 1 presents drug-level summary statistics for the full, unmatched, unbalanced drug sample.[13] Several important differences emerge between BTD and non-BTD drugs: BTD products are more likely to engage in other FDA expedited programs and to be anti-cancer drugs. Without controlling for other factors, BTD products spend significantly less time in regulatory approval and clinical development on average (Panel B). Further, BTD products are associated with higher adverse event rates, with differences increasing as the window of observation expands from two to six months after approval (Panel C). Density plots in Figures 3 and 4 illustrate similar trends. Taken together, the summary statistics in Table 1 suggest that BTD products are associated with shorter clinical development and regulatory review periods, as well as higher adverse event rates, facts that would be consistent with a trade-off between speed and safety rather than an increase in regulatory productivity. However, this simple comparison of averages may mask substantial selection and differences in key factors that are correlated with our outcomes of interest (e.g., disease type, receipt of other regulatory designations) that may be driving these trends. As such, Table 1 is a key source of motivation for a rigorous matching approach in order to make more interpretable statements about the impact of the BTD program.

[12] Some off-label use may be more like "pre-label use" as it can originate as a result of physicians learning that a drug is being tested in an additional indication. If a physician is not part of the clinical trial, they may still opt to prescribe the drug to their patients for a not-yet-approved indication. This further supports the case for looking only at a relatively short window of time after an initial approval, so as to avoid confounding from any of these possible factors.

[13] Restricting to the set of drugs whose applications were approved after the start of the BTD program reveals similar patterns (see Appendix Table C2).

5. Empirical Strategy and Results

The previous section establishes that BTD and non-BTD drugs have different characteristics, rendering direct comparisons between the two groups problematic. To address these concerns, in this section, we use a matching procedure to generate comparable "treatment" and "control" groups of drugs and compare outcomes using a difference-in-differences framework.

5.1 Matching

To identify the treatment group, we start with the set of 60 drugs that received the BTD after its establishment in 2012 ("true" BTD drugs). We then use nearest neighbor matching to identify a set of "imputed" BTD drugs—i.e., the set of pre-2012 (pre-BTD) drugs that, based on observable characteristics, would have received the BTD, had it existed at the time.

Our algorithm matches exactly on the drug's small molecule (vs. biologic) status. We also match coarsely on a drug's access to other FDA review programs (as described in Section 2)—namely Priority Review status, Fast Track status, Accelerated Approval status—as well as whether the drug was approved with a boxed warning, the drug's ATC code, and whether the drug's developer was a publicly listed vs. privately held firm. Matching on the drug's type, known pre-approval safety risks (indicated by boxed warnings), and therapeutic category will minimize key differences across drugs that influence time-to-market and post-approval safety risks. It is notable that many BTD drugs participate in other expedited review programs. For example, the modal BTD in our sample also has Priority Review. By matching on these features and then considering differences between groups, our estimates capture the additional effects of the BTD above and beyond other expedited regulatory programs and drug

features.[14] Matching on the developer firm type allows us to minimize differences in drug outcomes that might be related to firm R&D expertise, regulatory and/or clinical trial experience, and other capabilities and resources. More broadly, incorporating all of these drug characteristics allows us to construct controls for *both* the BTD-treated and non-treated drugs in the post-2012 period, such that we can be more confident that results seen in regression analysis are not driven by the inclusion of drugs with quite different features.

This matching procedure invokes the matching estimator of Abadie and Imbens (2006), but avoids using *contemporaneous* matching/synthetic methods to construct a control group, given the non-random nature of the BTD designation, which implies fundamental differences between contemporaneous BTD and non-BTD drugs. Under our matching procedure, we identify comparator products by matching on all observables but doing so in a sample of drugs that came to market just before the BTD was created.

Of course, this approach by itself, is insufficient, because there could be general improvements in the quality of medicines or changes in the speed and nature of drug development and regulatory approval over time (which could be misattributed to the BTD program in the "post period"). To address these potential sources of bias, we create a control group of non-BTD drugs and identify matched controls for them in the pre-BTD period. The matching of non-treated drugs in the post-period to highly similar drugs in the pre-period thus permits a difference-in-differences design for comparing

[14] In terms of programs interacting with one another, differences in timing are important and decrease the likelihood of this being a major issue. These are discussed in more detail in Appendix A, but by way of example, consider Priority Review: Priority Review can only be granted at the time of NDA submission, such that it could not mechanically interact with the BTD during drug development to that point. Rather, it is an indicator of the innovativeness of a new drug, making it a sensible criterion to match on, but given the timing, making it virtually impossible to interact with the BTD designation during clinical development.

"breakthrough" (and similar) drugs in the pre- and post-periods to non-breakthrough (and similar) drugs in the pre- and post- periods, respectively. Econometrically, this means that we can use a much greater share of the population of approved medicines (namely non-breakthrough drugs) to account for potential time trends and differences in outcomes such as adverse-event reporting and R&D practices over time. As long as changes in these outcomes are similar for drugs with matched breakthrough designation and for matched drugs without this designation in the pre-BTD era, we can identify the causal effect of the breakthroughs program. We perform a number of robustness tests, in Section 5.3, to support this assumption and bolster our analysis.

Table 2 describe the final samples of treatment and control groups chosen by the matching algorithm, which identifies 23 unique drug matches for the 60 BTD drugs and 109 matches for the 167 non-BTD drugs. Overall, 36 drugs (nine percent of the drug sample) were matched to both true BTD and non-BTD drugs. In our main analysis, these drugs were randomly allocated to either the pre-2012 treatment or control groups.[15] 37 drugs whose applications were submitted before July 9, 2012 were not matched to either true BTD drugs nor to the set of true non-BTD drugs and were dropped from the subsequent analysis.[16] [17]

[15] As a robustness check, we also regenerate 5,000 drug samples, each with its own random allocation of the 31 drugs to the treatment and control groups. The estimated mean and standard errors of the coefficients largely support our main findings.

[16] An examination of drugs that are not matched to either true BTD drugs nor to true non-BTD drugs provides support for our analysis. For example, we exclude spinosad (Natroba), a therapy that was approved in 2011 and treats scabies and head lice. None of the post-2012 drugs of any kind (neither true BTDs nor true non-BTDs) were approved to treat scabies or head lice.

[17] We investigate the robustness of our main findings to this exclusion decision by assigning unmatched drugs to the imputed true non-BTD sample. We find similar results (Appendix Table C3).

Panel A in Appendix Tables D1 and D2 compare drug characteristics across the true and imputed non-BTD and BTD drug samples. Notably, apart from one descriptor, there are no longer statistically significant differences between the imputed and true BTD samples, a good jumping off point for a more balanced analysis of the program's incremental impact.

Table 3 presents summary statistics on the 359 drugs in the treatment (N = 83) and control (N = 276) groups. As in the unmatched sample, BTD products are associated with faster time-to-approval and higher post-approval safety signals. However, in a preview of the results from our regression analysis, we see that in the algorithmically matched sample, the differences between the two groups in measures of review times and clinical development times *increase* in Table 3 (relative to Table 1). Appendix Table D1, Panels B and C provide additional support for our difference-in-differences approach. For example, across all three time-to-market measures, we see significantly longer times to market for true (post-2012) relative to imputed (pre-2012) non-BTD products, consistent with the fact there is a time trend towards longer development and approval times. Our empirical approach takes these trends into account and measures the extent to which the BTD program diverts measures of time-to-market for BTD drugs away from these trends. (In Appendix D, we discuss in further detail our empirical strategy and the channels that may impact clinical development time.)

5.2 ESTIMATION

Our empirical estimation proceeds as follows. For drug *d*, we estimate the following:

$$E[Y_d|X_d] = \exp\left[\alpha + \beta BTD_d + \lambda BTD_d \times AfterBTD_d + \gamma' \boldsymbol{X}_d\right] \quad (1)$$

where Y_d is a measure of time-to-market (e.g., number of days between NDA submission to approval) or adverse event outcomes (e.g., adverse event rates within five months of approval), BTD_d is an indicator for whether drug *d* is in the treatment group of actual and matched BTD medicines, $AfterBTD_d$ is an indicator for whether drug *d*'s application was submitted after July 9, 2012, and $\boldsymbol{X}_d$

is a vector of controls, including a drug's year of approval, small molecule status, Priority Review status, Fast Track status, Accelerated Approval status, and whether approved with a boxed warning.[18] [19] In addition, we control for ATC code and developer type to account for differences in technology, resources, and political economy concerns (see Appendix A for more details).

The coefficient of interest is λ, which measures whether the effect of the BTD on drugs that actually received the BTD, versus the matched sample that would have been expected to receive this designation, had it existed at the time. β measures the time-invariant difference for medicines that either actually received the BTD or would have been expected to receive this designation. It captures the other factors associated with clinically important medicines in the matched set of drugs.

The dependent variables are skewed and consist of non-negative count and rate data. As a result, we report estimates from negative binomial regression models with robust standard errors.[20] [21] Equation (1) estimates the impact of the BTD program under the assumption that secular changes in drug development and approval times, drug quality, and quality reporting (as proxied by adverse event rates) for drugs eligible for BTD designation are the same as such changes for non-BTD drugs.

[18] As a robustness check, we can also control for the drug's "cohort" by controlling for submission year. Appendix Table C4 shows that this results in results that are similar in sign and magnitude to our main findings.

[19] While we control for the novelty of the drug by controlling for a drug's year of approval and its ATC code, we also confirm the robustness of our results to the inclusion of additional controls for the novelty of the drug's mechanism of action (Appendix Table C5).

[20] Importantly for skewed data, negative binomial models do not assume that the conditional mean equals the variance, suggesting that such specifications are more appropriate than Poisson models. As discussed in Section 5.3.2, we probe the robustness of our estimates using an alternative specification and find similar results.

[21] We calculated the interclass correlation coefficient across ATCs with respect to our dependent variables, which did not lead to statistically significant differences across groups, indicating that clustering at the ATC level is not required.

5.3 RESULTS

Table 4 presents estimates of BTD on time-to-market. Columns 1–3 document that the BTD program is not *itself* associated with a decline in regulatory approval times. This establishes that our statistical design clears a basic falsification test: the program is not designed to have any impact on review times and therefore should not have any association with the observed length of regulatory review after controlling for factors that directly impact FDA review deadlines. As would be expected, Priority Review – a program that is explicitly designed to lower the time spent in regulatory review – is strongly associated with a decrease in time spent in regulatory approval, but is not a statistically significant predictor of time spent in clinical testing and development, periods of time before the designation can be granted to a drug.

Consistent with the BTD program's stated goals, we estimate a negative and statistically significant effect of the BTD program on late-stage clinical development times. Exponentiating the coefficients and differencing from one yields numbers that are interpretable as elasticities. Specifically, we find that relative to non-BTD products, BTD products experience a statistically significant 23 percent decline in time spent between both the start of Phase III trials and NDA submission (Columns 4-6) and start of Phase II to NDA submission (Columns 7-9). These findings suggest that the benefits of the BTD program in accelerating new drug development disproportionately evenly accrue throughout clinical development.[22]

Table 5 reports the impact of the BTD program on adverse event rates. Overall, the evidence do not to point to the fact that BTD drugs have higher AE rates during any of the widows of time

[22] Of course, the BTD designation can only impact drug development if the designation is granted. Since BTD designations are typically granted after the start of Phase II, we would expect the effect on time-to-market effect would be largest among drugs whose Phase III clinical trials begin after the drugs receive their BTD designation. We confirm this in Appendix Table C7.

considered. In contrast, Appendix Table C6 shows statistically significant increases in adverse event *levels* following approval, highlighting the importance of scaling observed events by the number of patients using these drugs.[23] Taken together, our estimates suggest that the BTD program has no statistically detectable effect on adverse event outcomes. Further, our estimates in Column 6 suggests that we can rule out increases in adverse event rates greater than 20 percent per month.

6. Mechanisms and Robustness Checks

The evidence thus far indicates that the BTD program led to a decrease in clinical development times, without a detectable impact on adverse event rates. A natural next question to ask is: what mechanism(s) might explain these findings?

6.1 Role of Firm Experience

It is not only possible, but likely that the types of intensive guidance on the planned drug development program and organizational commitment that come with the BTD are more valuable for less experienced firms. That is, highly experienced drug manufacturers are more likely to already have (much of) the regulatory science expertise required to select the most efficient trial designs possible. To explore this possibility, we split the sample at the median into the firms with low(er) vs. high(er) levels of firm experience with past drug commercialization and re-run our main specification on the split sample. The results are presented in Table 6. While the BTD has a negative effect on Phase III to submission for firms with both low and high levels of experience, the effect is greater in magnitude and more statistically significant "low experience" firms, suggesting that it is indeed these firms that are benefiting most from the BTD program in terms of reductions in later-stage clinical development. In contrast, the effects on Phase II to submission are similar across both firm types.

[23] In separate robustness checks (Appendix Table C8), we find that these results are robust to excluding controls for developer type.

6.2 Clinical Trial Characteristics

A key feature of the BTD program is regulatory guidance to "ensure that the design of the clinical trials is as efficient as practicable" (U.S. Food and Drug Administration 2021), suggesting the likely role of clinical trial design choices. Table 7 examines the impact of the BTD designation on two such features: trial size and study design complexity. If the regulatory guidance provided through the BTD program helps firms' clinical design choices, we would expect that BTD drugs would be more likely to have clinical trials that are small in size and/or less complex in their study designs.

We measure trial size by focusing on the number of patients (Column 1), trial facilities (Column 2), and trial arms (Column 3) across all of the drug's Phase III (Panel A) and Phase II (Panel B) trials. As proxies for study design complexity, we assess whether patients were randomly assigned to a treatment (Column 4) and whether the study was double-blinded (Column 5). Though study design choices may influence the rigor of scientific evidence associated with the drug's pivotal trials, there are important differences between study design complexity and study design rigor which we discuss further in Section 7.

Across our three measures of trial size, we do not find evidence that the BTD program was associated with differently sized trials. In contrast, late-stage study design appears to differ among BTD products: Columns 4 and 5 indicate that true BTD products were tested in Phase III trials that were less complex in their design relative to the trials of comparable drugs before the BTD was created. Specifically, BTD products that received the designation were significantly less likely to be tested in randomized and double-blind trials (by an incremental 15.9 and 44.6 percentage points respectively). Taken together, the evidence suggests that the BTD program increases the efficiency of the drug development process by facilitating the use of less complex study designs.

6.3 Robustness Checks

6.3.1 Alternative Specifications

In Appendix Table C9, we probe the robustness of our core empirical results to an alternative functional form, ordinary least squares (OLS). We present results that are very similar to those reported in Table 4. While these results are not directly interpretable as elasticities, we find that at the sample means, the BTD designation is associated with a period of time spent in Phase III to NDA submission that is 356 days shorter relative to a mean of 1,458 days (24 percent) and that the time between Phase II to NDA submission declines by 532 days relative to a mean of 2,225 days (24 percent). Echoing our findings in Table 5, we find no statistically significant evidence that the BTD was associated with differential subsequent rates of adverse events in nearly all windows of time following approval.

6.3.2 More Similar Drugs (Restricting to 2010-2018 Drug Approvals)

Our analysis focuses on drugs approved between 2006 and 2018. While our matching procedure allows us to use observable traits to identify "imputed" BTD drugs whose applications were submitted prior to the start of the BTD program (July 9, 2012), drugs approved in earlier years may not be representative of drugs approved after the BTD program (for example, due to changes in biotechnology after the first decade of the 21st century). To increase the likelihood that "imputed" BTD are more similar to "true" BTD drugs, we limit our analysis to drugs approved between 2010 and 2018 – i.e., dropping the earliest four years of data. The time-to-market results in Columns 1 to 3 of Appendix Table C10, echo our main findings in magnitude and direction, though the effects on time from Phase II to submission are not statistically significant. The adverse event results in Columns 4 to 8 largely echo the main findings.

6.3.3. Fast Track Status as a Placebo Test

An important assumption of this analysis is that the unique features of the BTD program drive observed changes in time-to-market and product safety. In particular, unlike other FDA expedited review programs, the BTD program offers intensive regulatory guidance and organizational commitment from senior managers *during the development phase itself*. To test the relevance of the timing of the regulatory program, we perform a placebo test in which we evaluate whether drugs that receive the Fast Track designation experience similar outcomes in clinical development times and adverse event rates. This is a sensible placebo test because the Fast Track designation provides nearly all of the same features of the BTD designation *except* intensive regulatory guidance and organizational commitment from senior managers during the development phase—these being the primary features that are most likely to affect the time spent in clinical development. The results in Appendix Table C11 support our main findings: following the implementation of the BTD, there are no declines in clinical development times and no differences in adverse event rates associated with Fast Track drugs.

7. Discussion And Conclusion

The high costs and risks of biopharmaceutical new product development call for setting socially beneficial regulatory priorities and an understanding of how both firms and regulators can balance the dual objectives of bringing novel new products to market and gathering additional information about their quality. In markets with entry regulation, regulatory policies can play an important role in prioritizing when and how products are assessed and shifting firms' positions on the speed-information trade-off curve – or potentially reaching a new regulatory isoquant.[24] As the COVID-19 pandemic has

[24] The results of the empirical analysis are consistent with the FDA moving from a point below the frontier to the frontier, without a change in resources. However, the interpretation of the results (that the BTD brought products to

shown, strong science combined with dedicated regulatory resources can "shift the curve" and accelerate clinical development (and thus overall commercialization) times for valuable new products, when they are built on a foundation of strong and rigorous, early-stage R&D and evidence.

This study suggests that the regulatory community's engagement with new products during the COVID-19 pandemic has was precedented for nearly a decade elsewhere in the pharmaceutical industry, with the BTD program having led to far faster late-stage development of new drugs. In particular, we find that the BTD program is associated with a 23 percent decline in time spent in the final and most costly phase of clinical development. We simultaneously find no evidence that the BTD program led to a concurrent increase in adverse event rates. In exploring mechanisms, we find that the BTD program is associated with the greatest impact among less experienced firms, suggesting that it may help reduce differential outcomes between large, highly experienced firms and relative newcomers to drug development. The BTD program is associated with late-stage trials that are less complex in their design.

This final finding bears significant and rigorous consideration. From a social planner's perspective, a reduction in the frequency of randomization and blinding in trials comes with both benefits and challenges. Traditionally both features add to trial complexity, but are also seen as reducing "risk of bias" in clinical trials (Higgins, Altman, and Sterne 2011). This suggests a decline in trial design complexity may be another channel through which the BTD shapes information gathering about product quality. But it is also important to recall that such features are not inherently linked to drug safety. Moreover, there may be other benefits (beyond speed-to-market) of these trial design choices. Indeed—and less intuitively—such design choices may actually lead to the collection of more (or more

market more quickly without compromising information about product quality, which is associated with improvements in welfare) remain largely the same.]

complete) clinical datasets. For example, non-randomized and/or unblinded trials may be better at achieving their target enrollment and may therefore actually produce more regulatory-grade data. This is not just a hypothetical point: it is known that 40 percent of cancer trails fail to achieve their planned patient recruitment (Monteleone 2016). In such a high-stakes setting, a non-blinded, "open-label" trial (i.e., one in which a patient knows that he or she will receive an experimental therapy) may be more attractive for patients and their families. Further, in diseases where the "natural history of disease" (i.e., progression in the absence of treatment or with the medical consensus standard therapy) is well documented, a control arm may not be necessary or ethical for evidence generation about drug efficacy. While a full analysis of the effect of changes in clinical design complexity is beyond the scope of this paper, policy-makers and researchers should consider the extent to which these characteristics impact time-to-market and drug quality in both the short and long term along with associated social benefits and costs.

Another set of policy questions bear exploring in the post-market period: once BTD drugs are approved, do those that were granted approval on the basis of unblinded or non-randomized appear to be prescribed inappropriately more often and/or do such medicines have different experiences with payers and/or in getting onto drug formularies? Exploring these downstream policy questions will be of great value in filling-out the policy analysis of the BTD program.

Our results have implications for other regulatory interventions aimed at incentivizing the development of novel products—both within the US and internationally. The European Union developed the PRIME program in 2016 "to enhance support for the development of medicines that target an unmet medical need." Much like the BTD, PRIME "is based on enhanced interaction and early dialogue with developers of promising medicines" and is designed "to optimise development plans and speed up evaluation so these medicines can reach patients earlier" (European Medicines Agency 2018). As such, learnings from the BTD program are likely to prove valuable to regulators in Europe—and

vice versa. Ongoing and robust analysis of regulatory review programs will be key to helping the international regulatory science community learn about such programs efficiently and design better policy going forward.

A full welfare analysis of regulatory policies to support the expedited development of new medicines is beyond the scope of this study. However, a few things can be said from various stakeholders' perspectives: for patients, the fact that regulators are focusing on providing resources to support the types of products that have important clinical value and address unmet medical needs is surely desirable. This study provides evidence that regulatory innovation aimed at bringing such products to market more quickly can work. Further, we see evidence that such polices are disproportionately helping to accelerate clinical development for less experienced firms—that is, such policy innovation and regulatory communication may help to bridge the experience gap between more established firms and relative newcomers. Finally, we note that programs like the BTD are likely to have positive spillovers that are difficult to measure. Although there is no direct link between BTD regulatory advice and decisions for non-BTD drugs (as each drug development program is unique), the FDA is always learning from its own experiences. As such, the BTD program may result in the development of improved endpoints, the initiation of new collaborations, and advances in the understanding of disease pathophysiology and natural history. Therefore, such learnings—initially utilized in the BTD context—could well provide for the basis for better or more efficient decisions for non-BTD drugs that follow.[25]

Our results provide specific support for the effectiveness of policies that increase the level of information provision from the regulator to the developer. These findings are consistent with other work that has shown that concrete steps to mitigate regulatory uncertainty is associated with a decline

[25] To the extent that there are positive spillovers that may have occurred within our period of observation, this would attenuate our effect sizes estimated.

in time-to-market for medical products (Stern 2017). More generally, our analysis highlights the importance of considering the trade-offs that may be inherent in the commercialization of new products and how dedicated resources may help to mitigate such trade-offs, when they are appropriately designed and targeted. While thoughtful policy design and subsequent rigorous policy analysis will remain of the utmost importance, these findings suggest the promise of regulatory innovation for achieving specific policy goals and making medical product regulation more efficient overall.

8. REFERENCES

Abadie, Alberto and Guido Imbens (2006) "Large Sample Properties of Matching Estimators for Average Treatment Effects." *Econometrica* 74(1): 235-267.

Anand, Krishnan S, M. Fazıl Paç, and Senthil Veeraraghavan (2010) "Quality–Speed Conundrum: Trade-offs in Customer-intensive Services." *Management Science* 57(1): 40-56.

Ball, Philip (2020) "The Lightning-Fast Quest for COVID Vaccines — and What It Means for Other Diseases." *Nature* 589 (7840): 16–18.

Bennet, Michael F (2012) S.2236 - 112th Congress (2011-2012): Advancing Breakthrough Therapies for Patients Act of 2012. https://www.congress.gov/bill/112th-congress/senate-bill/2236.

Califf, Robert M (2017) "Balancing the Need for Access With the Imperative for Empirical Evidence of Benefit and Risk." *JAMA* 318(7): 614–16.

Carpenter, Daniel P. (2002) "Groups, the Media, Agency Waiting Costs, and FDA Drug Approval." *American Journal of Political Science* 45 (3): 490-505.

Conrad, Ryan, Kimberly Taylor, Miranda Raggio, Afi Harrington, Grace Stark, Andrew Kish, and Amy Bertha (2017) "Breakthrough Therapy Designation: CDER Analysis of Requests 4 Years Into the Program." *Therapeutic Innovation and Regulatory Science* 51(4) 509-515.

Daniel, Gregory, Elizabeth Richardson, and Criag Streit (2015) "Breakthrough Therapy Designation: A Primer." *Brookings* https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2015/04/21/breakthrough-therapy-designation-a-primer/.

Darrow, Jonathan J., Jerry Avorn, and Aaron S. Kesselheim (2014) "New FDA Breakthrough-Drug Category — Implications for Patients." *New England Journal of Medicine* 370(13): 1252–58.

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

DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski (2003) "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 22(2): 151–85.

Dranove, David and David Meltzer (1994) "Do Important Drugs Reach the Market Sooner?" *The RAND Journal of Economics* 25(3): 402-423.

European Medicines Agency (2018) "PRIME: Priority Medicines." https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

Higgins, Julian PT, Douglas G Altman, and Jonathan AC Sterne (2011) "8 Assessing Risk of Bias in Included Studies." *Cochrane Handbook for Systematic Reviews of Interventions* https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm.

Hwang, Thomas J., Jessica M. Franklin, Christopher T. Chen, Julie C. Lauffenburger, Bishal Gyawali, Aaron S. Kesselheim, and Jonathan J. Darrow (2018) "Efficacy, Safety, and Regulatory Approval of Food and Drug Administration-designated Breakthrough and Nonbreakthrough Cancer Medicines." *Journal of Clinical Oncology* 36(18): 1805-1812.

Jarrell, G and Peltzman, S (1985) "The impact of product recalls on the wealth of sellers." *The Journal of Political Economy* 93(3): 512-536.

Jin, Jill (2014) "FDA Approval of New Drugs." *JAMA* 311(9): 978.

Kesselheim, Aaron S, Steven Woloshin, Wesley Eddings, Jessica M. Franklin, Kathryn M. Ross, and Lisa M. Schwartz (2016) "Physicians' Knowledge About FDA Approval Standards and Perceptions of the 'Breakthrough Therapy' Designation." *JAMA* 315(14): 1516.

Lackey, Leila, Graham Thompson, and Sara Eggers (2021) "FDA's Benefit–Risk Framework for Human Drugs and Biologics: Role in Benefit–Risk Assessment and Analysis of Use for Drug Approvals." *Therapeutic Innovation & Regulatory Science* 55(1): 170-179.

Liu, Sheng, and Aaron S. Kesselheim (2019) "Experiences With and Challenges Afforded by Expedited Regulatory Pathways." *Clinical Pharmacology & Therapeutics* 105(4): 795–97.

Martin, Linda, Melissa Hutchens, Conrad Hawkins, and Alaina Radnov (2017) "How Much Do Clinical Trials Cost?" *Nature Reviews Drug Discovery* 16(6): 381–82.

Miller, Kathleen L., and Janet Woodcock (2017) "Value Assessment in the Regulatory Context." *Value in Health* 20(2): 296–98.

Monteleone, Jason (2016) "Patient Recruitment: Clinical Research's 'White Whale'?" https://www.pivotalfinancialconsulting.com//single-post/2016/12/09/patient-recruitment-clinical-researchs-white-whale.

Naci, Huseyin, Katelyn R. Smalley, and Aaron S. Kesselheim (2017) "Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration." *JAMA* 318(7): 626–36.

Olson, Mary K (2008) "The Risk We Bear: The Effects of Review Speed and Industry User Fees on New Drug Safety." *Journal of Health Economics* 27(2): 175–200.

Pammolli, Fabio, Laura Magazzini, and Massimo Riccaboni. 2011. "The Productivity Crisis in Pharmaceutical R&D." *Nature Reviews Drug Discovery* 10(6): 428-438.

Peltzman, Sam (1973) "The Effect of Government Subsidies-in-Kind on Private Expenditures: The Case of Higher Education." *Journal of Political Economy* 81(1): 1–27.

Philipson, Tomas, Ernst R. Berndt, Adrian H.B. Gottschalk, and Eric Sun (2008) "Cost-benefit Analysis of the FDA: The Case of the Prescription Drug User Fee Acts." *Journal of Public Economics* 92(5-6): 1306-1325.

Philipson, Tomas and Eric Sun (2008) "Is the Food and Drug Administration Safe and Effective?" *Journal of Economic Perspectives* 22(1): 85-102.

Rhee, M and Haunschild, PR (2006) "The Liability of Good Reputation: A Study of Product Recalls in the US Automobile Industry." *Organization Science* 17(1): 101-117.

Schick A, Miller KL, Lanthier M, Dal Pan G, Nardinelli C (2017) "Evaluation of pre-marketing factors to predict post-marketing boxed warnings and safety withdrawals." *Drug Safety* 40(6):497-503.

Schuhmacher, Alexander, Oliver Gassmann, and Markus Hinder. (2106) "Changing R&D models in research-based pharmaceutical companies." *Journal of Translational Medicine* 14(1): 1-11.

Scott Morton, Fiona, and Margaret Kyle (2011) "Chapter Twelve - Markets for Pharmaceutical Products." In *Handbook of Health Economics Volume 2*, edited by Mark V. Pauly, Thomas G. Mcguire, and Pedro P. Barros. 763–823. Elsevier.

Shah, R, Ball, G and Netessine, S (2017) Plant Operations and Product Recalls in the Automotive Industry: An Empirical Investigation. *Management Science* 63(8): 2439-2459.

Shaywitz, David (2017) "The Startling History Behind Merck's New Cancer Blockbuster." *Forbes* https://www.forbes.com/sites/davidshaywitz/2017/07/26/the-startling-history-behind-mercks-new-cancer-blockbuster/.

Sherman RE, Li J, Shapley S, Robb M, Woodcock J (2013) Expediting Drug Development—the FDA's New "Breakthrough Therapy" Designation. *New England Journal of Medicine* 369(20):1877-80.

Song, Hummy, and Senthil Veeraraghavan (2018) "Quality of Care." *Handbook of Healthcare Analytics: Theoretical Minimum for Conducting 21st Century Research on Healthcare Operations* 79-108.

Stern, Ariel Dora (2017) "Innovation Under Regulatory Uncertainty: Evidence from Medical Technology." *Journal of Public Economics* 145: 181-200.

Thomas, Kim (2020) "'Are They Safe ... and How Have They Been Developed so Quickly?': An Expert Answers Nine Frequently Asked Questions about Covid-19 Vaccines." *The Guardian* https://www.theguardian.com/all-in-all-together/2020/dec/03/are-covid-19-vaccines-safe-and-how-will-they-work.

U.S. Food and Drug Administration (2012) "A Guide to Drug Safety Terms at FDA." https://www.fda.gov/media/74382/download.

U.S. Food and Drug Administration (2019) "Benefit-Risk Assessment Through Drug Lifecycle: FDA Discussion Document." https://healthpolicy.duke.edu/sites/default/files/2020-07/discussion_guide_b-r_assessment_may16_0.pdf.

U.S. Food and Drug Administration (2018) "Breakthrough Therapy." https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

U.S. Food and Drug Administration (2014) "Expedited Programs for Serious Conditions—Drugs and Biologics." Rockville, MD: US Department of Health and Human Services. (Updated 2020)

U.S. Food and Drug Administration (2021) "Frequently Asked Questions: Breakthrough Therapies." Rockville, MD: US Department of Health and Human Services.

Woodcock, Janet (2014) "Drug Development in Serious Diseases: The New 'Breakthrough Therapy Designation.'" *Clinical Pharmacology and Therapeutics* 95(5): 483-485.

Zimmer, Carl, Jonathan Corum, and Sui-Lee Wee (2021) "Coronavirus Vaccine Tracker." *The New York Times* Accessed April 28, 2021. https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html.

Figures and Tables

Figure 1: The Quality-Information Space for Regulators

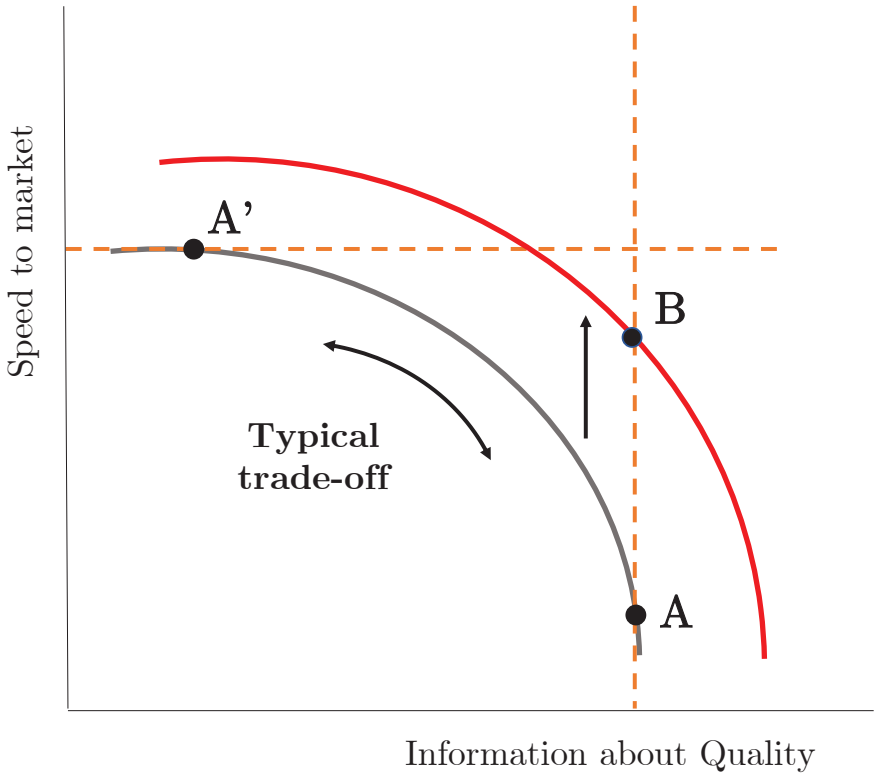
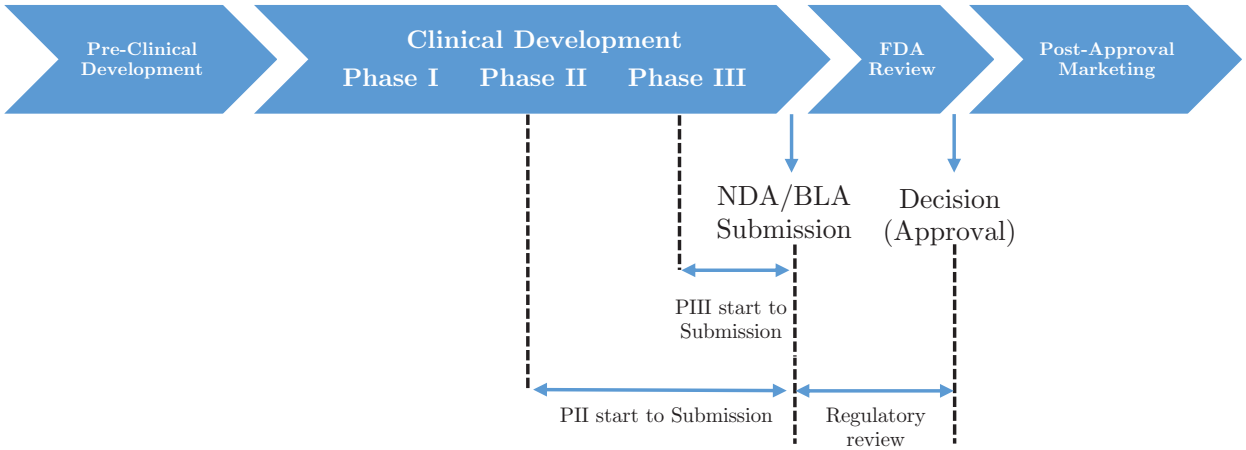
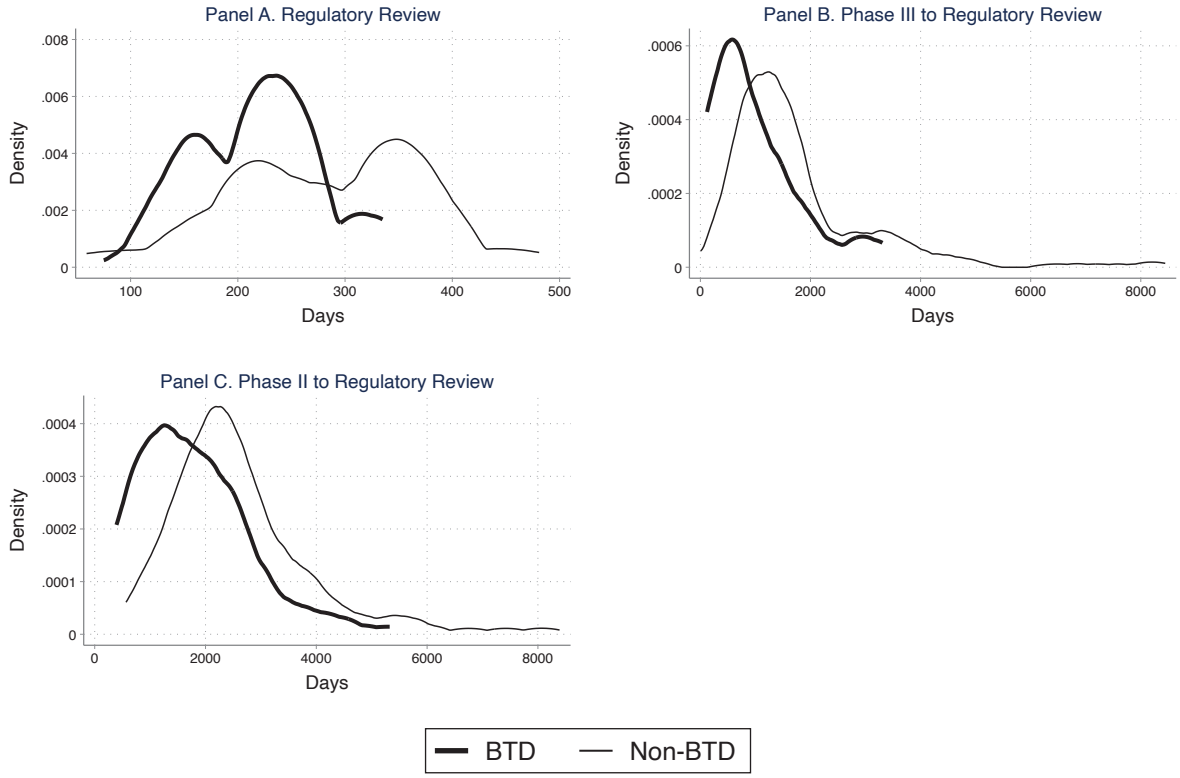


Figure 2: Timeline of Drug Development and Approval



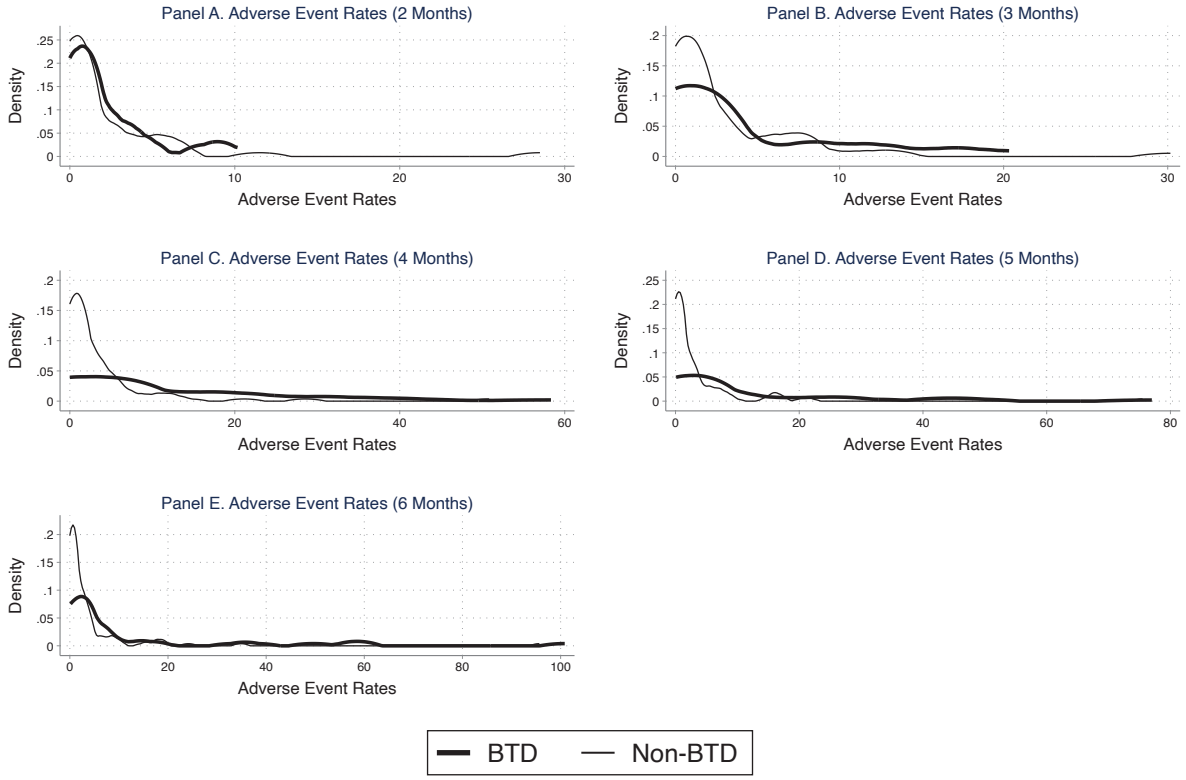
Notes: This figure shows the typical timeline of drug development and approval. In particular, it depicts our three measures of time-to-approval: (1) time from Phase II to NDA submission, (2) time from Phase III to NDA submission, and (3) time from NDA submission to FDA approval.

Figure 3: Distribution of Time-to-Market Outcomes



Notes: This figure shows the distribution of BTD and non-BTD time-to-market outcomes. Observations are at the drug-level. For more detailed data and variable descriptions, see Section 4.

Figure 4: Distribution of Adverse Event Outcomes



Notes: This figure shows the distribution of BTD and non-BTD adverse event rates. Observations are at the drug-level. For more detailed data and variable descriptions, see Section 4.

Table 1: Summary Statistics: Unmatched Drug Sample

	BTD N = 60		Non-BTD N = 336		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Small Molecule (0/1)	0.57	0.50	0.80	0.40	0.00***
Priority Review (0/1)	0.98	0.13	0.45	0.50	0.00***
Fast Track (0/1)	0.50	0.50	0.27	0.45	0.00***
Accelerated Approval (0/1)	0.35	0.48	0.09	0.28	0.00***
Black Box Warning (0/1)	0.23	0.43	0.38	0.49	0.00**
ATC: Cancer (0/1)	0.57	0.50	0.29	0.45	0.00***
ATC: Metabolism (0/1)	0.07	0.25	0.14	0.35	0.11
ATC: Antiinfectives (0/1)	0.15	0.36	0.10	0.31	0.30
ATC: Nervous System (0/1)	0.07	0.25	0.12	0.32	0.24
Sponsor: Private Firm (0/1)	0.12	0.32	0.2	0.40	0.14
Panel B. Time-to-Market Outcomes					
Regulatory Review (Months)	7.13	1.97	8.66	3.35	0.00***
Phase 2 to Regulatory Review (Months)	58.48	33.34	74.87	38.36	0.00**
Phase 3 to Regulatory Review (Months)	32.51	26.57	49.71	36.07	0.00***
Panel C. Adverse Event Rate Outcomes					
Within 2 Months	2.10	2.78	1.60	3.70	0.50
Within 3 Months	4.21	5.83	1.93	3.95	0.01**
Within 4 Months	10.66	14.35	2.36	5.45	0.00***
Within 5 Months	11.35	17.44	2.46	6.52	0.00***
Within 6 Months	12.25	22.03	2.83	7.98	0.00***

Notes: This table shows drug characteristics for the sample of 396 drugs that are approved between 2006 and 2018. All variables are measured at the drug-level. For example, "NDA to Approval (Months)" is the average number of months that a drug spends between NDA submission to approval. The top 4 most common ATC classes are shown. ATC categories that are not shown include: alimentary tract and metabolism; anti-infectives for systemic use; antineoplastic and immunomodulating agents; antiparasitic products, insecticides and repellents; blood and blood forming clots; cardiovascular system; dermatologicals; genitourinary system and sex hormones; musculo-skeletal system; nervous system; respiratory system; sensory organs; systemic hormonal preparations; and various. Column 5 presents p-values from t-tests comparing the difference of means. For more detailed data and variable descriptions, see Section 4.
*p<0.10, **p<0.05, ***p<0.001

Table 2: Synthetic Treatment and Control Group Counts

	Total	Non-BTD	BTD	Other
	(1)	(2)	(3)	(4)
Pre-BTD Program	169	109 (Imputed Non-BTD)	23 (Imputed BTD)	37
Post-BTD Program	227	167 (True Non-BTD)	60 (True BTD)	
Total	396	276	83	37

Notes: This table shows how drug approvals are distributed to synthetic treatment and control groups. The sample includes all drugs originally approved between 2006 and 2018. "Pre-BTD Program" refers to all drugs that were approved before July 9, 2012. "Post-BTD Program" refers to all drugs that were approved on/after July 9, 2012. "Other" refers to the set of pre-BTD program drugs that were matched to neither the set of true BTD drugs nor the set of true non-BTD drugs.

Table 3: Summary Statistics: Matched Drug Sample

	Imputed + True BTD N = 83		Imputed + True Non-BTD N = 276		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Small Molecule (0/1)	0.54	0.50	0.82	0.38	0.00***
Priority Review (0/1)	0.96	0.19	.042	0.49	0.00***
Fast Track (0/1)	0.48	0.50	0.28	0.45	0.00***
Accelerated Approval (0/1)	0.30	0.46	0.06	0.24	0.00***
Black Box Warning (0/1)	0 .33	0.47	0.37	0.48	0.50
ATC: Cancer (0/1)	0.59	0.49	0.28	0.45	0.00***
ATC: Metabolism (0/1)	0.05	0.22	0.15	0.36	0.01**
ATC: Antiinfectives (0/1)	0.12	0.33	0.11	0.31	0.69
ATC: Nervous System (0/1)	0.08	0.28	0 .12	0.33	0.33
Sponsor: Private Firm (0/1)	0.13	0.34	0.15	0.36	0.66
Panel B. Time-to-Market Outcomes					
Regulatory Review (Months)	6.98	1.97	8.91	3.41	0.00***
Phase 2 to Regulatory Review (Months)	58.62	31.29	77.78	40.37	0.00***
Phase 3 to Regulatory Review (Months)	32.85	24.18	52.16	38.21	0.00***
Panel C. Adverse Event Rate Outcomes					
Within 2 Months	1.90	2.60	1.69	3.90	0.77
Within 3 Months	3.54	5.37	2.08	4.08	0.07*
Within 4 Months	8.53	13.2	2.63	5.93	0.00***
Within 5 Months	9.07	15.69	2.66	7.06	0.00***
Within 6 Months	9.74	19.5	3.08	8.64	0.00***

Notes: This table shows drug characteristics for the matched sample of drugs that are approved between 2006 and 2018. All variables are measured at the drug-level. For example, "NDA to Approval (Months)" is the average number of months that a drug spends between NDA submission to approval. The top 4 most common ATC classes are shown. ATC categories that are not shown include: alimentary tract and metabolism; anti-infectives for systemic use; antineoplastic and immunomodulating agents; antiparasitic products, insecticides and repellents; blood and blood forming clots; cardiovascular system; dermatologicals; genitourinary system and sex hormones; musculo-skeletal system; nervous system; respiratory system; sensory organs; systemic hormonal preparations; and various. Column 5 presents p-values from t-tests comparing the difference of means. For more detailed data and variable descriptions, see Section 4.

*p<0.10, **p<0.05, ***p<0.001

Table 4: Impact on Time-to-Market

	Reg Review			Phase III to Reg Review			Phase II to Reg Review		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
BTD	-0.221**	-0.109	-0.055	-0.252**	-0.188	-0.135	-0.078	0.014	-0.026
	(0.074)	(0.082)	(0.081)	(0.123)	(0.130)	(0.121)	(0.092)	(0.107)	(0.100)
BTD x Post-2012	-0.044	-0.028	-0.058	-0.344*	-0.306*	-0.258*	-0.320**	-0.306**	-0.255**
	(0.087)	(0.085)	(0.084)	(0.176)	(0.158)	(0.144)	(0.123)	(0.118)	(0.111)
Small Molecule		-0.085**	-0.094**		0.127*	0.024		0.053	-0.000
		(0.040)	(0.042)		(0.073)	(0.084)		(0.067)	(0.073)
Priority Review		-0.239***	-0.240***		0.040	0.014		-0.014	0.023
		(0.047)	(0.045)		(0.098)	(0.095)		(0.074)	(0.075)
Private Firm		0.078	0.065		0.210*	0.128		0.157**	0.145*
		(0.053)	(0.056)		(0.111)	(0.110)		(0.080)	(0.079)
Mean	258.09	258.09	258.09	1,457.5	1,457.5	1,457.5	2,225.22	2,225.22	2,225.22
Controls: Drug Characteristics	N	Y	Y	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y	N	N	Y
Observations	359	359	359	340	340	340	310	310	310
log likelihood	-2156	-2141	-2129	-2745	-2724	-2707	-2563	-2551	-2540

Notes: This table report negative binomial model estimates of the effect of the BTD program on time-to-market outcomes. Observations are at the drug-level. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Clinical development times are observed for a subset of the sample, which accounts for the smaller number of observations in Columns 4-6 relative to Columns 1-2. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 6 imply that drugs experience a decrease in number of days spent between the start of Phase III and NDA submission after receiving BTD designation, a statistically significant $100 \times (\exp[-0.258] - 1) =$ -22.74%. Robust standard errors are in parentheses. For more detailed data and variable descriptions, see Section 4.
*p<0.10, **p<0.05, ***p<0.001

Table 5: Impact on Adverse Event Rates

	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)
BTD	-0.794	-0.499	-0.227	0.158	0.107
	(0.516)	(0.514)	(0.529)	(0.435)	(0.500)
BTD x Post-2012	0.463	0.765	0.766	0.331	-0.078
	(0.651)	(0.612)	(0.618)	(0.543)	(0.588)
Small Molecule	0.584	0.051	-0.001	-0.013	-0.468
	(0.376)	(0.327)	(0.301)	(0.317)	(0.334)
Priority Review	0.211	0.301	0.470*	0.723**	0.901***
	(0.342)	(0.280)	(0.259)	(0.269)	(0.270)
Private Firm	-0.610	-0.064	-0.842**	-0.633	0.224
	(0.654)	(0.456)	(0.405)	(0.397)	(0.413)
Mean	1.75	2.46	3.97	4.09	4.54
Controls: Drug Characteristics	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y
Observations	136	163	194	215	228
log likelihood	-200	-281	-384	-420	-466

Notes: This table report negative binomial model estimates of the effect of the BTD program on adverse event rates. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Adverse event rates are observed for a subset of the sample, which accounts for fewer than 359 observations. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 1 imply that drugs experience an $100 \times (\exp[0.463] - 1) = 58.88\%$ increase in adverse event rates in the 2 months after receiving the BTD designation, though the effects are not statistically significant. Robust standard errors are in parentheses. For more detailed data and variable descriptions, see Section 4.
*p<0.10, **p<0.05, ***p<0.001

Table 6: Mechanisms: Firm Experience

	Reg Review		Phase III to Reg Review		Phase II to Reg Review	
	Low Exp	High Exp	Low Exp	High Exp	Low Exp	High Exp
	(1)	(2)	(3)	(4)	(5)	(6)
BTD	-0.084	-0.082	0.078	-0.254	-0.048	0.199
	(0.099)	(0.147)	(0.143)	(0.193)	(0.131)	(0.178)
BTD x Post-2012	-0.077	0.054	-0.510**	-0.227	-0.290**	-0.459**
	(0.107)	(0.156)	(0.185)	(0.215)	(0.140)	(0.188)
Small Molecule	-0.110*	-0.039	0.019	0.006	-0.087	0.058
	(0.062)	(0.068)	(0.109)	(0.107)	(0.108)	(0.098)
Priority Review	-0.274***	-0.217**	0.056	-0.113	0.068	-0.097
	(0.051)	(0.089)	(0.115)	(0.147)	(0.096)	(0.136)
Private Firm	0.073	0.096	0.143	-0.090	0.081	0.163
	(0.069)	(0.141)	(0.132)	(0.168)	(0.089)	(0.142)
Mean	265.07	245.94	1,540.42	1,318.43	2,309.83	2,089.43
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y
Observations	228	131	213	127	191	119
log likelihood	-1334	-760	-1689	-981	-1557	-957

Notes: This table report negative binomial model estimates of the effect of the BTD program on time-to-market outcomes, by sponsor experience. "Low Exp" denotes the set of drugs with sponsors that have low levels of experience (below median number of previous drug approvals within the same year and ATC class). "High Exp" denotes the set of drugs with sponsors that have high levels of experience (above median number of previous drug approvals within the same year and ATC class). Observations are at the drug-level. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Robust standard errors are in parentheses. For more detailed data and variable descriptions, see Section 4.
*p<0.10, **p<0.05, ***p<0.001

Table 7: Mechanisms: Trial Characteristics

	Trial Size			Trial Design Complexity	
	Number of Patients (1)	Number of Facilities (2)	Number of Arms (3)	Randomized (0/1) (4)	Double Blinded Masking (0/1) (5)
Panel A. Phase III Trials					
BTD	-11.281	-48.254	-0.241	0.086	0.171
	(27.718)	(434.867)	(0.234)	(0.079)	(0.113)
BTD x Post-2012	1.778	-84.564	0.264	-0.159*	-0.446***
	(31.892)	(456.107)	(0.410)	(0.087)	(0.122)
Small Molecule	12.055	519.766*	-0.087	0.115**	0.105
	(19.642)	(312.414)	(0.218)	(0.043)	(0.065)
Priority Review	-7.043	-746.762	-0.187	-0.008	0.030
	(21.139)	(475.378)	(0.196)	(0.037)	(0.071)
Private Firm	-19.623	-62.320	-0.253	-0.227***	-0.214**
	(16.752)	(180.932)	(0.177)	(0.068)	(0.073)
Mean	108.84	1015.77	2.46	0.89	0.71
Observations	287	332	307	340	333
R^2	0.227	0.306	0.113	0.201	0.241
Panel B. Phase II Trials					
BTD	-54.124	-13.623	0.043	-0.036	-0.018
	(58.786)	(8.598)	(0.698)	(0.151)	(0.107)
BTD x Post-2012	52.214	1.015	0.295	-0.034	-0.087
	(57.624)	(8.657)	(0.785)	(0.163)	(0.123)
Small Molecule	27.966	-3.044	0.171	-0.102	-0.042
	(31.966)	(6.474)	(0.406)	(0.069)	(0.064)
Priority Review	-82.683*	-1.897	-1.124**	-0.131	-0.189**
	(44.206)	(7.192)	(0.440)	(0.088)	(0.071)
Private Firm	8.378	2.707	-0.329	0.056	-0.118
	(39.598)	(7.161)	(0.479)	(0.080)	(0.102)
Mean	197.51	27.29	3.19	0.77	0.52
Observations	281	242	243	224	281
R^2	0.188	0.126	0.164	0.382	0.420

Notes: This table report OLS model estimates of the effect of the BTD program on trial characteristics. Observations are at the drug-level. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Columns show fewer than 359 observations due to missing data on trial characteristics. Estimates in Panel A are conducted on the set of drugs that have non-missing data on the time between the start of Phase III trials and NDA submission. Estimates in Panel B are conducted on the set of drugs that have non-missing data on the time between the start of Phase II and NDA submission. Robust standard errors are in parentheses. For more detailed data and variable descriptions, see Section 4.
*p<0.10, **p<0.05, ***p<0.001

APPENDIX

APPENDIX A: ADDITIONAL DETAILS ON THE BTD PROGRAM

ORIGIN OF THE PROGRAM

The idea for a BTD program was first discussed in the context of a non-profit organization at the Friends of Cancer Research Conference on Clinical Cancer Research on November 10, 2011. The session included a panel with participants from academic, industry, NIH, and FDA. According to the issue brief published by Friends of Cancer Research:

> *"This panel was convened to identify consensus approaches for new, expedited development pathways for drugs that demonstrate substantial activity early in development. … The FDA recently released an innovation strategy in which they stated that identifying ways to expedite drug development for exceptional new drugs is a key priority for the Agency."*

After the panel, Friends of Cancer Research gathered further stakeholder input and support for a new expediated program, which coalesced into legislation creating the BTD program. Thirteen months after the panel, the BTD law was passed with bipartisan support as an amendment to the Food and Drug Administration Safety and Innovation Act, an iteration of the Prescription Drug User Fee bills.

To summarize, the BTD program was not developed by firms or a member of congress, but rather by an interdisciplinary group of cancer experts and advocates. It should not be surprising, therefore, that cancer drugs are disproportionately likely to benefit from the program: while the ATC class for oncology drugs makes up 29% of all non-BTD drugs in our data, it accounts for 50% of the BTD drug sample. To the extent that there is an interest lobby behind the BTD program, it is the cancer lobby (which is supported by multiple pharmaceutical companies but not uniquely by any subset). As we note in Section 5.2, the fact that we are controlling for both the ATC class for oncology drugs as well as firm status should thus account for any major differences along these dimensions. In addition, we also control for other factors (e.g., Priority Review status) that might also be subject to political economy concerns.

Engagement with Senior Regulators

A key component of the BTD program is that it ensures significance engagement on drug development by senior regulators in CDER. In contrast, a non-BTD development program, sponsors generally interface with only the review-level staff (e.g., medical officers and management up to the division director). Office directors and the Director of the Office of New Drugs would be briefed on final decisions for new drugs and consulted on any decisions that have significant policy or precedent-making implications.

Importantly and uniquely, for BTD drugs, decisions on the development program would receive guidance from the Medical Policy Council (MPC).[1] The MPC includes the most senior members of CDER, including: the Center Director, the Deputy Center Director for Clinical Science, the Director of the Office of New Drugs, and the Director of the Office of Surveillance and Epidemiology. The MPC works to problem-solve and reach internal consensus on decisions regarding the BTD drug development program. This allows the sponsor to have final decisions on critical aspects of their program, thus initiating and conducting pivotal trials more rapidly. The MPC does not otherwise advise on clinical development programs for other drugs, so its attention to BTD drugs is part of the program's value-add.

Differences vs. Fast Track Designation

While the qualifying criteria for BTD and Fast Track designation are similar, the key difference is that BTD requires clinical data showing a product's promise before a manufacturer can apply. From FDA guidance: "Unlike the information that could support Fast Track designation, which could include theoretical rationale, mechanistic rationale (based on nonclinical data), or evidence of nonclinical activity, breakthrough therapy designation requires preliminary clinical evidence of a treatment effect that may represent substantial improvement over available therapies for the treatment of a serious condition" (U.S. Food and Drug Administration 2014).

[1] For more information on the Medical Policy Council, see: https://www.fda.gov/media/85725/download.

Further, while both Fast Track designation and BTD require that the drug be used to treat a serious condition, Fast Track requires that the drug be used to treat an "unmet need" whereas the BTD requires that the drug be an "improvement over existing therapies". In terms of benefits: both programs offer rolling review and both offer standard "Actions to expedite development and review". But BTD also offers: "Intensive guidance" and "Organizational commitment" as described above. That several drugs in our sample receiving both designations is a testament to their partial overlap.[2]

FDA BUDGET

No direct funds were appropriated to support the BTD program. However, administering the BTD program was part of FDA's commitment to PDUFA VI, the fifth renewal of the federal act that provides the FDA with funds to support drug review.[3] It is likely, therefore, that some of the additional costs of administering the program were funded through an increase in user fees. Between 2006 and 2019, the share of FDA's budget that came from user fees increased from ~10 percent to ~50 percent. (However, much of this increase was due to the creation of FDA's Center for Tobacco Products in 2009, which is funded completely through user fees.)

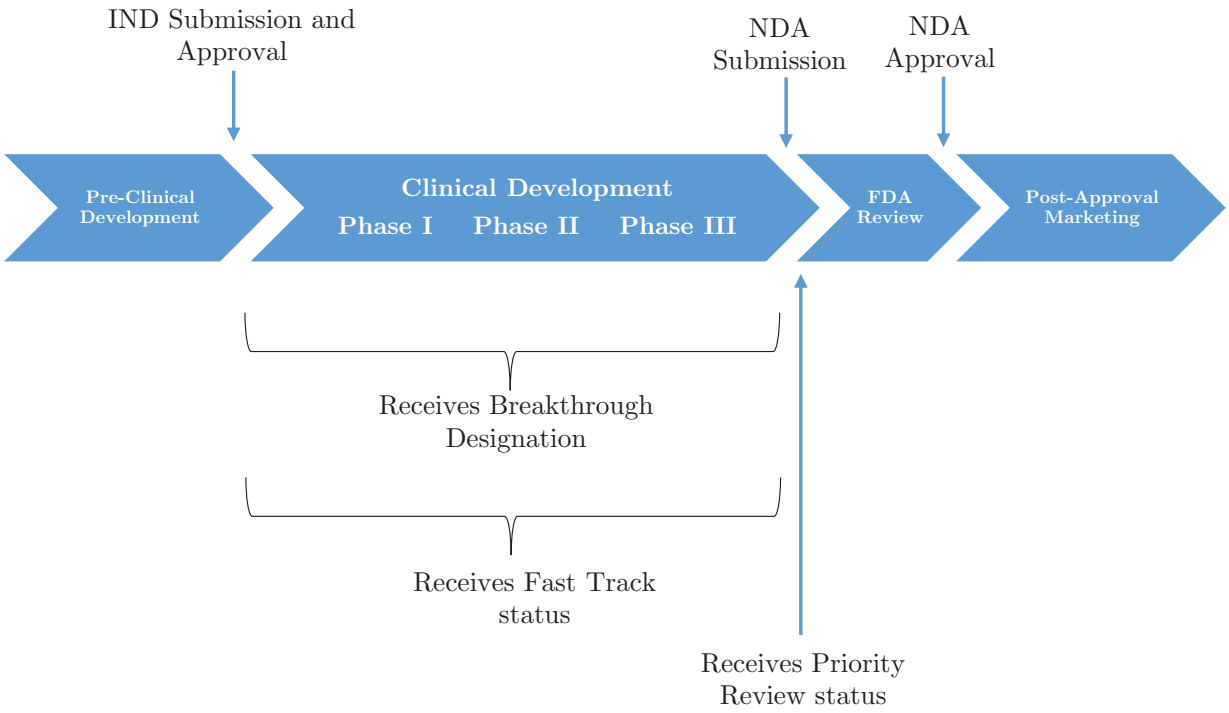
[2] The only BTD drug in the sample without Priority Review is idelalisib (Zydelig). As seen in Table 1, among BTD drugs, 50 percent (n=30) qualified for Fast Track and 35 percent (n=21) qualified for Accelerated Approval. Among non-BTD drugs in the post-2012 period, 49 percent (n=82) qualified for Priority Review, while only 34 percent (n=60) qualified for Fast Track and just 7 percent (n=11) qualified for Accelerated Approval.

[3] The Food and Drug Administration Reauthorization Act (FDARA) was signed into law on August 18, 2017. It includes the reauthorization of the Prescription Drug User Fee Act (PDUFA), which in turn, provides FDA with the necessary resources to maintain a predictable and efficient review process for human drug and biologic products. (https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-fiscal-years-2018-2022)

Appendix A References

U.S. Food and Drug Administration (2014) "Expedited Programs for Serious Conditions—Drugs and Biologics." Rockville, MD: US Department of Health and Human Services. (Updated 2020)

Figure A1: Timeline of Drug Development and FDA Expedited Programs



Notes: This figure shows the typical timeline of drug development and FDA Expedited Programs.

Table A1: FDA Expedited Review Programs

Program	Year Introduced	Drug Criteria
Priority Review Designation	1992	Drugs that provide a significant improvement in safety and effectiveness receive shortened review (6 months vs. the standard 10 months)
Accelerated Approval Pathway	1992	Drugs that provide a meaningful advantage over available therapies and demonstrate an effect on a meaningful clinical endpoint receive approval based on an intermediate clinical endpoint.
Fast Track Designation	1997	Drugs with nonclinical or clinical data that demonstrate the potential to address an unmet medical need or have been designated as a qualified infectious disease product receive expedited development and review and are eligible for rolling review.

Source: https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf

APPENDIX B: DATA CONSTRUCTION

PRIMARY ANALYSIS SAMPLE

Our sampling frame consisted of all New Molecular Entities (NME) approved by the FDA in calendar years 2006 through 2018. The relevant NMEs were collected from FDA reports and represent the "master list" of drugs for this study (Center for Drug Evaluation and Research 2021; Center for Drug Evaluation and Research 2015; Center for Drug Evaluation and Research 2020a).

The data include FDA application numbers, proprietary and established drug names, U.S. approval dates, and "Breakthrough Therapy" designations (Center for Drug Evaluation and Research 2020b; Friends of Cancer Research 2021a). Since the program's launch, the response to the BTD program has been enthusiastic: as of December 31st, 2020, the FDA's Center for Drug Evaluation and Research (CDER) had received 917 requests for BTD. The FDA granted 375 BTD requests and approved 190 applications for drugs with the BTD (Center for Drug Evaluation and Research 2020b; Center for Drug Evaluation and Research 2020c).[1] There is no penalty for applying to receive a BTD and this may encourage developers to submit an application (Daniel et al., 2015).[2]

We also collect information on other regulatory designations ("Fast Track" and "Accelerated Review"), FDA standard review, priority review, orphan drug designations, and drug indication(s) (Center for Drug Evaluation and Research 2021a; Center for Drug Evaluation and Research 2020c; U.S. Food and Drug Administration 2021a). As described in Section 4 of the main manuscript, we classify all drug indications into 14 mutually exclusive categories using the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification system. The 14 ATC classes are: alimentary tract and metabolism, anti-infectives for systemic use, antineoplastic and immunomodulating agents, antiparasitic products, insecticides and repellents,

[1] Recent efforts have led to the expansion of the breakthrough program to medical devices: the 21st Century Cures Act, passed in December of 2016, offers to provide a similar regulatory program to "breakthrough" devices for which no approved alternative exists; as of January 1, 2020, over 70 devices had received the designation.
[2] In Europe, the EMA's *PRIME Program* facilitates enhanced support for "the development of medicines that target an unmet medical need." It is similar to the BTD Program and offers "enhanced interaction and early dialogue" to drug developers with the goal "to optimise development plans and speed up evaluation so these medicines can reach patients earlier." (European Medicines Agency 2018).

blood and blood forming clots, cardiovascular system, dermatologicals, genitourinary system and sex hormones, musculoskeletal system, nervous system, respiratory system, sensory organs, systemic hormonal preparations, and various.

Data on boxed warnings (also sometimes referred to as "black box warnings") are collected from the NIH's "DailyMed SPL" resources data (National Institutes of Health 2021). We manually extract each drug's submission date from the "Original Approval" letter located in each drug's FDA Drug approval package, which is available from the Drugs@FDA database (U.S. Food and Drug Administration 2021b; Center for Drug Evaluation and Research 2021b).

Finally, we make two sample restrictions: first, we drop from our sample the 15 non-therapeutic products approved during our period of observation. These products are classified as diagnostic or contrast agents for imaging. Second, we drop nine drugs that are subsequently discontinued. Appendix Table B1 presents our final analysis sample 396 NMEs by calendar year of approval alongside counts by review and designation types.

MEASURING REGULATORY REVIEW TIMES

We calculated regulatory review times from the time the drug's manufacturer submitted the drug for approval (submission date) to the time FDA officially approved the drug (approval date).

MEASURING R&D TIMES (I.E., CLINICAL TRIALS TO SUBMISSION)

We calculated the length of elapsed time between major R&D milestones (the launch of Phase II and Phase III trials)[3] and FDA submission for products in the analysis sample (see Appendix Figure B1). We link each NME to its corresponding data from ClinicalTrials.gov trial following the steps below (see Appendix Figure B2 for sample size flowchart by steps):

1. We download the ClinicalTrial.gov pipe delimited files which contain data on all clinical trials registered up to date of access (Clinical Trials Transformation Initiative 2021).
2. We download the ClinicalTrial.gov pipe delimited files which contain data on all clinical trials registered up to date of access (Clinical Trials Transformation Initiative 2021).

[3] As reported in clinicaltrials.gov

3. We next restrict the ClinicalTrial.gov dataset based on the following criteria
    a. For a trial to be included in our clinical trial sample, its *overall status* must be "Completed" or, alternatively, the variable *primary completion date* is non-missing or the variable *completion date* is non-missing.
    b. The *study type* is "Interventional"
    c. The study *phase* is either "Phase 1 / 2", "Phase 2", "Phase 2 / 3", or "Phase 3." This primarily results in the exclusion of Phase 4 (i.e. post-market) studies, which often provide important clinical data, but are not part of the typical new product approval process.
    d. The study *intervention type* is either "Drug" or "Biological." This primarily results in the exclusion of studies of medical devices and surgical procedures.
    e. The study phase *start date* is populated. This is crucial, as the goal of linking approved drugs to their clinical studies is to understand the timeline of the development process. If a trial's launch date is not reported, the trial cannot provide information on the trial feature of interest.
4. We further retain the following ClinicalTrials.gov fields of interest: sponsor name(s), intervention name(s), condition(s), other study id(s), NCT id, trial start date.
5. We write an algorithm that links trials to NMEs, based on a match between cleaned and abbreviated product names, drug codes, original applicant names, and NME indications.
6. For each NME, we identify all phase II and Phase III trials in the ClinicalTrials.gov database.
7. We drop cases where trial start dates are *after* FDA submission dates.
8. We perform a number of quality checks on the trials identified through steps 1-6 above by comparing the study IDs to FDA trial IDs, which are manually collected from the *Table of Clinical Studies* in the Medical Review documents that are included in FDA drug approval packages.

Altogether, we are able to collect data on Phase III to NDA submission for 371 drugs (94 percent of the drug sample) and data on Phase II to NDA submission for 338 drugs (85 percent of the drug sample).[4] The

[4] For the remainder of drugs, the associated clinical studies could not be identified through either automated or manual review of FDA approval documents or clinical trial registries.

final sample of NMEs with both non-missing Phase II and/or Phase III start dates was 326. These 326 NMEs can be linked to 714 clinical trials, from which we calculate their corresponding phase start-to-submission times. Appendix Table B2 presents the average times to submission observed in our final sample of 326 NMEs.

Among the set of BTD drugs with available data on the timing of Phase II and Phase III launch dates and BTD approval dates (86 percent of the BTD sample), just 6 percent received BTD designations before their Phase II trials began. 22 percent received BTD designations during their Phase II program, and 71 percent received BTD designations only after their (earliest) Phase III trials had begun.

MEASURING POST-APPROVAL ADVERSE EVENTS

To study the safety of newly approved NMEs, we collect data on reported adverse events from the FDA's Adverse Event Reporting System (FAERS) (Center for Drug Evaluation and Research 2019).

We download quarterly event reports from 2006 through 2018 from two sets of adverse event data files: 1) the "Drug" files and 2) the "Demographic" files. The Drug data files (at the drug-report level) contain information on a drug's role in a given adverse event and, when available, the drug's FDA Application Number. The Demographic data files, which are at the level of a given report, include information on the date on which a report was filed.

In each of the quarterly *Drug* files from 2006 to 2018, we retained rows with the following characteristics:

1. There is a non-missing FDA report id (*primaryid*), which is used to link a reported adverse event to the *Demographic* data files.
2. In the file, a drug's role (*role_cod*) is coded as "Primary Suspect" – i.e. the drug is the primary product implicated in the reported adverse event.
3. The FDA application number (*nda_num*) is non-missing.

We link all matching application numbers to our analysis sample of 396 NMEs. We associate report dates from the *Demographic* file with each reported adverse event. Using the approval date for each NME, we calculate the number of adverse events occurring within windows of three and five months from the date of approval for each NME. By limiting these windows of time, we increase the likelihood that the adverse events reported are those that are attributable to use of the drug for its original approved indication, as secondary indications

for many drugs in our sample start to gain FDA approval around six months after the first indication. Our final sample includes 2,340,924 adverse event reports representing 378 of the 396 NMEs in our analysis sample (19 NMEs were not reported as having a primary role in any adverse events within six months of approval). Appendix Table B3 presents these adverse events counts (including when missing) for our analysis sample.

MEASURING POST-APPROVAL ADVERSE RATES

To generate adverse event *rates*, we divide the adverse event levels by the number of drug uses. Our proxy of drug usage comes from inpatient and outpatient drug claims records from the Optum Labs Data Warehouse (henceforth OLDW). Using this database, we obtain the number of unique claims for each drug and successfully match 372 of the 396 NMEs in our analysis sample to the OLDW. Because of requirements by the data provider, drug claim counts with 1 to 10 claims are censored. We replace such "small cells" with the average (i.e., 6) number of claims.

APPENDIX B REFERENCES

Center for Drug Evaluation and Research (2020a) "Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals." U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-approvals-and-databases/compilation-cder-new-molecular-entity-nme-drug-and-new-biologic-approvals.

Center for Drug Evaluation and Research (2020b) "CDER Breakthrough Therapy Designation Requests Received by Fiscal Year." U.S. Food and Drug Administration. https://www.fda.gov/media/95292/download.

Center for Drug Evaluation and Research (2020c) "CDER Breakthrough Therapy Designation Approvals." U.S. Food and Drug Administration. https://www.fda.gov/media/95302/download.

Center for Drug Evaluation and Research (2020d) "CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint." U.S. Food and Drug Administration. https://www.fda.gov/media/88907/download.

Center for Drug Evaluation and Research (2021a) "New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products." U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products.

Center for Drug Evaluation and Research (2021b) "Drugs@FDA Data Files." U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files.

Center for Drug Evaluation and Research (2015) "NDA and BLA Approval Reports - New Molecular Entity (NME) Drug and New Biologic Approvals." U.S. Food and Drug Administration. http://wayback.archive-it.org/7993/20170111082713/http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373420.htm.

Clinical Trials Transformation Initiative. "AACT Database." Accessed May 2, 2021. https://aact.ctti-clinicaltrials.org/pipe_files.

Daniel, Gregory, Elizabeth Richardson, and Criag Streit (2015) "Breakthrough Therapy Designation: A Primer." *Brookings* https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2015/04/21/breakthrough-therapy-designation-a-primer/.

European Medicines Agency (2018) "PRIME: Priority Medicines." https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

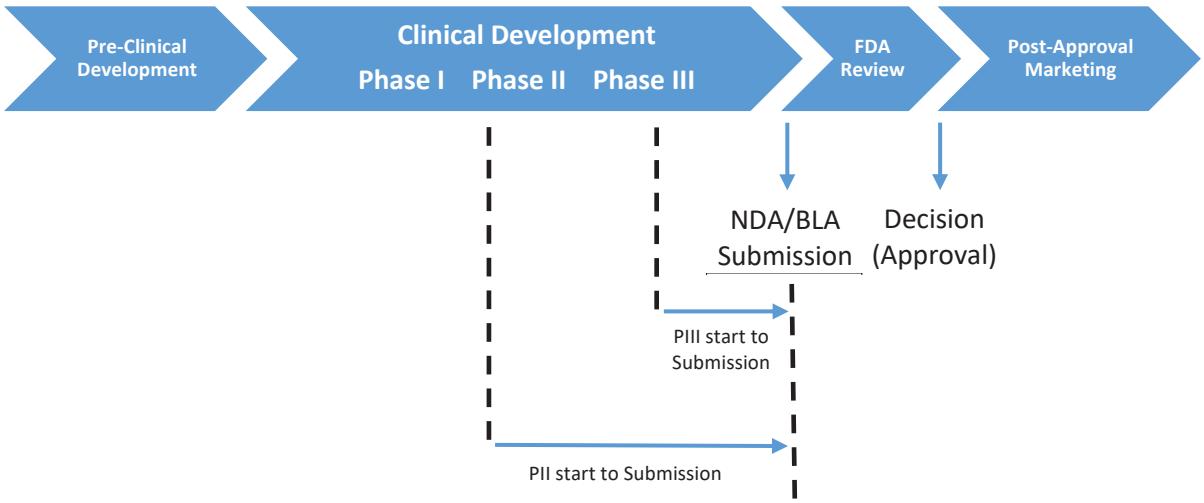
Friends of Cancer Research. "Breakthrough Therapies." Accessed May 2, 2021. https://friendsofcancerresearch.org/breakthrough-therapies.

National Institutes of Health. "DailyMed - SPL Resources." Accessed May 2, 2021. https://dailymed.nlm.nih.gov/dailymed/spl-resources.cfm.

U.S. Food and Drug Administration. "Drugs@FDA: FDA-Approved Drugs." Accessed May 2, 2021b. https://www.accessdata.fda.gov/scripts/cder/daf/.

U.S. Food and Drug Administration. "Search Orphan Drug Designations and Approvals." Accessed May 2, 2021a. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/.

Figure B1. FDA Drug R&D Path



Source: https://www.everycrsreport.com/reports/R44864.html, with some personal additions

Figure B2 Sample size pipeline for identifying clinical trials of interest (referring to steps listed in the text)

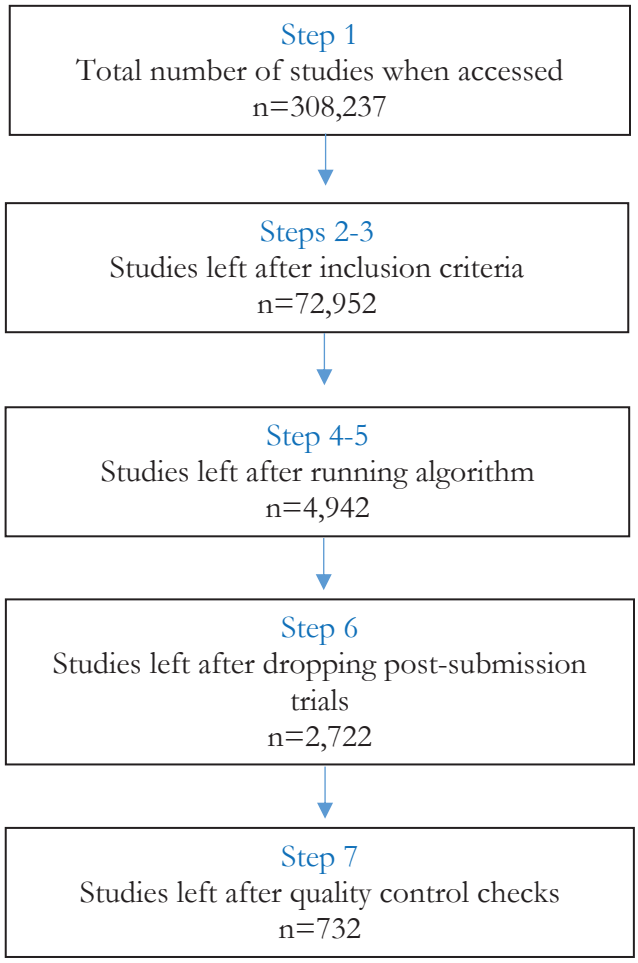


Table B1. Final NME sample by calendar year

Approval Year	n	Standard	Priority	Fast Track	Accelerated	Orphan	BTD	Boxed Warning
2006	21	11	10	4	3	5	0	7
2007	17	9	8	1	4	6	0	9
2008	20	12	8	0	2	7	0	6
2009	26	18	8	1	2	9	0	13
2010	21	11	10	0	0	6	0	10
2011	26	14	12	12	3	11	0	12
2012	35	21	14	13	4	13	0	14
2013	23	15	8	9	2	9	3	12
2014	38	15	23	17	8	17	9	13
2015	45	20	25	14	6	19	10	14
2016	20	6	13	8	6	8	7	7
2017	45	18	27	18	6	18	17	14
2018	59	16	43	24	4	34	14	11
Total	**396**	**186**	**209**	**121**	**50**	**162**	**60**	**142**

Table B2. Average times to submissions

	n	mean	SD	min	max
P II to submission (days)	**326**	**2,202**	**1,126**	**291**	**8,391**
P III to submission (days)	**326**	**1,373**	**945**	**1**	**7,205**

Table B3. Adverse event (AE) counts within 2 to 6 months of approval

Application Number	Application Type	Proprietary Name	Established Name	BTD	P2 info	P3 info	No AE	2	3	4	5	6
020427	NDA	SABRIL	VIGABATRIN					2	4	5	7	8
021201	NDA	ASCLERA	POLIDOCANOL					0	0	0	0	0
021502	NDA	ANTHELIOS SX	AVOBENZONE; ECAMSULE; OCTOCRYLENE		yes	yes		0	0	0	0	0
021526	NDA	RANEXA	RANOLAZINE			yes		0	0	0	0	6
021632	NDA	ERAXIS	ANIDULAFUNGIN		yes	yes		0	0	0	0	0
021641	NDA	AZILECT	RASAGILINE MESYLATE			yes		0	1	1	2	3
021742	NDA	BYSTOLIC	NEBIVOLOL HYDROCHLORIDE		yes	yes		1	1	5	13	16
021775	NDA	ENTEREG	ALVIMOPAN		yes	yes		0	0	0	0	1
021790	NDA	DACOGEN	DECITABINE			yes		0	0	8	8	11
021825	NDA	FERRIPROX	DEFERIPRONE			yes		0	0	0	0	0
021829	NDA	NEUPRO	ROTIGOTINE			yes		11	28	48	56	68
021856	NDA	ULORIC	FEBUXOSTAT		yes	yes		3	8	48	53	58
021883	NDA	DALVANCE	DALBAVANCIN HYDROCHLORIDE		yes	yes		0	0	2	3	3
021894	NDA	XENAZINE	TETRABENAZINE		yes	yes		0	1	2	4	7
021902	NDA	VEREGEN	SINECATECHINS			yes		0	0	0	0	0
021908	NDA	AMITIZA	LUBIPROSTONE			yes		0	0	0	0	1
021911	NDA	BANZEL	RUFINAMIDE					6	8	14	15	16
021928	NDA	CHANTIX	VARENICLINE TARTRATE		yes	yes		0	0	17	54	121
021938	NDA	SUTENT	SUNITINIB MALATE		yes	yes		57	71	73	73	107
021964	NDA	RELISTOR	METHYLNALTREXONE BROMIDE		yes	yes		0	3	3	5	5
021976	NDA	PREZISTA	DARUNAVIR ETHANOLATE		yes	yes		1	4	7	9	12
021977	NDA	VYVANSE	LISDEXAMFETAMINE DIMESYLATE		yes	yes		0	0	0	0	7
021985	NDA	TEKTURNA	ALISKIREN HEMIFUMARATE		yes	yes		5	45	181	216	270
021986	NDA	SPRYCEL	DASATINIB		yes	yes		6	8	24	27	29
021991	NDA	ZOLINZA	VORINOSTAT		yes	yes		1	1	3	3	6
021992	NDA	PRISTIQ	DESVENLAFAXINE SUCCINATE		yes	yes		1	6	26	40	55
021995	NDA	JANUVIA	SITAGLIPTIN PHOSPHATE		yes	yes		28	58	103	755	828
021999	NDA	INVEGA	PALIPERIDONE		yes	yes		0	9	82	174	270
022003	NDA	NOXAFIL	POSACONAZOLE		yes	yes		19	29	35	51	68
022004	NDA	OMNARIS	CICLESONIDE		yes	yes		0	0	0	0	0
022030	NDA	TOVIAZ	FESOTERODINE FUMARATE		yes	yes		8	13	14	21	25
022055	NDA	ALTABAX	RETAPAMULIN			yes		0	0	27	27	31
022059	NDA	TYKERB	LAPATINIB DITOSYLATE		yes	yes		107	213	669	757	830
022065	NDA	IXEMPRA KIT	IXABEPILONE		yes	yes		3	19	91	106	117
022068	NDA	TASIGNA	NILOTINIB HYDROCHLORIDE MONOHYDRATE		yes	yes		70	100	157	200	236
022074	NDA	SOMATULINE DEPOT	LANREOTIDE ACETATE		yes	yes		0	4	9	10	14
022081	NDA	LETAIRIS	AMBRISENTAN		yes	yes		5	18	41	63	91
022088	NDA	TORISEL	TEMSIROLIMUS		yes	yes		16	32	62	93	107
022106	NDA	DORIBAX	DORIPENEM			yes		27	48	64	73	89
022110	NDA	VIBATIV	TELAVANCIN HYDROCHLORIDE		yes	yes		0	1	1	5	10
022117	NDA	SAPHRIS	ASENAPINE MALEATE		yes	yes		0	3	20	29	49
022128	NDA	SELZENTRY	MARAVIROC		yes	yes		0	5	25	41	56
022129	NDA	ULESFIA	BENZYL ALCOHOL			yes		0	0	3	3	3
022134	NDA	LASTACAFT	ALCAFTADINE			yes		0	0	0	0	0
022145	NDA	ISENTRESS	RALTEGRAVIR POTASSIUM		yes	yes		9	21	68	85	107
022150	NDA	FIRAZYR	ICATIBANT ACETATE			yes		6	8	9	10	13
022156	NDA	CLEVIPREX	CLEVIDIPINE			yes		0	0	0	0	0
022161	NDA	LEXISCAN	REGADENOSON			yes		0	0	22	28	33

022181	NDA	KUVAN	SAPROPTERIN DIHYDROCHLORIDE		yes	yes	0	1	4	6	7
022187	NDA	INTELENCE	ETRAVIRINE		yes	yes	40	64	86	113	138
022192	NDA	FANAPT	ILOPERIDONE			yes	0	0	0	0	0
022201	NDA	FIRMAGON	DEGARELIX ACETATE		yes	yes	0	0	0	1	1
022206	NDA	RAPAFLO	SILODOSIN		yes	yes	2	4	7	8	10
022212	NDA	DUREZOL	DIFLUPREDNATE		yes	yes	0	0	0	0	0
022225	NDA	BRIDION	SUGAMMADEX SODIUM		yes	yes	11	20	26	35	49
022247	NDA	DUAVEE	BAZEDOXIFENE ACETATE; ESTROGENS, CONJUGATED		yes	yes	0	0	0	0	0
022249	NDA	TREANDA	BENDAMUSTINE HYDROCHLORIDE		yes	yes	3	7	19	27	34
022250	NDA	AMPYRA	DALFAMPRIDINE		yes	yes	0	3	83	115	154
022252	NDA	NATAZIA	DIENOGEST; ESTRADIOL VALERATE		yes	yes	9	12	17	29	36
022253	NDA	VIMPAT	LACOSAMIDE		yes	yes	1	6	13	26	35
022256	NDA	SAVELLA	MILNACIPRAN HYDROCHLORIDE		yes	yes	7	13	17	26	36
022268	NDA	COARTEM	ARTEMETHER; LUMEFANTRINE			yes	4	5	7	8	11
022271	NDA	NESINA	ALOGLIPTIN BENZOATE		yes	yes	22	27	39	50	60
022275	NDA	SAMSCA	TOLVAPTAN			yes	1	1	1	4	5
022288	NDA	BEPREVE	BEPOTASTINE BESILATE		yes	yes	0	0	0	0	0
022291	NDA	PROMACTA	ELTROMBOPAG OLAMINE		yes	yes	7	16	25	39	48
022304	NDA	NUCYNTA	TAPENTADOL HYDROCHLORIDE		yes	yes	2	5	8	11	15
022307	NDA	EFFIENT	PRASUGREL HYDROCHLORIDE		yes	yes	14	28	41	63	79
022308	NDA	BESIVANCE	BESIFLOXACIN HYDROCHLORIDE		yes	yes	0	0	2	2	4
022311	NDA	MOZOBIL	PLERIXAFOR		yes	yes	6	10	14	18	20
022334	NDA	AFINITOR	EVEROLIMUS		yes	yes	102	215	374	534	682
022341	NDA	VICTOZA	LIRAGLUTIDE RECOMBINANT		yes	yes	46	89	503	567	639
022345	NDA	POTIGA	EZOGABINE		yes	yes	6	12	20	54	85
022350	NDA	ONGLYZA	SAXAGLIPTIN HYDROCHLORIDE		yes	yes	2	3	37	43	48
022363	NDA	LIVALO	PITAVASTATIN CALCIUM			yes	8	12	20	20	20
022383	NDA	ARCAPTA NEOHALER	INDACATEROL MALEATE		yes	yes	54	91	150	209	262
022393	NDA	ISTODAX	ROMIDEPSIN		yes		0	0	0	0	0
022395	NDA	QUTENZA	CAPSAICIN		yes	yes	0	0	0	0	0
022399	NDA	HORIZANT	GABAPENTIN ENACARBIL		yes	yes	0	0	4	7	12
022405	NDA	CAPRELSA	VANDETANIB		yes	yes	21	36	66	81	105
022406	NDA	XARELTO	RIVAROXABAN		yes	yes	82	176	251	335	484
022408	NDA	NATROBA	SPINOSAD		yes	yes	0	0	0	0	0
022416	NDA	APTIOM	ESLICARBAZEPINE ACETATE		yes	yes	9	13	15	19	22
022425	NDA	MULTAQ	DRONEDARONE HYDROCHLORIDE			yes	6	60	142	182	272
022433	NDA	BRILINTA	TICAGRELOR		yes	yes	41	62	96	121	157
022458	NDA	ELELYSO	TALIGLUCERASE ALFA			yes	0	0	4	4	4
022465	NDA	VOTRIENT	PAZOPANIB HYDROCHLORIDE		yes	yes	36	61	116	171	221
022468	NDA	FOLOTYN	PRALATREXATE		yes		5	9	13	18	23
022474	NDA	ELLA	ULIPRISTAL ACETATE		yes	yes	0	0	0	1	2
022505	NDA	EGRIFTA	TESAMORELIN ACETATE		yes	yes	0	0	4	4	5
022512	NDA	PRADAXA	DABIGATRAN ETEXILATE MESYLATE		yes	yes	300	1,095	2,003	3,909	5,694
022522	NDA	DALIRESP	ROFLUMILAST		yes	yes	76	101	149	194	230
022526	NDA	ADDYI	FLIBANSERIN			yes	0	0	0	1	2
022527	NDA	GILENYA	FINGOLIMOD		yes	yes	60	112	311	440	585
022529	NDA	BELVIQ	LORCASERIN HYDROCHLORIDE		yes	yes	0	0	0	0	0
022535	NDA	ESBRIET	PIRFENIDONE	yes	yes	yes	52	85	136	224	267
022562	NDA	CARBAGLU	CARGLUMIC ACID		yes	yes	0	1	1	1	1

022567	NDA	VIIBRYD	VILAZODONE HYDROCHLORIDE		yes		0	0	0	0	1
022575	NDA	VPRIV	VELAGLUCERASE ALFA	yes	yes		0	2	4	5	10
050786	NDA	PYLERA	BISMUTH SUBCITRATE POTASSIUM; METRONIDAZOLE; TETRACYCLINE		yes		0	0	0	0	0
125141	BLA	MYOZYME	ALGLUCOSIDASE ALFA	yes	yes		0	0	0	0	0
125147	BLA	VECTIBIX	PANITUMUMAB	yes	yes		0	0	0	0	0
125151	BLA	ELAPRASE	IDURSULFASE	yes	yes		0	0	0	0	0
125156	BLA	LUCENTIS	RANIBIZUMAB	yes	yes		0	0	0	0	0
125160	BLA	CIMZIA	CERTOLIZUMAB PEGOL		yes		0	0	0	0	0
125164	BLA	MIRCERA	METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA	yes	yes		0	0	0	0	0
125166	BLA	SOLIRIS	ECULIZUMAB		yes		0	0	0	0	0
125249	BLA	ARCALYST	RILONACEPT		yes		0	0	0	0	0
125261	BLA	STELARA	USTEKINUMAB	yes	yes		0	0	0	0	0
125268	BLA	NPLATE	ROMIPLOSTIM	yes	yes		0	0	0	0	0
125274	BLA	DYSPORT	ABOBOTULINUMTOXIN A		yes		0	0	0	0	0
125276	BLA	ACTEMRA	TOCILIZUMAB		yes		0	0	0	0	0
125277	BLA	KALBITOR	ECALLANTIDE	yes	yes		0	0	0	0	0
125288	BLA	NULOJIX	BELATACEPT	yes	yes		0	0	0	0	0
125289	BLA	SIMPONI	GOLIMUMAB	yes	yes		0	0	0	0	0
125291	BLA	LUMIZYME	ALGLUCOSIDASE ALFA	yes	yes		0	0	0	0	0
125293	BLA	KRYSTEXXA	PEGLOTICASE	yes	yes		0	0	0	0	0
125294	BLA	GRANIX	TBO-FILGRASTIM		yes		0	0	0	0	0
125319	BLA	ILARIS	CANAKINUMAB	yes	yes		0	0	0	0	0
125320	BLA	PROLIA	DENOSUMAB	yes	yes		0	0	0	0	0
125326	BLA	ARZERRA	OFATUMUMAB	yes	yes		0	0	0	0	0
125327	BLA	VORAXAZE	GLUCARPIDASE	yes			0	0	0	0	0
125338	BLA	XIAFLEX	COLLAGENASE CLOSTRIDIUM HISTOLYTICUM		yes		0	0	0	0	0
125349	BLA	RAXIBACUMAB	RAXIBACUMAB	yes	yes		0	0	0	0	0
125359	BLA	ERWINAZE	ASPARAGINASE ERWINIA CHRYSANTHEMI				0	0	0	0	0
125360	BLA	XEOMIN	INCOBOTULINUMTOXIN A		yes		0	0	0	0	0
125370	BLA	BENLYSTA	BELIMUMAB	yes	yes		0	0	0	0	0
125377	BLA	YERVOY	IPILIMUMAB	yes	yes		0	0	0	0	0
125387	BLA	EYLEA	AFLIBERCEPT	yes	yes		0	0	0	0	0
125388	BLA	ADCETRIS	BRENTUXIMAB VEDOTIN	yes	yes		0	0	4	5	5
125390	BLA	MYALEPT	METRELEPTIN	yes			0	0	0	2	3
125409	BLA	PERJETA	PERTUZUMAB	yes	yes		0	0	2	6	14
125418	BLA	ZALTRAP	ZIV-AFLIBERCEPT	yes	yes		2	3	5	10	14
125422	BLA	JETREA	OCRIPLASMIN	yes	yes		0	0	0	2	2
125427	BLA	KADCYLA	ADO-TRASTUZUMAB EMTANSINE	yes	yes		19	33	50	65	77
125431	BLA	TANZEUM	ALBIGLUTIDE	yes	yes		0	0	0	1	1
125460	BLA	VIMIZIM	ELOSULFASE ALFA	yes	yes		0	2	31	34	38
125469	BLA	TRULICITY	DULAGLUTIDE	yes	yes		0	5	19	56	136
125476	BLA	ENTYVIO	VEDOLIZUMAB	yes	yes		7	11	28	46	59
125477	BLA	CYRAMZA	RAMUCIRUMAB	yes	yes		4	8	17	37	55
125486	BLA	GAZYVA	OBINUTUZUMAB	yes	yes	yes	2	8	10	16	22
125496	BLA	SYLVANT	SILTUXIMAB	yes			1	1	1	2	2
125499	BLA	PLEGRIDY	PEGINTERFERON BETA-1A		yes		4	4	7	17	31
125504	BLA	COSENTYX	SECUKINUMAB	yes	yes		17	41	166	197	614
125509	BLA	ANTHIM	OBILTOXAXIMAB			X					
125511	BLA	NATPARA	PARATHYROID HORMONE	yes	yes		0	0	0	1	1
125513	BLA	STRENSIQ	ASFOTASE ALFA	yes	yes	yes	14	37	78	140	201
125514	BLA	KEYTRUDA	PEMBROLIZUMAB	yes	yes	yes	154	301	400	507	593
125516	BLA	UNITUXIN	DINUTUXIMAB	yes	yes		1	2	4	8	11
125521	BLA	TALTZ	IXEKIZUMAB		yes	yes	2	8	39	75	142

125522	BLA	REPATHA	EVOLOCUMAB		yes	yes	34	58	685	734	1,511
125526	BLA	NUCALA	MEPOLIZUMAB		yes	yes	1	8	16	31	44
125547	BLA	PORTRAZZA	NECITUMUMAB		yes	yes	2	3	4	7	13
125554	BLA	OPDIVO	NIVOLUMAB	yes	yes	yes	66	110	350	462	605
125557	BLA	BLINCYTO	BLINATUMOMAB	yes	yes	yes	10	25	107	121	136
125559	BLA	PRALUENT	ALIROCUMAB		yes	yes	9	20	206	231	251
125561	BLA	KANUMA	SEBELIPASE ALFA	yes	yes	yes	2	3	7	10	17
200327	NDA	TEFLARO	CEFTAROLINE FOSAMIL		yes	yes	0	1	1	1	1
200603	NDA	LATUDA	LURASIDONE HYDROCHLORIDE		yes	yes	0	0	1	5	6
200677	NDA	SIGNIFOR	PASIREOTIDE DIASPARTATE		yes	yes	0	0	10	17	20
200796	NDA	EDARBI	AZILSARTAN KAMEDOXOMIL		yes	yes	0	0	4	9	11
201023	NDA	JEVTANA KIT	CABAZITAXEL			yes	2	13	25	36	49
201280	NDA	TRADJENTA	LINAGLIPTIN		yes	yes	4	19	63	132	174
201292	NDA	GILOTRIF	AFATINIB DIMALEATE		yes	yes	1	27	65	87	118
201532	NDA	HALAVEN	ERIBULIN MESYLATE		yes	yes	32	60	81	106	126
201699	NDA	DIFICID	FIDAXOMICIN		yes	yes	0	1	4	10	13
202022	NDA	EDURANT	RILPIVIRINE HYDROCHLORIDE		yes	yes	5	9	9	9	11
202067	NDA	ONFI	CLOBAZAM		yes	yes	14	27	35	40	48
202155	NDA	ELIQUIS	APIXABAN		yes	yes	5	18	80	106	141
202192	NDA	JAKAFI	RUXOLITINIB PHOSPHATE		yes	yes	2	15	47	88	142
202276	NDA	STENDRA	AVANAFIL		yes	yes	0	0	0	0	0
202292	NDA	MYTESI	CROFELEMER			yes	0	0	0	0	0
202293	NDA	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL		yes	yes	17	31	84	102	121
202324	NDA	INLYTA	AXITINIB		yes	yes	59	100	164	221	322
202379	NDA	ZYTIGA	ABIRATERONE ACETATE		yes	yes	76	131	216	282	390
202429	NDA	ZELBORAF	VEMURAFENIB		yes	yes	55	135	239	374	480
202450	NDA	TUDORZA PRESSAIR	ACLIDINIUM BROMIDE		yes	yes	0	0	0	2	7
202514	NDA	ZIOPTAN	TAFLUPROST			yes	1	2	7	8	21
202535	NDA	PREPOPIK	CITRIC ACID; MAGNESIUM OXIDE; SODIUM PICOSULFATE			yes	1	2	2	2	2
202570	NDA	XALKORI	CRIZOTINIB		yes	yes	115	212	286	360	470
202611	NDA	MYRBETRIQ	MIRABEGRON		yes	yes	13	18	25	31	45
202714	NDA	KYPROLIS	CARFILZOMIB		yes	yes	2	8	14	31	47
202806	NDA	TAFINLAR	DABRAFENIB MESYLATE		yes	yes	38	72	108	152	191
202811	NDA	LINZESS	LINACLOTIDE		yes	yes	0	0	0	1	2
202833	NDA	PICATO	INGENOL MEBUTATE		yes	yes	0	0	16	19	24
202834	NDA	FYCOMPA	PERAMPANEL		yes	yes	3	4	11	24	28
202992	NDA	AUBAGIO	TERIFLUNOMIDE		yes	yes	0	3	8	24	41
203085	NDA	STIVARGA	REGORAFENIB		yes	yes	10	37	74	110	160
203100	NDA	STRIBILD	COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR DISOPROXIL FUMARATE		yes	yes	0	0	1	1	2
203108	NDA	STRIVERDI RESPIMAT	OLODATEROL HYDROCHLORIDE		yes	yes	1	1	6	12	15
203188	NDA	KALYDECO	IVACAFTOR		yes	yes	3	4	37	48	54
203202	NDA	NORTHERA	DROXIDOPA		yes	yes	0	0	0	0	0
203214	NDA	XELJANZ	TOFACITINIB CITRATE		yes	yes	19	59	124	231	332
203314	NDA	TRESIBA	INSULIN DEGLUDEC		yes	yes	17	28	43	48	66
203341	NDA	BOSULIF	BOSUTINIB MONOHYDRATE		yes	yes	5	12	22	32	43
203388	NDA	ERIVEDGE	VISMODEGIB		yes		16	28	42	70	92
203415	NDA	XTANDI	ENZALUTAMIDE		yes	yes	9	25	129	186	246
203441	NDA	GATTEX KIT	TEDUGLUTIDE RECOMBINANT		yes	yes	0	0	0	1	4
203469	NDA	ICLUSIG	PONATINIB HYDROCHLORIDE		yes	yes	13	19	97	111	126
203505	NDA	OSPHENA	OSPEMIFENE		yes	yes	0	0	0	0	1

203567	NDA	JUBLIA	EFINACONAZOLE		yes	yes		0	0	5	6	6
203568	NDA	KYNAMRO	MIPOMERSEN SODIUM		yes	yes		0	0	0	0	1
203585	NDA	SYNRIBO	OMACETAXINE MEPESUCCINATE		yes			0	0	1	1	8
203756	NDA	COMETRIQ	CABOZANTINIB S-MALATE		yes	yes		1	1	4	10	14
203858	NDA	JUXTAPID	LOMITAPIDE MESYLATE		yes	yes		0	0	1	2	2
203971	NDA	XOFIGO	RADIUM RA-223 DICHLORIDE		yes	yes		5	9	21	28	60
203975	NDA	ANORO ELLIPTA	UMECLIDINIUM BROMIDE; VILANTEROL TRIFENATATE		yes	yes		0	0	0	0	0
204026	NDA	POMALYST	POMALIDOMIDE		yes	yes		139	339	436	599	863
204042	NDA	INVOKANA	CANAGLIFLOZIN		yes	yes		10	20	44	53	72
204063	NDA	TECFIDERA	DIMETHYL FUMARATE		yes	yes		22	52	107	200	328
204114	NDA	MEKINIST	TRAMETINIB DIMETHYL SULFOXIDE		yes	yes		38	59	81	109	125
204153	NDA	LUZU	LULICONAZOLE		yes	yes		0	0	0	0	0
204275	NDA	BREO ELLIPTA	FLUTICASONE FUROATE; VILANTEROL TRIFENATATE		yes	yes		1	1	4	7	8
204370	NDA	VRAYLAR	CARIPRAZINE HYDROCHLORIDE		yes	yes		0	0	0	0	0
204384	NDA	SIRTURO	BEDAQUILINE FUMARATE		yes			0	0	0	1	1
204410	NDA	OPSUMIT	MACITENTAN		yes	yes		1	12	121	160	228
204427	NDA	KERYDIN	TAVABOROLE		yes	yes		0	0	0	0	0
204447	NDA	TRINTELLIX	VORTIOXETINE HYDROBROMIDE		yes	yes		0	0	2	4	14
204569	NDA	BELSOMRA	SUVOREXANT		yes	yes		0	0	0	4	7
204629	NDA	JARDIANCE	EMPAGLIFLOZIN		yes	yes		8	44	109	149	175
204671	NDA	SOVALDI	SOFOSBUVIR	yes	yes	yes		3	22	113	265	628
204684	NDA	IMPAVIDO	MILTEFOSINE		yes			0	3	4	4	6
204760	NDA	MOVANTIK	NALOXEGOL OXALATE		yes	yes		0	0	0	0	0
204790	NDA	TIVICAY	DOLUTEGRAVIR SODIUM		yes	yes		4	4	19	20	23
204819	NDA	ADEMPAS	RIOCIGUAT		yes	yes		2	14	27	42	60
204886	NDA	ZONTIVITY	VORAPAXAR SULFATE		yes	yes		0	0	0	1	2
204958	NDA	KENGREAL	CANGRELOR		yes	yes		0	1	3	3	6
205266	NDA	ODOMZO	SONIDEGIB PHOSPHATE		yes			4	7	9	12	14
205353	NDA	FARYDAK	PANOBINOSTAT LACTATE		yes	yes		11	42	71	130	209
205422	NDA	REXULTI	BREXPIPRAZOLE		yes	yes		2	6	117	121	131
205435	NDA	SIVEXTRO	TEDIZOLID PHOSPHATE		yes	yes		1	1	1	7	7
205437	NDA	OTEZLA	APREMILAST		yes	yes		86	225	436	694	1,033
205494	NDA	CERDELGA	ELIGLUSTAT TARTRATE		yes	yes		0	1	2	4	5
205552	NDA	IMBRUVICA	IBRUTINIB	yes	yes	yes		7	17	39	77	125
205598	NDA	MACRILEN	MACIMORELIN ACETATE			yes	X					
205677	NDA	HETLIOZ	TASIMELTEON		yes	yes		0	0	0	0	0
205718	NDA	AKYNZEO	NETUPITANT; PALONOSETRON HYDROCHLORIDE			yes		0	0	0	0	0
205739	NDA	VELTASSA	PATIROMER SORBITEX CALCIUM		yes	yes		0	0	2	2	2
205750	NDA	CHOLBAM	CHOLIC ACID			yes		0	0	1	1	2
205755	NDA	ZYKADIA	CERITINIB	yes	yes	yes		19	32	44	57	76
205832	NDA	OFEV	NINTEDANIB ESYLATE	yes	yes	yes		15	62	105	170	227
205834	NDA	HARVONI	LEDIPASVIR; SOFOSBUVIR	yes	yes	yes		52	141	319	588	920
205836	NDA	BRIVIACT	BRIVARACETAM		yes	yes		2	7	12	17	20
205858	NDA	ZYDELIG	IDELALISIB	yes	yes	yes		25	60	94	136	179
206038	NDA	ORKAMBI	IVACAFTOR; LUMACAFTOR	yes	yes	yes		48	147	247	371	505
206143	NDA	CORLANOR	IVABRADINE HYDROCHLORIDE		yes	yes		22	45	110	132	149
206162	NDA	LYNPARZA	OLAPARIB		yes	yes		5	26	54	81	131

206192	NDA	COTELLIC	COBIMETINIB FUMARATE			yes		26	42	74	97	112
206256	NDA	BELEODAQ	BELINOSTAT		yes			0	0	1	5	5
206316	NDA	SAVAYSA	EDOXABAN TOSYLATE		yes	yes		0	0	0	0	10
206333	NDA	KYBELLA	DEOXYCHOLIC ACID		yes	yes		0	0	0	0	0
206334	NDA	ORBACTIV	ORITAVANCIN DIPHOSPHATE		yes	yes		0	0	1	1	1
206426	NDA	RAPIVAB	PERAMIVIR		yes	yes		14	33	43	46	47
206488	NDA	EXONDYS 51	ETEPLIRSEN		yes	yes		0	0	0	0	0
206494	NDA	AVYCAZ	AVIBACTAM SODIUM; CEFTAZIDIME		yes	yes		0	0	0	0	0
206500	NDA	VARUBI	ROLAPITANT HYDROCHLORIDE		yes	yes		0	0	0	2	3
206619	NDA	VIEKIRA PAK (COPACKAGED)	DASABUVIR SODIUM ; OMBITASVIR; PARITAPREVIR; RITONAVIR	yes	yes	yes		9	30	413	466	561
206709	NDA	DIACOMIT	STIRIPENTOL		yes		X					
206829	NDA	ZERBAXA	CEFTOLOZANE SULFATE; TAZOBACTAM SODIUM		yes			0	2	12	12	21
206843	NDA	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE		yes	yes		171	276	381	529	635
206940	NDA	VIBERZI	ELUXADOLINE		yes	yes		0	0	0	0	0
206947	NDA	LENVIMA	LENVATINIB MESYLATE		yes	yes		24	41	65	89	119
207078	NDA	LOKELMA	SODIUM ZIRCONIUM CYCLOSILICATE		yes	yes		0	0	1	1	1
207103	NDA	IBRANCE	PALBOCICLIB	yes	yes	yes		50	139	302	507	681
207145	NDA	XADAGO	SAFINAMIDE MESYLATE		yes	yes		0	3	3	3	9
207318	NDA	NUPLAZID	PIMAVANSERIN TARTRATE	yes	yes	yes		2	7	240	279	352
207500	NDA	CRESEMBA	ISAVUCONAZONIUM SULFATE		yes	yes		1	2	11	13	14
207533	NDA	ARISTADA	ARIPIPRAZOLE LAUROXIL			yes		0	0	0	0	8
207561	NDA	GENVOYA	COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE		yes	yes		2	18	30	42	66
207620	NDA	ENTRESTO	SACUBITRIL; VALSARTAN		yes	yes		69	181	380	604	862
207695	NDA	EUCRISA	CRISABOROLE		yes	yes		3	78	179	322	471
207795	NDA	VYZULTA	LATANOPROSTENE BUNOD		yes	yes		0	0	12	13	14
207924	NDA	OLUMIANT	BARICITINIB		yes	yes		33	53	86	123	151
207947	NDA	UPTRAVI	SELEXIPAG		yes	yes		0	7	45	93	145
207953	NDA	YONDELIS	TRABECTEDIN		yes	yes		18	32	54	86	115
207981	NDA	LONSURF	TIPIRACIL HYDROCHLORIDE; TRIFLURIDINE		yes	yes		6	19	49	89	139
207988	NDA	ZURAMPIC	LESINURAD		yes	yes		0	0	0	0	0
207997	NDA	RYDAPT	MIDOSTAURIN	yes	yes	yes		34	68	104	133	163
207999	NDA	OCALIVA	OBETICHOLIC ACID		yes	yes		0	0	23	27	31
208051	NDA	NERLYNX	NERATINIB MALEATE		yes	yes		0	0	0	0	0
208065	NDA	TAGRISSO	OSIMERTINIB MESYLATE	yes	yes	yes		16	35	55	76	99
208073	NDA	XIIDRA	LIFITEGRAST		yes	yes	X					
208078	NDA	FIRDAPSE	AMIFAMPRIDINE PHOSPHATE	yes		yes		2	2	18	19	19
208082	NDA	AUSTEDO	DEUTETRABENAZINE			yes		2	4	12	17	21
208114	NDA	DEFITELIO	DEFIBROTIDE SODIUM		yes	yes		4	7	14	20	23
208169	NDA	XURIDEN	URIDINE TRIACETATE	yes		yes		0	0	0	0	0
208254	NDA	RHOPRESSA	NETARSUDIL DIMESYLATE		yes	yes	X					
208261	NDA	ZEPATIER	ELBASVIR; GRAZOPREVIR	yes	yes	yes		1	10	29	48	93
208325	NDA	PARSABIV	ETELCALCETIDE		yes	yes		2	11	27	41	50
208341	NDA	EPCLUSA	SOFOSBUVIR; VELPATASVIR	yes	yes	yes		6	28	49	86	126
208383	NDA	BEVYXXA	BETRIXABAN		yes	yes	X					
208434	NDA	ALECENSA	ALECTINIB HYDROCHLORIDE	yes	yes	yes		15	23	43	54	62

208447	NDA	ZEJULA	NIRAPARIB TOSYLATE	yes	yes	yes		12	38	185	283	362
208462	NDA	NINLARO	IXAZOMIB CITRATE		yes	yes		37	104	194	282	385
208471	NDA	ADLYXIN	LIXISENATIDE		yes	yes		2	3	7	9	10
208573	NDA	VENCLEXTA	VENETOCLAX	yes	yes	yes		61	122	192	245	298
208610	NDA	BAXDELA	DELAFLOXACIN MEGLUMINE		yes	yes		0	0	0	0	0
208623	NDA	GALAFOLD	MIGALASTAT HYDROCHLORIDE		yes	yes		0	0	0	0	1
208627	NDA	TPOXX	TECOVIRIMAT		yes	yes	X					
208684	NDA	EMFLAZA	DEFLAZACORT			yes		0	0	0	0	3
208700	NDA	LUTATHERA	LUTETIUM DOTATATE LU-177		yes	yes		0	1	1	1	3
208716	NDA	VERZENIO	ABEMACICLIB	yes	yes	yes		1	8	19	37	59
208743	NDA	TYMLOS	ABALOPARATIDE		yes	yes		0	0	1	2	5
208745	NDA	TRULANCE	PLECANATIDE		yes	yes		0	0	19	19	20
208772	NDA	ALUNBRIG	BRIGATINIB	yes	yes	yes		7	12	14	17	24
208794	NDA	XERMELO	TELOTRISTAT ETIPRATE		yes	yes		9	24	305	453	574
208854	NDA	SYMPROIC	NALDEMEDINE TOSYLATE		yes	yes		0	0	3	10	22
208945	NDA	XEPI	OZENOXACIN			yes		0	0	0	0	0
209092	NDA	KISQALI	RIBOCICLIB SUCCINATE	yes	yes	yes		48	92	140	201	257
209115	NDA	RUBRACA	RUCAPARIB CAMSYLATE	yes	yes	yes		8	16	160	184	224
209176	NDA	RADICAVA	EDARAVONE		yes	yes		9	12	19	34	54
209195	NDA	VOSEVI	SOFOSBUVIR; VELPATASVIR; VOXILAPREVIR	yes	yes	yes		0	5	12	25	41
209229	NDA	LUCEMYRA	LOFEXIDINE HYDROCHLORIDE			yes		0	0	0	0	0
209241	NDA	INGREZZA	VALBENAZINE TOSYLATE	yes	yes	yes		1	4	161	163	410
209299	NDA	TAVALISSE	FOSTAMATINIB DISODIUM		yes	yes		0	0	8	9	18
209363	NDA	SOLOSEC	SECNIDAZOLE		yes	yes		0	0	0	0	0
209394	NDA	MAVYRET	GLECAPREVIR; PIBRENTASVIR	yes	yes	yes		3	11	49	77	132
209521	NDA	SEYSARA	SARECYCLINE HYDROCHLORIDE		yes	yes	X					
209531	NDA	SPINRAZA	NUSINERSEN SODIUM		yes	yes		2	15	41	63	127
209570	NDA	BENZNIDAZOLE	BENZNIDAZOLE		yes	yes		0	0	0	0	0
209606	NDA	IDHIFA	ENASIDENIB MESYLATE		yes	yes		7	14	26	37	52
209627	NDA	ANNOVERA	ETHINYL ESTRADIOL; SEGESTERONE ACETATE			yes	X					
209637	NDA	OZEMPIC	SEMAGLUTIDE		yes	yes		0	1	17	20	27
209776	NDA	VABOMERE	MEROPENEM; VABORBACTAM			yes		0	0	0	0	0
209803	NDA	STEGLATRO	ERTUGLIFLOZIN		yes	yes		2	2	5	11	19
209816	NDA	NUZYRA	OMADACYCLINE TOSYLATE		yes	yes	X					
209936	NDA	ALIQOPA	COPANLISIB DIHYDROCHLORIDE		yes	yes		1	1	2	4	9
209939	NDA	PREVYMIS	LETERMOVIR	yes	yes	yes		0	0	0	5	10
210166	NDA	MOTEGRITY	PRUCALOPRIDE SUCCINATE		yes	yes		0	1	1	1	1
210238	NDA	DOPTELET	AVATROMBOPAG MALEATE		yes	yes		0	0	12	12	15
210251	NDA	BIKTARVY	BICTEGRAVIR SODIUM; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE		yes	yes		3	17	31	55	75
210259	NDA	CALQUENCE	ACALABRUTINIB	yes	yes	yes		12	15	19	33	47
210303	NDA	ZEMDRI	PLAZOMICIN SULFATE		yes	yes		0	0	0	0	0
210365	NDA	EPIDIOLEX	CANNABIDIOL		yes	yes	X					
210450	NDA	ORILISSA	ELAGOLIX SODIUM		yes	yes		0	1	36	42	45
210491	NDA	SYMDEKO	IVACAFTOR; IVACAFTOR, TEZACAFTOR	yes	yes	yes		30	81	136	226	305
210493	NDA	AKYNZEO	FOSNETUPITANT CHLORIDE HYDROCHLORIDE;			yes		0	0	0	0	0

			PALONOSETRON HYDROCHLORIDE									
210496	NDA	BRAFTOVI	ENCORAFENIB		yes	yes		0	0	0	0	0
210498	NDA	MEKTOVI	BINIMETINIB		yes	yes		0	0	0	0	0
210589	NDA	OMEGAVEN	FISH OIL TRIGLYCERIDES			yes		0	0	0	1	1
210598	NDA	YUPELRI	REVEFENACIN		yes	yes		0	0	5	7	7
210656	NDA	DAURISMO	GLASDEGIB		yes	yes		7	12	20	25	25
210795	NDA	KRINTAFEL	TAFENOQUINE SUCCINATE	yes	yes	yes		17	17	27	28	29
210806	NDA	PIFELTRO	DORAVIRINE		yes	yes		0	0	0	2	4
210854	NDA	XOFLUZA	BALOXAVIR MARBOXIL		yes	yes		6	25	163	352	380
210861	NDA	VITRAKVI	LAROTRECTINIB	yes	yes			1	6	6	8	8
210867	NDA	MOXIDECTIN	MOXIDECTIN		yes	yes	X					
210868	NDA	LORBRENA	LORLATINIB	yes	yes	yes		28	65	93	137	137
210910	NDA	AEMCOLO	RIFAMYCIN		yes	yes	X					
210922	NDA	ONPATTRO	PATISIRAN SODIUM	yes	yes	yes		2	15	33	49	77
210923	NDA	MULPLETA	LUSUTROMBOPAG		yes	yes		4	5	6	7	8
210951	NDA	ERLEADA	APALUTAMIDE		yes	yes		0	2	17	46	56
211109	NDA	XERAVA	ERAVACYCLINE DIHYDROCHLORIDE		yes	yes		0	0	0	0	1
211155	NDA	COPIKTRA	DUVELISIB		yes	yes		1	4	20	24	27
211172	NDA	TEGSEDI	INOTERSEN SODIUM		yes	yes		0	0	0	0	5
211192	NDA	TIBSOVO	IVOSIDENIB		yes	yes		1	2	14	17	17
211288	NDA	VIZIMPRO	DACOMITINIB		yes	yes		0	1	3	3	3
211349	NDA	XOSPATA	GILTERITINIB FUMARATE		yes	yes		28	42	83	85	85
211651	NDA	TALZENNA	TALAZOPARIB TOSYLATE		yes	yes		3	9	10	15	18
761025	BLA	PRAXBIND	IDARUCIZUMAB	yes		yes		1	2	7	10	13
761029	BLA	ZINBRYTA	DACLIZUMAB		yes	yes		0	0	1	7	54
761032	BLA	SILIQ	BRODALUMAB		yes	yes		2	3	5	6	8
761033	BLA	CINQAIR	RESLIZUMAB		yes	yes		0	0	0	0	4
761034	BLA	TECENTRIQ	ATEZOLIZUMAB	yes	yes	yes		77	136	229	285	325
761035	BLA	EMPLICITI	ELOTUZUMAB	yes	yes	yes		22	45	66	88	121
761036	BLA	DARZALEX	DARATUMUMAB	yes	yes	yes		27	130	186	269	326
761037	BLA	KEVZARA	SARILUMAB		yes	yes		9	12	34	37	42
761038	BLA	LARTRUVO	OLARATUMAB	yes	yes	yes		7	18	26	40	60
761040	BLA	BESPONSA	INOTUZUMAB OZOGAMICIN	yes	yes	yes		14	22	26	32	41
761046	BLA	ZINPLAVA	BEZLOTOXUMAB		yes	yes		0	0	0	1	1
761047	BLA	MEPSEVII	VESTRONIDASE ALFA-VJBK		yes	yes		0	0	0	0	0
761049	BLA	BAVENCIO	AVELUMAB	yes	yes			13	26	48	59	72
761051	BLA	POTELIGEO	MOGAMULIZUMAB-KPKC	yes	yes	yes		3	6	20	31	38
761052	BLA	BRINEURA	CERLIPONASE ALFA	yes	yes			0	1	4	4	5
761053	BLA	OCREVUS	OCRELIZUMAB	yes	yes	yes		62	88	224	279	350
761055	BLA	DUPIXENT	DUPILUMAB	yes	yes	yes		7	13	165	179	193
761061	BLA	TREMFYA	GUSELKUMAB		yes	yes		4	13	39	47	53
761063	BLA	EMGALITY	GALCANEZUMAB-GNLM		yes	yes		46	210	308	535	906
761065	BLA	TROGARZO	IBALIZUMAB-UIYK	yes	yes	yes	X					
761067	BLA	ILUMYA	TILDRAKIZUMAB-ASMN		yes	yes		0	0	0	0	7
761068	BLA	CRYSVITA	BUROSUMAB-TWZA	yes	yes	yes		0	0	0	14	16
761069	BLA	IMFINZI	DURVALUMAB	yes	yes	yes		0	0	0	0	0
761070	BLA	FASENRA	BENRALIZUMAB		yes	yes		0	4	18	49	109
761077	BLA	AIMOVIG	ERENUMAB-AOOE		yes	yes		21	52	1,679	2,075	5,614
761079	BLA	PALYNZIQ	PEGVALIASE-PQPZ		yes	yes		0	6	25	57	98
761083	BLA	HEMLIBRA	EMICIZUMAB	yes	yes	yes		0	1	12	16	28
761089	BLA	AJOVY	FREMANEZUMAB-VFRM		yes	yes		30	98	154	261	360
761090	BLA	TAKHZYRO	LANADELUMAB (SHP643)	yes	yes	yes		24	49	78	88	121
761092	BLA	REVCOVI	ELAPEGADEMASE-LVLR			yes	X					
761094	BLA	OXERVATE	CENEGERMIN-BKBJ	yes	yes		X					
761097	BLA	LIBTAYO	CEMIPLIMAB-RWLC	yes	yes	yes		15	24	39	49	67
761102	BLA	ASPARLAS	CALASPARGASE PEGOL-MKNL		yes		X					

761104	BLA	LUMOXITI	MOXETUMOMAB PASUDOTOX-TDFK		yes	yes		0	0	1	2	4
761107	BLA	GAMIFANT	EMAPALUMAB-LZSG	yes	yes	yes		0	0	1	2	2
761108	BLA	ULTOMIRIS	RAVULIZUMAB-CWVZ		yes	yes		3	41	53	53	53
761116	BLA	ELZONRIS	TAGRAXOFUSP-ERZS	yes	yes		X					

Appendix C: Additional Figures and Tables

Table C1: Impact of BTD on Phase IV Trials

	Any Phase IV Trial (Mean = 0.57)		
	(1)	(2)	(3)
BTD	-0.141	-0.059	-0.054
	(0.113)	(0.131)	(0.136)
BTD x Post-2012	0.226*	0.174	0.169
	(0.134)	(0.146)	(0.150)
NDA		-0.053	-0.064
		(0.063)	(0.066)
Priority Review		-0.121*	-0.086
		(0.068)	(0.070)
Private Firm		-0.114	-0.115
		(0.077)	(0.080)
Controls: Drug Characteristics	N	Y	Y
Controls: Disease	N	N	Y
Observations	343	343	343
R^2	0.133	0.177	0.226

Notes: This table reports estimates of the effect of the BTD program on the likelihood of a Phase IV clinical trial. The outcome is an indicator for whether any Phase IV clinical trial is required. Observations are at the drug-level and estimates are from OLS regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; and ATC class. Several columns show fewer than 359 observations due to missing data. Robust standard errors are in parentheses. For additional detail on the sample, see Section 5.1.
*p<0.10, **p<0.05, ***p<0.001

Table C2: Summary Statistics: Post-BTD Sample

	BTD N = 60		Non-BTD N = 167		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Small Molecule (0/1)	0.57	0.50	0.79	0.41	0.00***
Priority Review (0/1)	0.98	0.13	0.49	0.50	0.00***
Fast Track (0/1)	0.50	0.50	0.36	0.48	0.06*
Accelerated Approval (0/1)	0.35	0.48	0.07	0.25	0.00***
Black Box Warning (0/1)	0.23	0 .43	0.33	0.47	0.17
ATC: Cancer (0/1)	0.57	0.50	0.28	0.45	0.00***
ATC: Metabolism (0/1)	0.07	0.25	0.16	0.36	0.08*
ATC: Antiinfectives (0/1)	0.15	0.36	0.13	0.34	0.73
ATC: Nervous System (0/1)	0.07	0.25	0.11	0.31	0.36
Sponsor: Private Firm (0/1)	0.12	0.32	0.16	0.36	0.46
Panel B. Time-to-Market Outcomes					
Regulatory Review (Months)	7.13	1.97	9.24	3.03	0.00***
Phase 2 to Regulatory Review (Months)	58.48	33.34	85.85	43.23	0.00***
Phase 3 to Regulatory Review (Months)	32.51	26.57	57.56	44.79	0.00***
Panel C. Adverse Event Rate Outcomes					
Within 2 Months	2.10	2.78	2.20	4.53	0.92
Within 3 Months	4.21	5.83	2.87	4.83	0.24
Within 4 Months	10.66	14.35	3.59	7.10	0.00***
Within 5 Months	11.35	17.44	3.78	8.90	0.00***
Within 6 Months	12.25	22.03	4.17	10.82	0.00***

Notes: This table shows drug characteristics for the sample of 227 drugs whose NDAs were submitted between July 9, 2012 and December 31, 2018. All variables are measured at the drug-level. For example, "NDA to Approval (Months)" is the average number of months that a drug spends between NDA submission to approval. The top 4 most common ATC classes are shown. ATC categories that are not shown include: alimentary tract and metabolism; anti-infectives for systemic use; antineoplastic and immunomodulating agents; antiparasitic products, insecticides and repellents; blood and blood forming clots; cardiovascular system; dermatologicals; genitourinary system and sex hormones; musculo-skeletal system; nervous system; respiratory system; sensory organs; systemic hormonal preparations; and various. Column 5 presents p-values from t-tests comparing the difference of means.
*p<0.10, **p<0.05, ***p<0.001

Table C3: Impact of BTD Program: Assigning Unmatched Drugs as Imputed Non-BTD drugs

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review 3	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
BTD	-0.093	-0.176	-0.037	-0.683	-0.677	-0.356	-0.013	0.060
	(0.075)	(0.113)	(0.095)	(0.479)	(0.489)	(0.509)	(0.447)	(0.502)
BTD x Post-2012	-0.045	-0.250*	-0.249**	0.367	0.888	0.918	0.521	-0.030
	(0.080)	(0.142)	(0.110)	(0.636)	(0.612)	(0.605)	(0.554)	(0.593)
Small Molecule	-0.114**	0.013	-0.002	0.577	0.074	0.072	0.064	-0.357
	(0.040)	(0.078)	(0.068)	(0.372)	(0.323)	(0.295)	(0.314)	(0.332)
Priority Review	-0.218***	0.088	0.025	0.085	0.161	0.314	0.522**	0.741**
	(0.044)	(0.086)	(0.067)	(0.312)	(0.255)	(0.229)	(0.246)	(0.251)
Private Firm	0.032	0.157*	0.153**	-0.277	-0.050	-0.564*	-0.446	0.043
	(0.048)	(0.088)	(0.059)	(0.494)	(0.347)	(0.327)	(0.318)	(0.323)
Mean	256.95	1,438.48	2,199.22	1.69	2.35	3.66	3.8	4.21
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	396	371	338	151	181	217	239	253
log likelihood	-2355	-2949	-2760	-220	-304	-416	-453	-496

Notes: This table report estimates of the effect of the BTD program on time-to-market and adverse event rates using a drug sample where drugs that are not algorithmically matched to the true BTD or true non-BTD are categorized as imputed non-BTD. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Several columns show fewer than 396 observations due to missing data. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 2 imply that drugs experience a decrease in number of days spent between the start of Phase III and NDA submission after receiving BTD designation, a statistically significant $100 \times (\exp[-0.282] - 1)$ = -24.57%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001]

Table C4: Impact of BTD Program: Controlling for Drug Cohort

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review 3	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
BTD	-0.066	-0.079	-0.002	-0.689	-0.561	-0.296	0.244	0.185
	(0.084)	(0.122)	(0.100)	(0.458)	(0.544)	(0.526)	(0.462)	(0.458)
BTD x Post-2012	-0.046	-0.315**	-0.315**	-0.103	0.496	0.823	0.334	0.030
	(0.089)	(0.147)	(0.111)	(0.583)	(0.610)	(0.582)	(0.521)	(0.520)
Small Molecule	-0.104**	0.025	0.017	0.391	-0.106	-0.120	-0.107	-0.453
	(0.041)	(0.086)	(0.072)	(0.403)	(0.359)	(0.303)	(0.300)	(0.306)
Priority Review	-0.232***	-0.023	0.031	0.127	0.112	0.319	0.678**	0.836***
	(0.047)	(0.097)	(0.076)	(0.312)	(0.277)	(0.250)	(0.247)	(0.248)
Private Firm	0.055	0.148	0.146*	-0.187	0.050	-0.711*	-0.579	0.186
	(0.055)	(0.111)	(0.079)	(0.712)	(0.487)	(0.432)	(0.391)	(0.412)
Mean	258.09	1,457.5	2,225.22	1.75	2.46	3.97	4.09	4.54
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	359	340	310	136	163	194	215	228
log likelihood	-2137	-2707	-2538	-200	-285	-385	-419	-463

Notes: This table report estimates of the effect of the BTD program on time-to-market and adverse event rates in regressions that control for drug cohort (as measured by submission year). Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; and ATC class. Several columns show fewer than 359 observations due to missing data. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 2 imply that drugs experience a decrease in number of days spent between the start of Phase III and NDA submission after receiving BTD designation, a statistically significant $100 \times (\exp[-0.315] - 1)$ = -27.02%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table C5: Impact of BTD Program: Controlling for Novelty of Drug Mechanism of Action

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review 3	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
BTD	-0.040	-0.090	-0.011	-0.750	-0.502	-0.279	0.082	0.045
	(0.081)	(0.122)	(0.101)	(0.542)	(0.532)	(0.534)	(0.436)	(0.482)
BTD x Post-2012	-0.060	-0.262*	-0.267**	0.423	0.787	0.766	0.318	-0.090
	(0.084)	(0.145)	(0.113)	(0.695)	(0.633)	(0.616)	(0.538)	(0.566)
Small Molecule	-0.108**	-0.002	-0.007	0.363	0.069	0.105	0.125	-0.396
	(0.043)	(0.083)	(0.076)	(0.401)	(0.322)	(0.298)	(0.312)	(0.321)
Priority Review	-0.245***	-0.004	0.018	0.331	0.335	0.486**	0.810***	0.916***
	(0.045)	(0.093)	(0.075)	(0.337)	(0.271)	(0.243)	(0.246)	(0.260)
Private Firm	0.046	0.086	0.141*	-0.659	-0.054	-0.796**	-0.555	0.249
	(0.058)	(0.103)	(0.077)	(0.666)	(0.461)	(0.400)	(0.394)	(0.404)
Mean	258.09	1457.5	2225.22	1.75	2.46	3.97	4.09	4.54
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	359	340	310	136	163	194	215	228
log likelihood	-2128	-2703	-2539	-199	-279	-383	-416	-464

Notes: This table report estimates of the effect of the BTD program on time-to-market and adverse event rates in regressions that control for the novelty of the drug's mechanism of action. A drug is considered to have a novel mechanism of action if no previous drug approved contained the mechanism of action. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; and ATC class. Several columns show fewer than 359 observations due to missing data. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 2 imply that drugs experience a decrease in number of days spent between the start of Phase III and NDA submission after receiving BTD designation, a statistically significant $100 \times (\exp[-0.267] - 1)$ = -23.43%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table C6: Impact on Adverse Event Levels

	2 Months (1)	3 Months (2)	4 Months (3)	5 Months (4)	6 Months (5)
BTD	0.106	0.025	0.189	0.142	0.120
	(0.467)	(0.459)	(0.400)	(0.404)	(0.405)
BTD x Post-2012	1.355**	1.221**	0.992**	1.062**	1.013**
	(0.538)	(0.523)	(0.482)	(0.484)	(0.489)
Small Molecule	0.757**	0.792**	0.625**	0.657**	0.464
	(0.286)	(0.277)	(0.291)	(0.278)	(0.289)
Priority Review	-0.257	-0.291	-0.229	-0.255	-0.370
	(0.287)	(0.279)	(0.240)	(0.246)	(0.249)
Private Firm	-1.947***	-1.502***	-1.583***	-1.611***	-1.650***
	(0.332)	(0.328)	(0.292)	(0.287)	(0.284)
Mean	10.05	22.22	55.47	78.68	116.01
Controls: Drug Characteristics	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y
Observations	359	359	359	359	359
log likelihood	-888	-1149	-1460	-1592	-1715

Notes: This table report estimates of the effect of the BTD program on adverse event levels. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Several columns show fewer than 359 observations due to missing data. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 1 imply that drugs experience an $100 \times (\exp[1.355] - 1) = 287.68\%$ increase in adverse event levels in the 2 months after receiving the BTD designation, though the effects are not statistically significant. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table C7: Impact of BTD Program: Excluding Clinical Trials that Occur Post-Designation

	Dep Variable: Phase III to Reg Review		Dep Variable: Phase II to Reg Review	
	Original Sample	Excl. BTD drugs that Occur After Phase III	Original Sample	Excl. BTD drugs that Occur After Phase II
	(1)	(2)	(3)	(4)
BTD	-0.135	-0.109	-0.026	-0.007
	(0.121)	(0.124)	(0.100)	(0.103)
BTD x Post-2012	-0.258*	-0.737**	-0.255**	-0.212
	(0.144)	(0.230)	(0.111)	(0.342)
Small Molecule	0.024	0.051	-0.000	0.010
	(0.084)	(0.090)	(0.073)	(0.084)
Priority Review	0.014	-0.041	0.023	0.025
	(0.095)	(0.094)	(0.075)	(0.081)
Private Firm	0.128	0.155	0.145*	0.166*
	(0.110)	(0.115)	(0.079)	(0.086)
Mean	1,457.5	1,493.72	2,225.22	2,314.49
Controls: Drug Characteristics	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y
Observations	340	303	310	259
log likelihood	-2707	-2417	-2540	-2128

Notes: This table report estimates of the effect of the BTD program on time-to-market and adverse event rates. Columns 1 and 3 use the original drug sample and replicates the results shown in Table 4, Columns 6 and 9, respectively. Columns 2 and 4 use drug samples that excludes BTD drugs whose BTD designation is given after the start of the focal trial. For example, Column 2 excludes drugs whose Phase III trial begins after the BTD designation is given. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001]

Table C8: Impact of BTD Program: No Controls For Developer Type

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review 3	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
BTD	-0.053	-0.116	-0.023	-0.805	-0.496	-0.262	0.131	0.113
	(0.081)	(0.121)	(0.100)	(0.521)	(0.514)	(0.511)	(0.426)	(0.506)
BTD x Post-2012	-0.062	-0.282**	-0.260**	0.453	0.762	0.792	0.341	-0.073
	(0.084)	(0.144)	(0.110)	(0.650)	(0.610)	(0.607)	(0.540)	(0.594)
NDA	-0.099**	0.022	-0.009	0.564	0.046	-0.078	-0.099	-0.433
	(0.042)	(0.083)	(0.073)	(0.377)	(0.325)	(0.301)	(0.307)	(0.324)
Priority Review	-0.240***	0.021	0.024	0.219	0.300	0.475*	0.726**	0.890***
	(0.045)	(0.099)	(0.076)	(0.342)	(0.279)	(0.262)	(0.273)	(0.269)
Mean	258.09	1,457.5	2,225.22	1.75	2.46	3.97	4.09	4.54
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	359	340	310	136	163	194	215	228
log likelihood	-2130	-2708	-2542	-200	-281	-386	-421	-466

Notes: This table report estimates of the effect of the BTD program on time-to-market and adverse event rates in regressions that do not control for developer type. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Several columns show fewer than 359 observations due to missing data. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 2 imply that drugs experience a decrease in number of days spent between the start of Phase III and NDA submission after receiving BTD designation, a statistically significant $100 \times (\exp[-0.282] - 1)$ = -24.57%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001]

Table C9: Impact of BTD Program: OLS Specification

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review 3	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
BTD	-18.087	-156.115	-95.839	-1.640	-0.784	-1.903	-1.308	-2.611
	(18.830)	(172.973)	(223.392)	(1.182)	(0.916)	(1.315)	(1.676)	(2.205)
BTD x Post-2012	-11.916	-356.289*	-532.372**	0.111	1.683	6.805**	5.657	6.100
	(19.819)	(211.957)	(240.915)	(1.326)	(1.367)	(2.938)	(3.427)	(4.375)
nda	-27.581**	66.315	49.072	0.843	0.423	-2.252	-2.767	-4.502
	(11.099)	(117.242)	(163.239)	(0.610)	(1.062)	(2.468)	(2.875)	(3.724)
Priority (0/1)	-61.925***	52.583	91.219	0.633	0.182	1.078	2.360	3.500*
	(12.363)	(187.932)	(209.280)	(0.784)	(0.702)	(1.257)	(1.542)	(1.921)
Private Sponsor	11.451	328.042	326.385	-0.812	-0.039	-0.992	-0.585	0.213
(0/1)	(14.897)	(238.876)	(213.757)	(0.910)	(0.937)	(1.121)	(1.516)	(1.818)
Mean	258.09	1,457.5	2,225.22	1.75	2.46	3.97	4.09	4.54
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	359	340	310	136	163	194	215	228
R^2	0.305	0.233	0.259	0.211	0.251	0.270	0.227	0.204

Notes: This table report estimates of the effect of the BTD program on time-to-market outcomes using OLS specifications. Observations are at the drug-level. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Several columns show fewer than 359 observations due to missing data. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table C10: Impact of BTD Program: Restricted to 2010-2018 Approvals

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review 3	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
BTD	-0.024	-0.121	-0.083	-1.235**	-0.826	-0.862	0.033	0.228
	(0.100)	(0.164)	(0.126)	(0.606)	(0.682)	(0.591)	(0.533)	(0.684)
BTD x Post-2012	-0.074	-0.296*	-0.188	0.905	1.171	1.362**	0.416	-0.235
	(0.098)	(0.175)	(0.130)	(0.704)	(0.731)	(0.682)	(0.629)	(0.760)
Small Molecule	-0.104**	0.021	0.019	-0.032	-0.201	-0.155	-0.154	-0.623*
	(0.044)	(0.100)	(0.082)	(0.392)	(0.310)	(0.305)	(0.330)	(0.336)
Priority Review	-0.287***	0.052	0.025	0.386	0.262	0.488*	0.787**	1.033***
	(0.043)	(0.114)	(0.084)	(0.379)	(0.304)	(0.274)	(0.295)	(0.299)
Private Firm	0.040	0.125	0.097	-1.777**	-0.558	-1.344**	-1.039**	-0.415
	(0.062)	(0.130)	(0.089)	(0.843)	(0.503)	(0.438)	(0.449)	(0.477)
Mean	261.97	1,528.82	2,351.97	2.07	2.88	4.65	4.72	5.2
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	294	277	263	106	129	156	175	187
log likelihood	-1710	-2227	-2176	-172	-244	-335	-370	-408

Notes: This table report estimates of the effect of the BTD program on time-to-market outcomes for the sample of drugs approved between 2010 and 2018. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 2 imply that drugs experience a decrease in number of days spent between the start of Phase III and NDA submission after receiving BTD designation, by $100 \times (\exp[-0.166] - 1)$ = -15.30%, though the effects are not statistically significant. Robust standard errors are in parentheses.

*p<0.10, **p<0.05, ***p<0.001

Table C11: Fast Track as Placebo

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review 3	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Fast	0.114	0.080	0.055	0.462	0.537	0.400	0.690*	-0.035
	(0.095)	(0.102)	(0.083)	(0.461)	(0.441)	(0.383)	(0.377)	(0.406)
Fast x Post-2012	-0.059	-0.062	-0.097	0.230	0.106	0.416	-0.168	0.548
	(0.099)	(0.135)	(0.107)	(0.518)	(0.506)	(0.456)	(0.456)	(0.478)
Small Molecule	-0.071*	0.101	0.078	0.529	-0.035	-0.037	-0.121	-0.518
	(0.043)	(0.083)	(0.066)	(0.380)	(0.316)	(0.300)	(0.307)	(0.327)
Priority Review	-0.282***	-0.042	-0.016	-0.015	0.231	0.575**	0.762**	0.910***
	(0.044)	(0.093)	(0.070)	(0.367)	(0.259)	(0.240)	(0.257)	(0.261)
Private Firm	0.040	0.148	0.128*	-0.186	0.105	-0.693*	-0.497	0.285
	(0.052)	(0.110)	(0.077)	(0.584)	(0.408)	(0.402)	(0.399)	(0.393)
Mean	261.01	1,461.24	2,232.33	1.73	2.59	4.07	4.17	4.6
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	347	327	303	130	155	186	204	218
log likelihood	-2068	-2612	-2487	-192	-271	-368	-396	-439

Notes: This table report estimates of the effect of the BTD program on time-to-market outcomes using drugs with Fast Track status as a placebo. Observations are at the drug-level and estimates are from negative binomial regressions. The sample for this analysis consists of 347 drugs. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

APPENDIX D: EXAMINATION OF PROGRAM EFFECTS

There are 2 channels that may impact clinical development times that we are likely capturing with our estimates: (1) time trends (e.g., is regulatory review getting longer/shorter over our period of observation?) and (2) program effects of the BTD itself (given that imputed BTD drugs did not benefit from the BTD). In this Appendix, we probe the extent to which each of these channels drive our main findings.

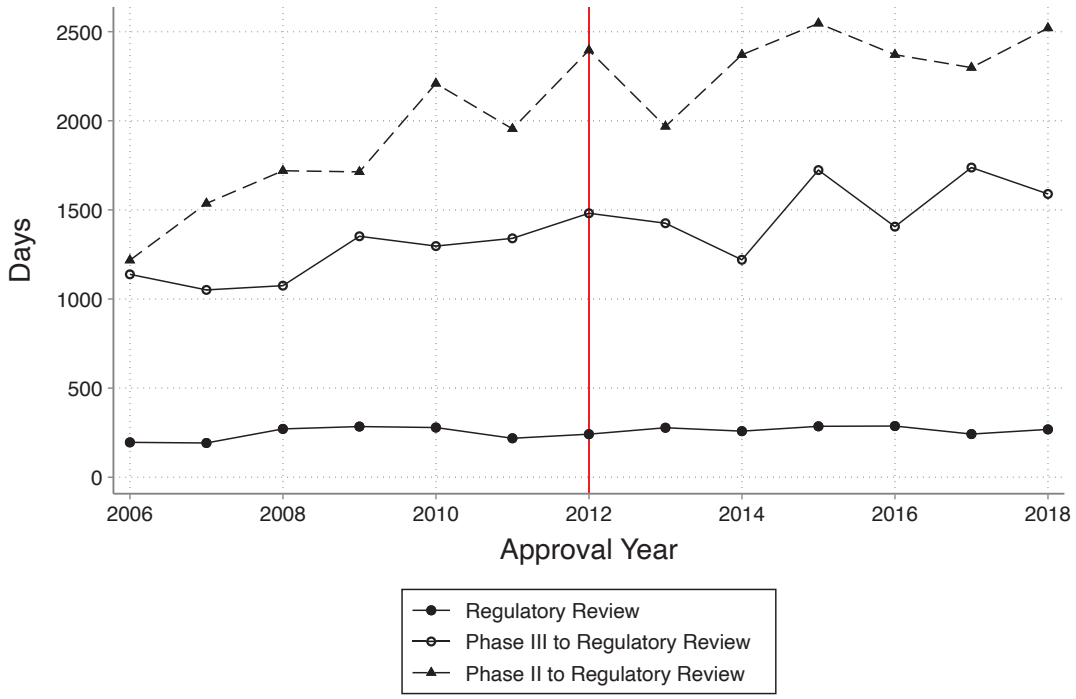
Appendix Figure D1 shows phase 3 to submission, phase 2 to submission, regulatory approval over time. Development times are clearly increasing over our period of observation. This figure is consistent with other published statistics and supports using a difference-in-differences approach in regression analysis. In short, channel 1 is likely playing a role in the observed data, so it needs to be accounted for in all analyses so as to make sure that the focal estimates are only reporting on channel 2. In Appendix Table D1, we compare outcomes for imputed non-BTD and true non-BTD drugs. The comparison of means in Panels B and C show that P2 / P3 to submission is higher for true non-BTD, consistent with the time trend towards longer clinical development times and again supporting the need for the difference-in-differences approach to analysis.

Figure D2 shows trends in mean outcomes for two samples: (1) true BTD vs. non-BTD and (2) imputed and true BTD vs. non-BTD. Panels A and C document a clear level change in trends for BTD vs. non-BTD drugs between 2006 and 2018. This provides support for channel 2. Panels B and D provides further support for this channel: following 2012, true BTD drugs show a clear divergence away from the time trend towards longer clinical development times.

To provide additional validity for our empirical strategy, Appendix Table D1 also compares characteristics for imputed non-BTD and true non-BTD in Panel A. A comparison of sponsor research experience—as measured by previous drug experience (as measured by the number of past FDA drug approvals obtained prior to the focal drug approval)—reveals little differences across the two samples. Looking to the remaining drug characteristics, Appendix Table D1 reveals several differences: imputed BTDs are more likely to be small molecules and non-imputed BTDs are more likely to participate in the Priority Review and Fast Track expedited programs. We directly control for differences in small molecule status and expedited program participation in our regressions.

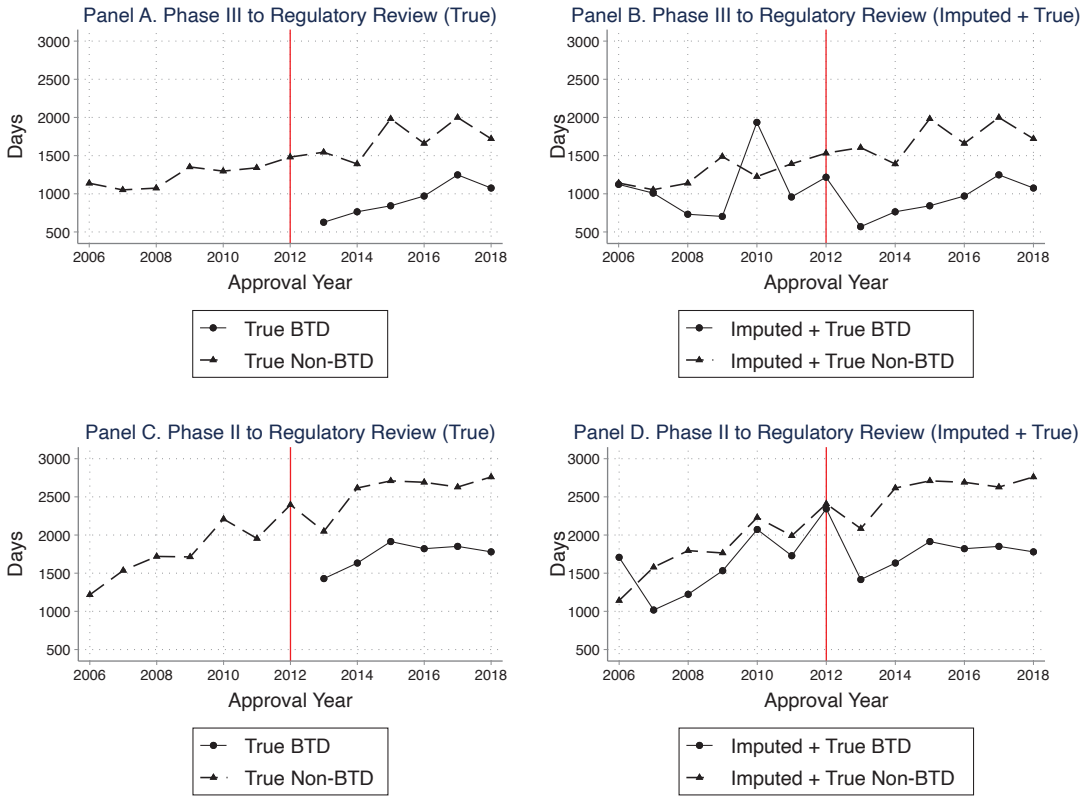
Finally, Appendix Table D3 reproduces our main regression outcomes with additional controls for time trends. The results are robust to this more granular way of controlling for changes in drug development over time.

Figure D1: TRENDS IN TIME-TO-MARKET



Notes: This figure shows trends in time-to-market outcomes for the 396 drugs that are approved between 2006 and 2018. Observations are at the drug-level. For more detailed data and variable descriptions, see Section 4.

Figure D2: TRENDS IN TIME-TO-MARKET FOR BTD VS. NON-BTD SAMPLE



Notes: This figure shows trends in time-to-market outcomes for the 396 drugs that are approved between 2006 and 2018. Panels A and C show average time-to-market outcomes for true BTD and true non-BTD drugs. Panels B and C show average time-to-market outcomes for imputed and true BTD and non-BTD drugs. Observations are at the drug-level. For more detailed data and variable descriptions, see Section 4.

Table D1: Summary Statistics: Imputed and True Non-BTD Sample

	Imputed N = 109		True N = 167		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Small Molecule (0/1)	0.87	0.34	0.79	0.41	0.09*
Priority Review (0/1)	0.30	0.46	0.49	0.50	0.00***
Fast Track (0/1)	0.16	0.36	0.36	0.48	0.00***
Accelerated Approval (0/1)	0.06	0.23	0.07	0.25	0.72
Black Box Warning (0/1)	0.42	0.50	0.33	0.47	0.12
ATC: Cancer (0/1)	0.28	0.45	0.28	0.45	1.00
ATC: Metabolism (0/1)	0.15	0.36	0.16	0.36	0.84
ATC: Antiinfectives (0/1)	0.06	0.25	0.13	0.34	0.07*
ATC: Nervous System (0/1)	0.15	0.36	0.11	0.31	0.34
Sponsor: Private Firm (0/1)	0.15	0.36	0.16	0.36	0.84
Sponsor: Research Experience (# Approved Drugs)	3.34	3.98	3.71	4.54	0.49
Panel B. Time-to-Market Outcomes					
Regulatory Review (Months)	8.40	3.89	9.24	3.03	0.04**
Phase 2 to Regulatory Review (Months)	63.03	29.48	85.85	43.23	0.00***
Phase 3 to Regulatory Review (Months)	44.03	23.21	57.56	44.79	0.00***
Panel C. Adverse Event Outcomes					
Within 2 Months	1.21	3.16	2.20	4.53	0.21
Within 3 Months	1.31	3.02	2.87	4.83	0.03**
Within 4 Months	1.47	3.85	3.59	7.1	0.03**
Within 5 Months	1.25	3.14	3.78	8.9	0.02**
Within 6 Months	1.69	4.20	4.17	10.82	0.06*

Notes: This table compares drug characteristics for true and imputed non-BTD drugs. All variables are measured at the drug-level. For example, "NDA to Approval (Months)" is the average number of months that a drug spends between NDA submission to approval. The top 4 most common ATC classes are shown. ATC categories that are not shown include: alimentary tract and metabolism; anti-infectives for systemic use; antineoplastic and immunomodulating agents; antiparasitic products, insecticides and repellents; blood and blood forming clots; cardiovascular system; dermatologicals; genitourinary system and sex hormones; musculo-skeletal system; nervous system; respiratory system; sensory organs; systemic hormonal preparations; and various. Column 5 presents p-values from t-tests comparing the difference of means.
*p<0.10, **p<0.05, ***p<0.001

Table D2: Summary Statistics: Imputed and True BTD Sample

	Imputed N = 23		True N = 60		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Small Molecule (0/1)	0.48	0.51	0.57	0.50	0.48
Priority Review (0/1)	0.91	0.29	0.98	0.13	0.13
Fast Track (0/1)	0.43	0.51	0.50	0.50	0.60
Accelerated Approval (0/1)	0.17	0.39	0.35	0.48	0.12
Black Box Warning (0/1)	0.57	0.51	.23	0.43	0.00***
ATC: Cancer (0/1)	0.65	0.49	0.57	0.5	0.48
ATC: Metabolism (0/1)	0.00	0.00	0.07	0.25	0.21
ATC: Antiinfectives (0/1)	0.04	0.21	0.15	0.36	0.19
ATC: Nervous System (0/1)	0.13	0.34	0.07	0.25	0.36
Panel B. Time-to-Market Outcomes					
Sponsor: Private Firm (0/1)	0.17	0.39	0.12	0.32	0.50
Firm Experience (# Approved Drugs)	2.65	3.49	5.6	5.71	0.02**
Panel C. Adverse Event Outcomes					
Regulatory Review (Months)	6.58	1.97	7.13	1.97	0.26
Phase 2 to Regulatory Review (Months)	58.99	25.65	58.48	33.34	0.95
Phase 3 to Regulatory Review (Months)	33.71	17.29	32.51	26.57	0.85
Within 2 Months	1.10	1.57	2.10	2.78	0.37
Within 3 Months	1.09	1.83	4.21	5.83	0.12
Within 4 Months	1.29	1.62	10.66	14.35	0.05*
Within 5 Months	2.21	3.85	11.35	17.44	0.08*
Within 6 Months	2.58	4.74	12.25	22.03	0.13

Notes: This table compares drug characteristics for true and imputed BTD drugs. All variables are measured at the drug-level. For example, "NDA to Approval (Months)" is the average number of months that a drug spends between NDA submission to approval. The top 4 most common ATC classes are shown. ATC categories that are not shown include: alimentary tract and metabolism; anti-infectives for systemic use; antineoplastic and immunomodulating agents; antiparasitic products, insecticides and repellents; blood and blood forming clots; cardiovascular system; dermatologicals; genitourinary system and sex hormones; musculo-skeletal system; nervous system; respiratory system; sensory organs; systemic hormonal preparations; and various. Column 5 presents p-values from t-tests comparing the difference of means.

*p<0.10, **p<0.05, ***p<0.001

Table D3: Impact of BTD Program: Controlling for Time Trends

	Time-to-Market			Adverse Event Rates				
	Reg Review	Phase III to Reg Review	Phase II to Reg Review	2 Months	3 Months	4 Months	5 Months	6 Months
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
BTD	-0.055	-0.135	-0.026	-0.794	-0.499	-0.227	0.158	0.107
	(0.081)	(0.121)	(0.100)	(0.516)	(0.514)	(0.529)	(0.435)	(0.500)
BTD x Post-2012	-0.058	-0.258*	-0.255**	0.463	0.765	0.766	0.331	-0.078
	(0.084)	(0.144)	(0.111)	(0.651)	(0.612)	(0.618)	(0.543)	(0.588)
Small Molecule	-0.094**	0.024	-0.000	0.584	0.051	-0.001	-0.013	-0.468
	(0.042)	(0.084)	(0.073)	(0.376)	(0.327)	(0.301)	(0.317)	(0.334)
Priority Review	-0.240***	0.014	0.023	0.211	0.301	0.470*	0.723**	0.901***
	(0.045)	(0.095)	(0.075)	(0.342)	(0.280)	(0.259)	(0.269)	(0.270)
Private Firm	0.065	0.128	0.145*	-0.610	-0.064	-0.842**	-0.633	0.224
	(0.056)	(0.110)	(0.079)	(0.654)	(0.456)	(0.405)	(0.397)	(0.413)
Mean	258.09	1,457.5	2,225.22	1.75	2.46	3.97	4.09	4.54
Controls: Drug Characteristics	Y	Y	Y	Y	Y	Y	Y	Y
Controls: Disease	Y	Y	Y	Y	Y	Y	Y	Y
Observations	359	340	310	136	163	194	215	228
log likelihood	-2129	-2707	-2540	-200	-281	-384	-420	-466

Notes: This table report estimates of the effect of the BTD program on time-to-market and adverse event rates in regressions that additionally control for time trends. Observations are at the drug-level and estimates are from negative binomial regressions. Additional controls include Fast Track status; Accelerated Approval status; whether the drug is approved with a boxed warning; ATC class; and the year of initial approval. Several columns show fewer than 359 observations due to missing data. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 2 imply that drugs experience a decrease in number of days spent between the start of Phase III and NDA submission after receiving BTD designation, a statistically significant $100 \times (\exp[-0.258] - 1)$ = -22.74%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001