REGULATORY INCENTIVES FOR INNOVATION:

THE FDA'S BREAKTHROUGH THERAPY DESIGNATION

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Abstract

In approving new medical products, regulators confront a tradeoff between speeding a new product to market and collecting additional information about its quality. Alternatively, with the right allocation of resources, this tradeoff function may be "shifted outward," thereby allowing important products to come to market more quickly without compromising quality evaluation. We study the FDA's Breakthrough Therapy Designation (BTD), a novel policy tool that was created to accelerate the clinical development and regulatory approval processes for developers of high-value therapies by increasing feedback and communication with regulators during later phases of drug development. Using algorithmic matching models, we assess the impact of the BTD program on measures of (1) time-to-market and (2) post-approval drug safety. We find that the BTD program shortened late-stage clinical development times by 24 percent. We do not find evidence of a difference in the *ex post* safety profile of drugs with (vs. without) the BTD. In exploring mechanisms, we find support for reduced BTD trial design complexity, but not for trial size as driving these findings. The results suggest that targeted policy tools can shorten R&D periods without compromising the quality of new products.

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1. INTRODUCTION

In new product development, firms must strike a balance between pushing a new product to market and gathering additional information about its quality—which encompasses safety, efficacy, cross-product heterogeneity, and manufacturing—which can delay product entry. Prominent discussions of this tradeoff have been seen recently in the context of Covid-19 vaccine development. For example, 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." Meanwhile headlines like " '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.

The growing cadre of approved Covid-19 vaccines are illustrative in that they have shown that with dedicated regulatory resources and expedited review processes, high-quality products can be brought to market more quickly than has historically been the case. In a 2020 *Nature* article (Ball 2020), Dan Barouch, director of the Center for Virology and Vaccine Research at Harvard Medical School noted that with sufficient resources, "the development process can be accelerated substantially without compromising on safety." We find that the feat of swift, high-quality Covid-19 vaccine development is not unique: in the context of new therapies for critical diseases, the provision of additional resources to support faster commercialization has led to swifter patient access to therapies without evidence of safety profile compromise.

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). In markets with entry regulation, regulators play an important role in designing policies that balance timely approval to ensure expeditious patient access to novel medical products against information about product quality. 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, and must balance the benefit-risk trade-offs between efficacy and safety (Califf 2017; Lackey, Thompson, and Eggers 2021; Miller and Woodcock 2017; U.S. Food and Drug Administration 2019).

For new medicines, the costs of new product development are considerable, as high as $2.6 billion (DiMasi et al. 2003; DiMasi et al. 2016). While patients are typically eager to have faster access to valuable medicines, such high costs serve to further underscore drug developers' interest in faster approvals. These preferences sharpen the tradeoff between development times and information gathering and raise a number of questions for managers and policy makers. Perhaps most tantalizing among them: can new products be brought to market faster in ways that do *not* compromise information about product quality?

We examine this question 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 and more transparent for firms engaged in new drug development for serious diseases by facilitating increased interaction between senior regulators and drug developers (Sherman et al. 2013; Daniel et al. 2015; U.S. Food and Drug Administration 2020).

Anecdotally, the BTD program is believed to shorten drug development and review times.[1] 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" to support timely progression through the drug development process, without changing approval standards (such as the types of efficacy and safety data needed). However, survey evidence suggests that the BTD is poorly understood by clinicians. 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.

This raises questions about available product information: if new products are brought to market more quickly, a dearth of information about quality may result in unintended consequences – even in the presence

[1] 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

of widespread benefits. Observational studies have suggested that medicines that experience shorter regulatory review may be linked with higher adverse events levels (Darrow et al. 2014; Olson 2008) but other researchers have failed to find evidence for this relationship (Philipson et al. 2008; Schick et al. 2017). More broadly, the notion of trade-offs between speed and quality has been examined in the operations management literature (Anand et al. 2011; see Song and Veeraraghavan 2018 for an overview), with applications to domains such as consulting and personal care. Thus, to the extent that a program facilitates faster commercialization, it is natural to ask about the quality of the resulting products that emerge.

To our knowledge, no studies have attempted a comprehensive, econometrically-driven evaluation of the impact of the BTD program on the outcomes (1) time-to-market and (2) product quality. Without understanding the program's impact on these key outcomes, it is impossible to assess whether the program itself represents a new instantiation of the compromise between speed and information gathering in new product development or a novel policy paradigm that mitigates tradeoffs by shifting the implicit regulatory production function outward, allowing for quality products (drugs) to reach users (patients) more quickly. We present a conceptual framework for how each of these scenarios would be expected to present and find evidence that is consistent with the BTD, representing a tradeoff-mitigating shift in the relationship between speed and information rather than a move along a traditional tradeoff curve. We take advantage of a dataset comprising the universe of drugs that were approved by the FDA over our period of study in order to model outcomes of interest while accounting for other relevant factors.

A key challenge for estimating the causal impact of the BTD program is the ability to identify an appropriate control group for BTD drugs. In the medical literature, Hwang et al. (2018) compare safety outcomes for the subset of BTD vs. non-BTD cancer drugs, but this study ignores the possibility that drugs that are eligible for the BTD are likely to be quite different for those that did not receive this designation.[2] We overcome these challenges by constructing treatment and control groups using algorithmic matching and using a difference-in-

[2] This is especially true given the high bar for receiving the designation, which is more stringent than for any other regulatory designation (Woodcock 2014). Additionally, the BTD may be rescinded if subsequent clinical data do not meet the standards for designation.

difference design to estimate the value of the BTD program. The treatment (respectively, control) group includes all BTD (non-BTD) medicines and medicines in the pre-BTD era that have the key features of BTD (non-BTD) drugs, as determined by a statistical matching procedure.

With this design, we find that products receiving the BTD spent, on average, 24 percent less time in the final stage of clinical development. A shortening of the development process of this magnitude is economically meaningful: in our comprehensive dataset, BTD products 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. Moreover, this estimate does not take into account the health benefits to patients of faster access to medicines, nor does it account the additional profits associated with a longer period of on-patent drug sales for the drugmaker.

The benefits of faster product development are most compelling when product quality is not compromised, which we explore directly. Focusing on product safety, a component of drug quality that often receives the most attention in studies of risk-reward, we consider whether faster clinical development among BTD products generates higher rates of 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 is crucial if BTD drugs are prescribed more frequently by physicians 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 following approval.

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.[3] More broadly, the results presented here provide new evidence to suggest that targeted policies can be designed in order to

[3] An analog to this finding in the operations literature would be a setting in which service speed does not lead to a degradation in service quality.

accelerate new product development without necessarily leading to lower product quality. For practitioners and managers in regulated industries in particular, these findings provide encouraging evidence for the feasibility and potential benefits of regulatory policy innovation.

2. BACKGROUND

In developed countries (and in many emerging markets), 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 in hand, 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] [5] Drug developers frequently 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 (typically Phase III trials) ranged from approximately 50 to 60 percent. Following these clinical trials, developers file a New Drug Application (NDA) or Biologics License Application (BLA) for FDA marketing approval. The entire process is long: 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.

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 2020), which created the Breakthrough Therapy Designation (BTD) with the intention of shortening this timeline for important new drugs treating serious conditions (U.S. Food and Drug Administration 2014; Bennett

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

[5] For ongoing regulatory surveillance, many firms are also required to pursue phase IV trials. These (post-market) studies usually include several thousand diseased volunteers and are meant to monitor drug safety and efficacy in an ongoing way.

2012). Unlike other FDA expedited programs (Priority Review, Accelerated Approval, and Fast Track), the BTD program requires substantial preliminary evidence of efficacy over existing therapies, and in return, offers significant engagement on drug development by senior regulators (U.S. Food and Drug Administration 2014) (see Appendix A for a summary of other FDA expedited programs). Firms are expected to submit a BTD request along with or soon after completing their Phase I or II trials, suggesting that any effect of the BTD on clinical development times should be detectable in the final stage 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 lessening 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 (e.g., which endpoints to measure in trials, which comparators to use, 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 the complete application (Daniel et al. 2015; U.S. Food and Drug Administration 2020). The level of evidence that is required by the FDA for approval does not differ between BTD and non-BTD drugs. This is also true for the type of trial design used in confirmatiory studies, which is based on characteristics of the drug and disease, not BTD status.

3. CONCEPTUAL FRAMEWORK

In new product development, firms must strike a balance between pushing a new product to market and gathering additional information about its quality. Too little information before going to market may lead to unforeseen negative outcomes, whereas overly burdensome information requirements may delay users' access to new products and deter new 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 occulsion device).

In markets with entry regulation, the regulatory body articulates the policies that balance timely approval against (requisite) information gathering to ensure product quality. In such settings, regulatory policy determines the point along an implicit tradeoff 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. Implicit in the choice of point A is that the regulator believes this is the combination of information (regulatory requirements) and the speed of commercialization that maximizes public welfare.

Indeed, many regulatory programs – such as expedited review programs for new drugs – are designed to better balance the costs of information gathering against the speed of patient access to new products. For example, the absence of other therapies for a very severe illness may mean that point A' (which corresponds to faster time-to-market coupled with less information about quality at the time) may still lead to greater welfare (Isakov et al. 2018). With the BTD program and the detailed interactions between drug developers and the FDA that it facilitates, 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 tradeoff curve to point B.

4. DATA

We collect the universe of New Molecular Entities (NMEs) approved by the FDA from 2006 to 2018. For each drug, we obtain the date of U.S. approval, approved indication, expedited review program status (e.g., 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 target condition for each drug when it first came to market – and classify all drug indications into 14 mutually-exclusive 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 drugs (Appendix Table B1).[6]

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

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 time the drug's developer submits its completed NDA (the submission date) to the time the FDA officially approves the drug (the approval date). The regulatory review period may also include time that the sponsor spends responding to FDA questions and additional requests for data.[7] To measure time spent in 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 launch of Phase III trials and NDA submission.

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), which we use as a proxy for such information. 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 database. Combined with FAERS data, we generate adverse event rates within windows of three and five months from the date of approval for each NME.

Table 1 presents drug-level summary statistics for our full, unmatched drug sample. 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 (Panel B). Finally, BTD products are associated with higher adverse event rates, with differences increasing as the window of observation expands from three to five months (Panel C). Density plots in Figures 3 and 4 illustrate similar trends.

Taken together, this simple evidence suggests that BTD products are associated with shorter clinical development and regulatory review periods, as well as greater adverse event rates. However, this simple comparison

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

of averages may mask substantial differences in factors (e.g., disease type, receipt of other regulatory designations) that may be driving these trends.

5. EMPIRICAL STRATEGY AND RESULTS

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

5.1 ESTIMATION

To identify the treatment group, we start with the set of 60 drugs that received the BTD ("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. This matching procedure is 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 BTD and non-BTD drugs. To adjust for the possibility of secular improvements in the quality of all medicines, we use a difference-in-difference design and construct a control group of actual non-BTD drugs (after 2012), and their pre-2012 matches.[8] This approach identifies the effect of the BTD program under the assumption that the quality of drugs eligible and ineligible for BTD were identical *before* the BTD designation, and we perform a number of robustness tests, in Section 5.3, to support this assumption.

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 three months of approval), BTD_d is an indicator for

[8] See Appendix C for more explanation of our methods and why they are expected to yield more appropriate and conservative estimates.

whether drug *d* is in the treatment group of actual and matched BTD medicines, $AfterBTD_d$ is an indicator for whether drug *d* is approved 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, whether approved with a boxed warning, and developer firm type.

The coefficient of interest is λ —which measures whether the effect of the BTD was larger for drugs that actually received the BTD versus the matched sample that would have been expected to receive this designation. β measures the time invariant outcome for medicines that either actually received the BTD or would have been expected to receive this designation and we would expect it to be positive, as it captures other factors associated with clinically important medicines in a matched set of drug classes.

The dependent variables are skewed and non-negative count and rate data. As a result, we report estimates from negative binomial regression models with robust standard errors.[9] [10] Equation (1) estimates the impact of the BTD program under the assumption that secular improvements in drug quality (as proxied by adverse event rates) for drugs that are eligible for BTD designation are identical to improvements in quality for non-BTD drugs.

5.2 RESULTS

Table 2 presents summary statistics on the 351 drugs in the treatment (N = 89) and control (N = 262) groups. Table 3 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 expected, Priority Review – a program that is explicitly designed to

[9] 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.

[10] 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.

lower the time spent in regulatory review – is strongly associated with a decrease in time spent in regulatory approval relative to clinical testing and development.

Consistent with the program's 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 interpretable as elasticities. Specifically, we find that relative to non-BTD products, BTD products experience at least a 24 percent statistically significant decline in time spent between Phase III trials and NDA submission (Columns 4-6). In contrast, there is a smaller and less statistically significant decline in the time between Phase II trials and NDA submission (Columns 7-9), suggesting that the benefits of the BTD program disproportionately benefit firms in the latest stage of clinical development.

Table 4 reports the impact of the BTD program on adverse event rates. Out of the six specifications in this table, only one has a statistically significant association of the BTD program with adverse event rates: Column 3 indicates that the BTD program is associated with an 145.7 percent increase in the rate of adverse events in the three months following approval, though this is off of a relatively low base and these effects do not persist when the window of observation expands to five months (Columns 4-6). In contrast, Appendix Table D1 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.[11]

5.3 Mechanisms and Robustness Checks

5.3.1 Trial Characteristics

The evidence so far suggests that BTD led to a decrease in clinical development times, with limited effects on adverse event rates. A natural next question to ask is: what mechanisms might be driving this result? A key feature of the BTD benefit is regulatory guidance that "ensure[s] that the design of the clinical trials is as efficient as practicable." (U.S. Food and Drug Administration 2021). Table 5 examines the impact of the BTD designation on two trial design features: trial size and trial design complexity. 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

[11] In separate robustness checks (Appendix Tables D2 and D3), we find that these results are robust to excluding controls for developer type.

drug's Phase III (Panel A) and Phase II (Panel B) trials. We proxy for trial design complexity by assessing whether patients were randomly assigned to a treatment and control group (Column 4) and whether the study was double-blinded (Column 5).

Across our three measures, we do not find evidence that the BTD program was associated with differential trial sizes. In contrast, Columns 4 and 5 hint at a likely mechanism for our findings. These columns 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 20.8 and 55.9 percentage points respectively).

5.3.1 Robustness Checks

Appendix D presents four sets of robustness checks that support our main results. First, we show that our results remain unchanged when we exclude controls for developer type. Second, we show that our results are robust to an OLS specification. Third, we show that our findings remain largely unchanged when we restrict our analysis to a set of more contemporary drugs (drugs approved between 2010 and 2018 only). Finally, we show that our main results survive placebo tests that analyze the impact of the Fast Track designation on time-to-market and drug adverse event rates.

6. Discussion And Conclusion

The high costs and risks of new product development call for 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 shifting firms' positions on the speed-information trade-off curve – or potentially reaching a new regulatory isoquant. As the Covid-19 pandemic has 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.

This study suggests that the scientific community's response to the pandemic has been ongoing for nearly a decade elsewhere in the pharmaceutical industry, with the BTD program having also impacted the length of

clinical research. In particular, we find that the BTD program leads to a 24 percent decline in time spent in the most costly phase of clinical development and little evidence that the BTD program led to a concurrent increase in adverse event rates. In addition, we explore mechanisms and show that the BTD program is associated with late-stage trials that are less complex in design.

A reduction in the frequency of randomization and blinding in trials has 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). But such features are not inherently linked to drug safety. Moreover, there may be other benefits (beyond speed-to-market) of these trial design choices. For example, such trials may be better at achieving their target enrollment. In a setting where it is known that 40% of cancer trails fail to achieve their planned patient recruitment (Monteleone 2016), 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" is well documented, a control arm may not be necessary or ethical for evidence generation about drug efficacy. Policy-makers and researchers will need to consider the extent to which these characteristics impact time-to-market and drug quality in both the short and long term.

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 has developed the PRIME program "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).

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 is surely desirable. This study provides evidence that regulatory innovation aimed at bringing such products to market quickly can work.

Our results provide support for the effectiveness of policies that increase the level of information provision from the regulator to the developer. These findings are consistent with previous work that has shown that other concrete steps to mitigate regulatory uncertainy is associated with a decline in time-to-market for medical products (Stern 2017). More generally, our analysis highlights the importance of considering the tradeoffs that may be inherent in the commercialization of new products and how dedicated resources may help to mitigate such tradeoffs, when they are appropriately designed and targeted.

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Figures and Tables

Figure 1: The Quality-Information Space for Regulators

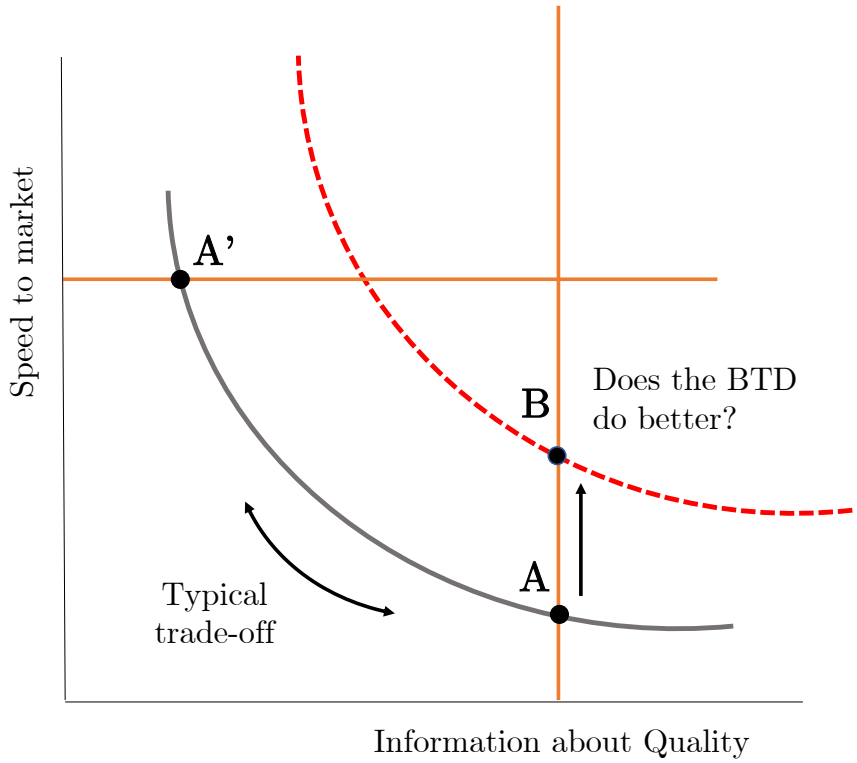
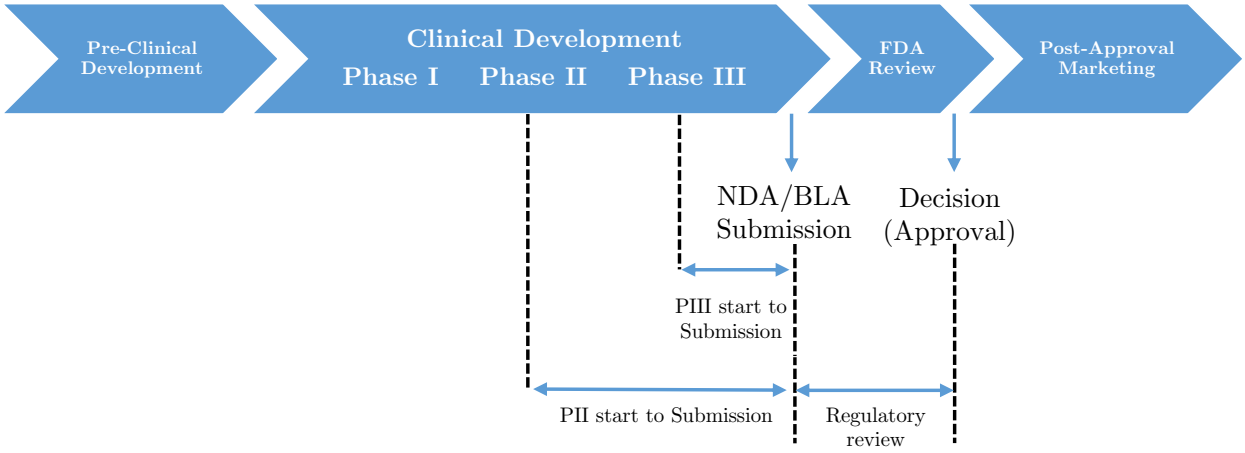
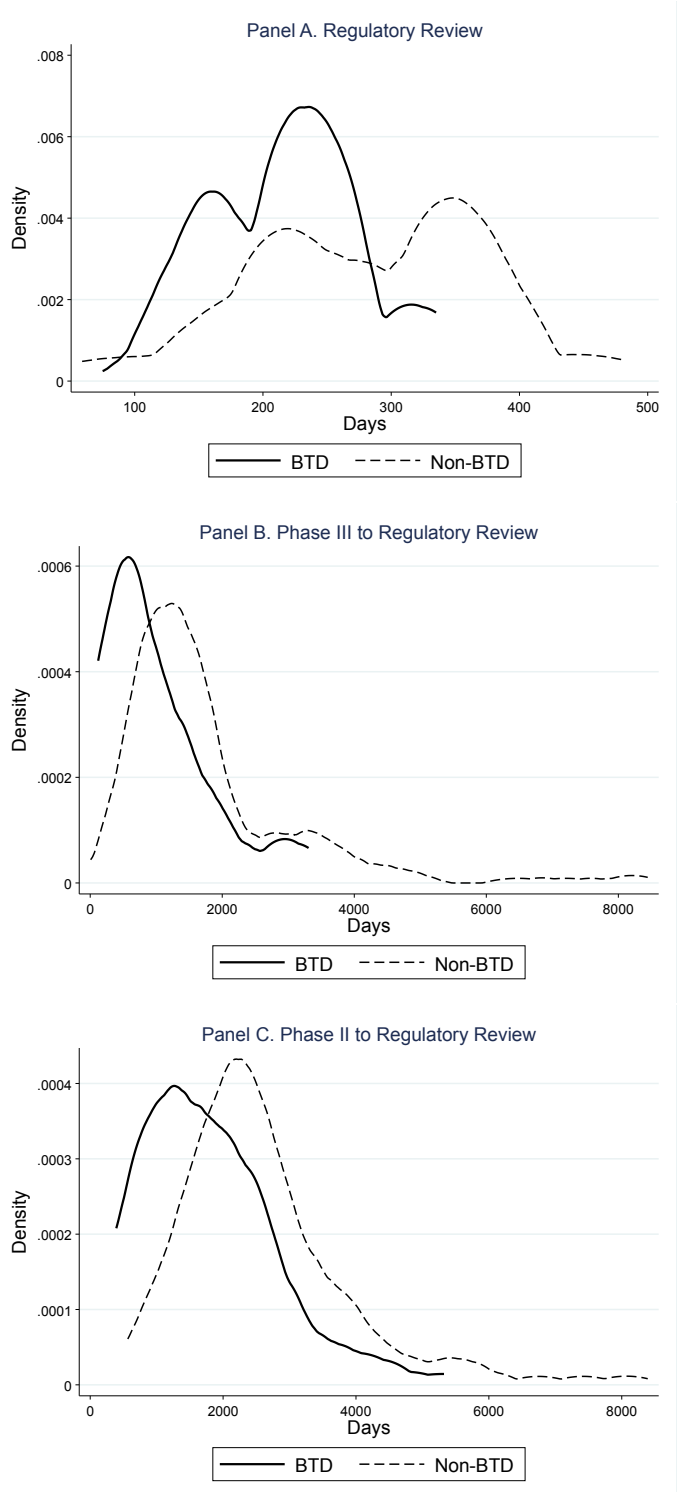


Figure 2: Timeline of Drug Development and Approval



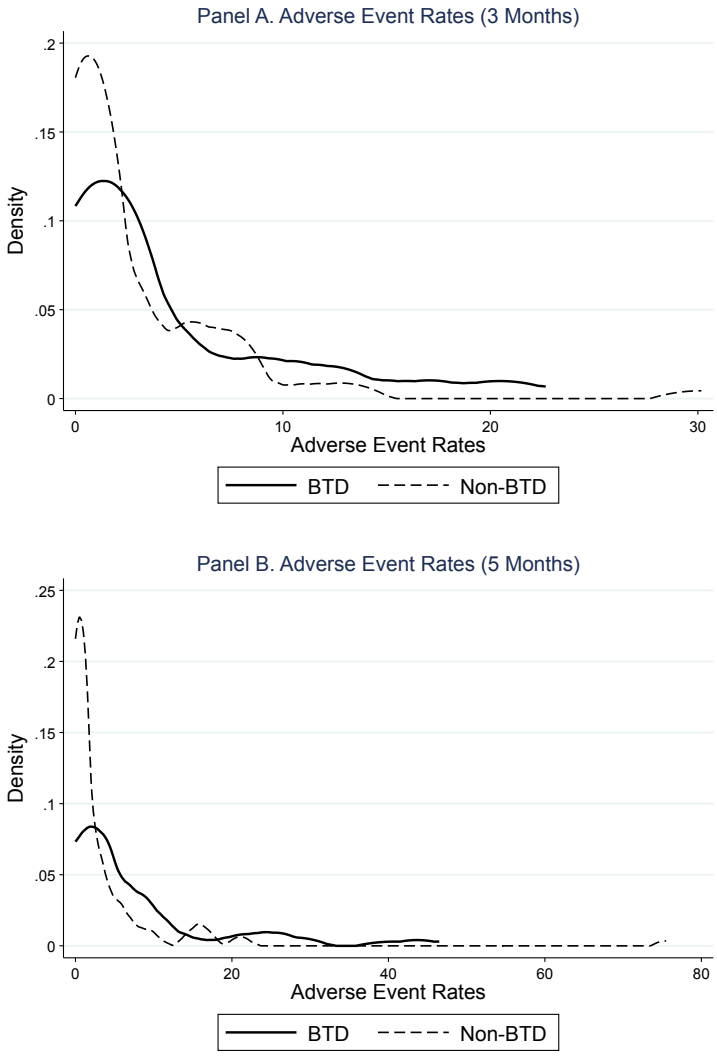
Notes: This figure shows the typical timeline of drug development and approval. In particular, it depicts our three measures of time-to-approval: (1) time from Phase II to NDA submission, (2) time from Phase III to NDA submission, and (3) time from NDA submission to FDA approval.

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 drug-level.

Figure 4: Distribution of Adverse Event Outcomes



Notes: This figure shows the distribution of BTD and non-BTD adverse event rates. Observations are at drug-level.

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***
Boxed Warning (0/1)	0.23	0.43	0.38	0.49	0.03**
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
Private Firm (0/1)	0.23	0.43	0.29	0.45	0.41
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 Outcomes					
Adverse Events: Within 3 Months	41.00	54.65	20.64	72.46	0.04**
Adverse Events: Within 5 Months	132.92	148.80	74.32	267.95	0.10
Adverse Event Rates: Within 3 Months	4.43	5.87	1.79	3.75	0.00**
Adverse Event Rates: Within 5 Months	7.39	10.42	2.16	6.02	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. The top 4 most common ATC classes are shown. Column 5 presents p-values from t-tests comparing the difference of means.
*p<0.10, **p<0.05, ***p<0.001

Table 2: Summary Statistics: Matched Drug Sample

	Synthetic Treatment Imputed + True BTD N = 89		Synthetic Control Imputed + True Non-BTD N = 262		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Small Molecule (0/1)	0.57	0.50	0.83	0.38	0.00***
Priority Review (0/1)	0.98	0.15	0.42	0.49	0.00***
Fast Track (0/1)	0.48	0.50	0.29	0.45	0.00***
Accelerated Approval (0/1)	0.31	0.47	0.06	0.23	0.00***
Boxed Warning (0/1)	0.33	0.47	0.35	0.48	0.62
ATC: Cancer (0/1)	0.60	0.49	0.26	0.44	0.00***
ATC: Metabolism (0/1)	0.04	0.21	0.17	0.38	0.00**
ATC: Antiinfectives (0/1)	0.12	0.33	0.11	0.31	0.67
ATC: Nervous System (0/1)	0.07	0.25	0.13	0.33	0.13
Private Firm (0/1)	0.24	0.43	0.22	0.42	0.7767
Panel B. Time-to-Market Outcomes					
Regulatory Review (Months)	6.83	1.92	9.03	3.37	0.00***
Phase 2 to Regulatory Review (Months)	57.62	31.58	79.4	40.64	0.00***
Phase 3 to Regulatory Review (Months)	32.92	24.12	53.26	38.77	0.00***
Panel C. Adverse Event Outcomes					
Adverse Events - Within 3 Months	34.64	55.08	20.71	76.48	0.11
Adverse Events - Within 5 Months	114.61	156.38	79.90	295.08	0.29
Adverse Event Rates - Within 3 Months	3.39	5.29	1.95	3.91	0.03**
Adverse Event Rates - Within 5 Months	5.67	9.26	2.40	6.64	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. Column 5 presents p-values from t-tests comparing the difference of means.
*p<0.10, **p<0.05, ***p<0.001

Table 3: 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	-0.276***	-0.135*	-0.065	-0.304**	-0.181	-0.116	-0.142	-0.092	-0.117
	(0.071)	(0.082)	(0.083)	(0.123)	(0.134)	(0.133)	(0.103)	(0.112)	(0.113)
BTD x Post-2012	0.012	-0.008	-0.059	-0.292*	-0.328**	-0.275*	-0.256*	-0.229*	-0.194
	(0.084)	(0.085)	(0.084)	(0.176)	(0.159)	(0.155)	(0.131)	(0.123)	(0.122)
NDA		-0.095**	-0.112**		0.121	0.019		0.041	-0.004
		(0.037)	(0.039)		(0.079)	(0.089)		(0.069)	(0.075)
Priority Review		-0.231***	-0.234***		0.028	0.020		0.024	0.079
		(0.047)	(0.045)		(0.101)	(0.100)		(0.078)	(0.080)
Private Firm		0.025	0.033		0.190**	0.155*		0.145**	0.126*
		(0.045)	(0.047)		(0.093)	(0.090)		(0.070)	(0.066)
Mean	258.32	258.32	258.32	1472.70	1472.70	1472.70	2237.01	2237.01	2237.01
Controls: Drug Characteristics	N	Y	Y	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y	N	N	Y
Observations	351	351	351	331	331	331	302	302	302
log likelihood	-2098	-2083	-2071	-2676	-2657	-2640	-2501	-2488	-2478

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 4 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 $100 \times (\exp[-0.292] - 1) =$ -25.32%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table 4: Impact on Adverse Event Rates

	3 Months AE Rates			5 Months AE Rates		
	(1)	(2)	(3)	(4)	(5)	(6)
BTD	0.178	-0.055	-0.419	0.780*	0.302	0.156
	(0.529)	(0.542)	(0.485)	(0.426)	(0.418)	(0.415)
BTD x Post-2012	0.527	0.634	0.899*	0.054	0.376	0.678
	(0.606)	(0.600)	(0.541)	(0.515)	(0.490)	(0.476)
NDA		0.376	0.479**		0.447*	0.761**
		(0.248)	(0.232)		(0.253)	(0.240)
Priority Review		0.202	0.195		0.599**	0.314
		(0.274)	(0.257)		(0.261)	(0.246)
Private Firm		-0.661**	-0.799***		-0.625**	-0.766**
		(0.289)	(0.242)		(0.252)	(0.234)
Mean	2.43	2.43	2.43	3.31	3.31	3.31
Controls: Drug Characteristics	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y
Observations	195	195	195	258	258	258
log likelihood	-356	-352	-328	-520	-512	-492

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 for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Adverse event rates are observed for a subset of the sample, which accounts for fewer than 351 observations. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 3 imply that drugs experience an increase in adverse event rates in the 3 months after receiving BTD designation, a statistically significant $100 \times (\exp[0.899] - 1) = 145.71\%$. Robust standard errors are in parentheses. *p<0.10, **p<0.05, ***p<0.001

Table 5: 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	-46.689	-8.732	-0.246	0.145**	0.302**
	(470.354)	(29.122)	(0.249)	(0.073)	(0.101)
BTD x Post-2012	-277.987	-12.681	0.292	-0.208**	-0.559***
	(455.462)	(31.891)	(0.457)	(0.081)	(0.114)
NDA	331.924	5.060	-0.050	0.138**	0.130*
	(276.397)	(18.885)	(0.228)	(0.047)	(0.067)
Priority Review	-603.846	3.873	-0.167	-0.003	0.005
	(524.952)	(22.534)	(0.208)	(0.047)	(0.074)
Private Firm	518.141	16.025	-0.173	-0.095*	-0.081
	(400.226)	(23.886)	(0.170)	(0.052)	(0.059)
Mean	982.56	108.65	2.46	0.88	0.70
Observations	323	277	298	331	322
Panel B. Phase II Trials					
BTD	-60.329	-6.819	-0.606	-0.076	0.026
	(63.206)	(10.397)	(0.810)	(0.134)	(0.112)
BTD x Post-2012	58.765	-6.079	0.874	-0.003	-0.142
	(61.923)	(9.818)	(0.912)	(0.150)	(0.123)
NDA	22.840	-1.677	0.198	-0.108	-0.039
	(31.979)	(6.632)	(0.399)	(0.071)	(0.062)
Priority Review	-82.524*	-2.838	-0.906**	-0.093	-0.192**
	(47.690)	(8.024)	(0.447)	(0.085)	(0.077)
Private Firm	10.558	2.946	-0.087	0.021	0.069
	(32.493)	(5.958)	(0.377)	(0.071)	(0.073)
Mean	198.17	27.55	3.24	0.77	0.51
Observations	277	238	239	218	274

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 351 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.
*p<0.10, **p<0.05, ***p<0.001

APPENDIX

APPENDIX A: ADDITIONAL DETAIL ON OTHER FDA REVIEW PROGRAMS

It is worth comparing the BTD with other expedited programs (Priority Review, Accelerated Approval, and Fast Track) and considering how they interact. 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 potential medicines that are expected to provide a significant improvement in safety and efficacy relative to existing therapies. Manufacturers can submit evidence from clinical trials and regulators inform applicants about the granting of this designation within 60 days of the drug marketing application.[1] Products receiving Priority Review benefit from a shortened period of regulatory review, receiving a regulatory decision regarding market approval in six months rather than the standard 10 months (U.S. Food and Drug Administration 2020).

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, a physical sign, that predict clinical benefit, but is not by themselves a measure of benefit (U.S. Food and Drug Administration 2020). For example, in HIV drug development, viral load can be used as a surrogate endpoint (i.e., rather than waiting for death or severe disease progression as a study endpoint). The use of surrogate endpoints can meaningfully reduce the size and/or duration of clinical trials and lower the costs associated with clinical development (Liu and Kesselheim, 2019; Naci et al., 2017).

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

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

allows products to receive expedited development and review, most sponsors request the designation during the IND phase of drug development (FDA, 2020; FDA, 2014).

Appendix Table A1 and Figure A1 summarize these programs and provide additional detail on their features and content. All BTD recipients automatically receive Fast Track designation features, although *de facto* there is also quite a bit of overlap between the BTD and other programs. As noted in Table 1, almost all received Priority Review and 35 percent came to market via Accelerated Approval.

REFERENCES

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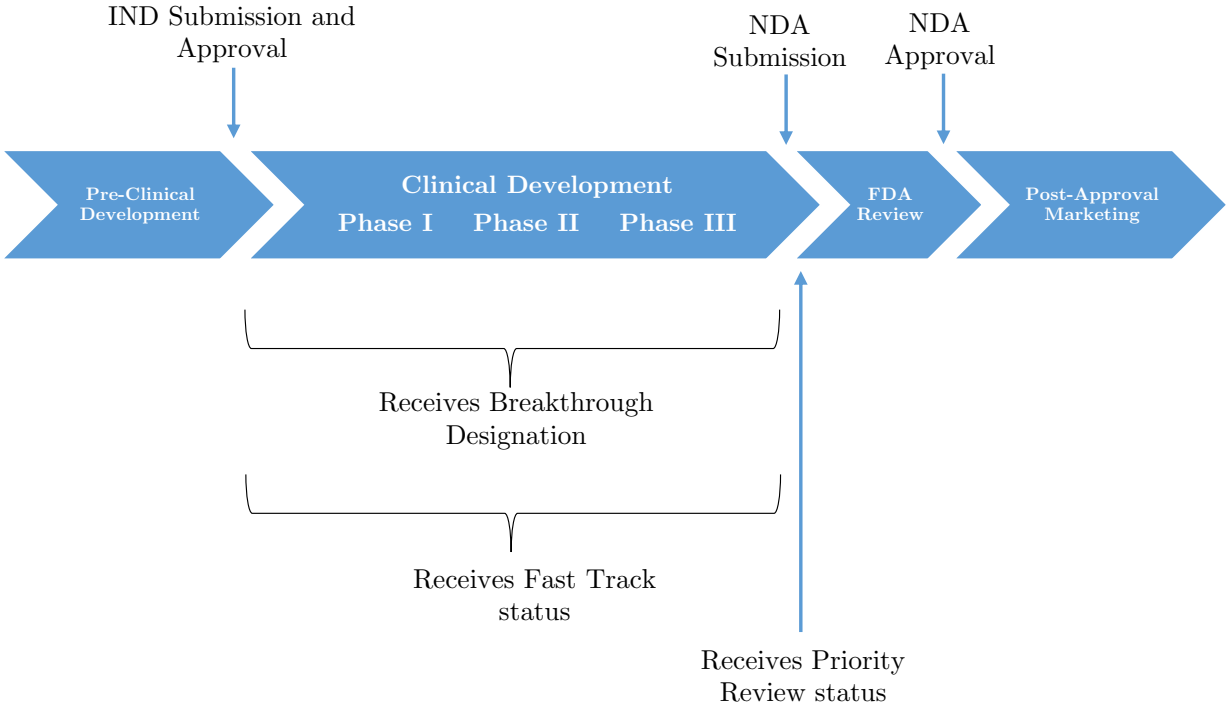
Naci, Huseyin, Katelyn R. Smalley, and Aaron S. Kesselheim (2017) "Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration." *JAMA* 318(7): 626–36.

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

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 9 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 database. 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 Optum database. 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.

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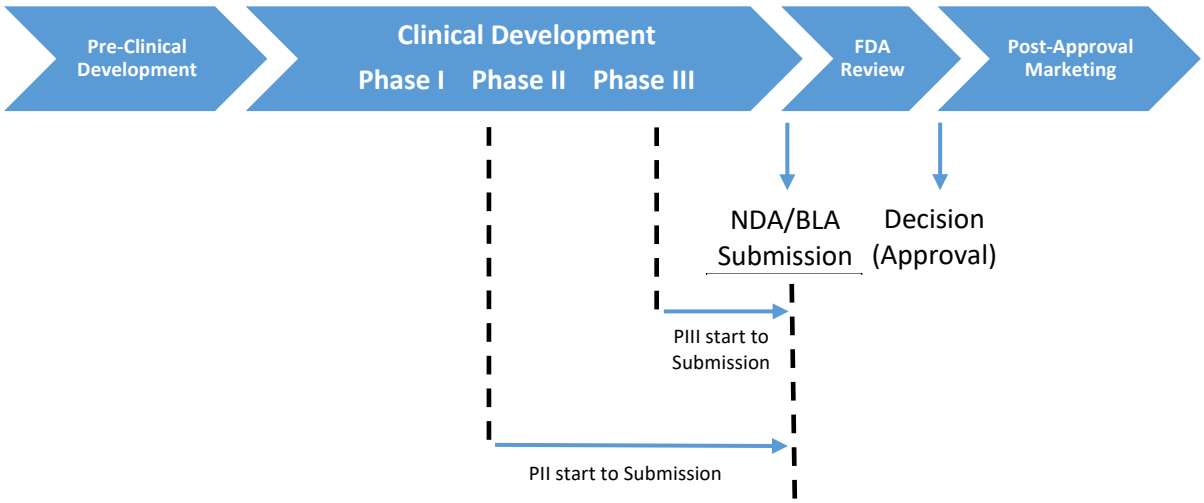
Figure B1. FDA Drug R&D Path



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)

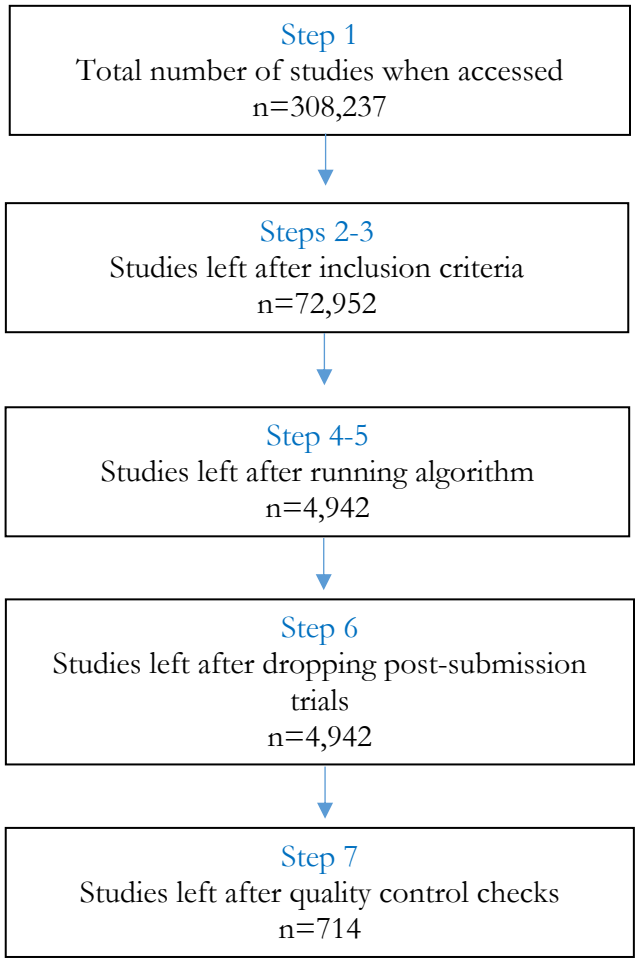


Table B1. Final NME sample by calendar year

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 3 and 5 months of approval

Application Number	Application Type	Proprietary Name	Established Name	BTD	No AE	3	5
020427	NDA	SABRIL	VIGABATRIN			4	7
021201	NDA	ASCLERA	POLIDOCANOL			0	0
021502	NDA	ANTHELIOS SX	AVOBENZONE; ECAMSULE; OCTOCRYLENE			0	0
021526	NDA	RANEXA	RANOLAZINE			0	0
021632	NDA	ERAXIS	ANIDULAFUNGIN			0	0
021641	NDA	AZILECT	RASAGILINE MESYLATE			1	2
021742	NDA	BYSTOLIC	NEBIVOLOL HYDROCHLORIDE			1	13
021775	NDA	ENTEREG	ALVIMOPAN			0	0
021790	NDA	DACOGEN	DECITABINE			0	8
021825	NDA	FERRIPROX	DEFERIPRONE			0	0
021829	NDA	NEUPRO	ROTIGOTINE			28	56
021856	NDA	ULORIC	FEBUXOSTAT			8	53
021883	NDA	DALVANCE	DALBAVANCIN HYDROCHLORIDE			0	3
021894	NDA	XENAZINE	TETRABENAZINE			1	4
021902	NDA	VEREGEN	SINECATECHINS			0	0
021908	NDA	AMITIZA	LUBIPROSTONE			0	0
021911	NDA	BANZEL	RUFINAMIDE			8	15
021928	NDA	CHANTIX	VARENICLINE TARTRATE			0	54
021938	NDA	SUTENT	SUNITINIB MALATE			71	73
021964	NDA	RELISTOR	METHYLNALTREXONE BROMIDE			3	5
021976	NDA	PREZISTA	DARUNAVIR ETHANOLATE			4	9
021977	NDA	VYVANSE	LISDEXAMFETAMINE DIMESYLATE			0	0
021985	NDA	TEKTURNA	ALISKIREN HEMIFUMARATE			45	216
021986	NDA	SPRYCEL	DASATINIB			8	27
021991	NDA	ZOLINZA	VORINOSTAT			1	3
021992	NDA	PRISTIQ	DESVENLAFAXINE SUCCINATE			6	40
021995	NDA	JANUVIA	SITAGLIPTIN PHOSPHATE			58	755
021999	NDA	INVEGA	PALIPERIDONE			9	174
022003	NDA	NOXAFIL	POSACONAZOLE			29	51
022004	NDA	OMNARIS	CICLESONIDE			0	0
022030	NDA	TOVIAZ	FESOTERODINE FUMARATE			13	21
022055	NDA	ALTABAX	RETAPAMULIN			0	27
022059	NDA	TYKERB	LAPATINIB DITOSYLATE			213	757
022065	NDA	IXEMPRA KIT	IXABEPILONE			19	106
022068	NDA	TASIGNA	NILOTINIB HYDROCHLORIDE MONOHYDRATE			100	200
022074	NDA	SOMATULINE DEPOT	LANREOTIDE ACETATE			4	10
022081	NDA	LETAIRIS	AMBRISENTAN			18	63
022088	NDA	TORISEL	TEMSIROLIMUS			32	93
022106	NDA	DORIBAX	DORIPENEM			48	73
022110	NDA	VIBATIV	TELAVANCIN HYDROCHLORIDE			1	5

022117	NDA	SAPHRIS	ASENAPINE MALEATE	3	29
022128	NDA	SELZENTRY	MARAVIROC	5	41
022129	NDA	ULESFIA	BENZYL ALCOHOL	0	3
022134	NDA	LASTACAFT	ALCAFTADINE	0	0
022145	NDA	ISENTRESS	RALTEGRAVIR POTASSIUM	21	85
022150	NDA	FIRAZYR	ICATIBANT ACETATE	8	10
022156	NDA	CLEVIPREX	CLEVIDIPINE	0	0
022161	NDA	LEXISCAN	REGADENOSON	0	28
022181	NDA	KUVAN	SAPROPTERIN DIHYDROCHLORIDE	1	6
022187	NDA	INTELENCE	ETRAVIRINE	64	113
022192	NDA	FANAPT	ILOPERIDONE	0	0
022201	NDA	FIRMAGON	DEGARELIX ACETATE	0	1
022206	NDA	RAPAFLO	SILODOSIN	4	8
022212	NDA	DUREZOL	DIFLUPREDNATE	0	0
022225	NDA	BRIDION	SUGAMMADEX SODIUM	20	35
022247	NDA	DUAVEE	BAZEDOXIFENE ACETATE; ESTROGENS, CONJUGATED	0	0
022249	NDA	TREANDA	BENDAMUSTINE HYDROCHLORIDE	7	27
022250	NDA	AMPYRA	DALFAMPRIDINE	3	115
022252	NDA	NATAZIA	DIENOGEST; ESTRADIOL VALERATE	12	29
022253	NDA	VIMPAT	LACOSAMIDE	6	26
022256	NDA	SAVELLA	MILNACIPRAN HYDROCHLORIDE	13	26
022268	NDA	COARTEM	ARTEMETHER; LUMEFANTRINE	5	8
022271	NDA	NESINA	ALOGLIPTIN BENZOATE	27	50
022275	NDA	SAMSCA	TOLVAPTAN	1	4
022288	NDA	BEPREVE	BEPOTASTINE BESILATE	0	0
022291	NDA	PROMACTA	ELTROMBOPAG OLAMINE	16	39
022304	NDA	NUCYNTA	TAPENTADOL HYDROCHLORIDE	5	11
022307	NDA	EFFIENT	PRASUGREL HYDROCHLORIDE	28	63
022308	NDA	BESIVANCE	BESIFLOXACIN HYDROCHLORIDE	0	2
022311	NDA	MOZOBIL	PLERIXAFOR	10	18
022334	NDA	AFINITOR	EVEROLIMUS	215	534
022341	NDA	VICTOZA	LIRAGLUTIDE RECOMBINANT	89	567
022345	NDA	POTIGA	EZOGABINE	12	54
022350	NDA	ONGLYZA	SAXAGLIPTIN HYDROCHLORIDE	3	43
022363	NDA	LIVALO	PITAVASTATIN CALCIUM	12	20
022383	NDA	ARCAPTA NEOHALER	INDACATEROL MALEATE	91	209
022393	NDA	ISTODAX	ROMIDEPSIN	0	0
022395	NDA	QUTENZA	CAPSAICIN	0	0
022399	NDA	HORIZANT	GABAPENTIN ENACARBIL	0	7
022405	NDA	CAPRELSA	VANDETANIB	36	81
022406	NDA	XARELTO	RIVAROXABAN	176	335
022408	NDA	NATROBA	SPINOSAD	0	0

022416	NDA	APTIOM	ESLICARBAZEPINE ACETATE		13	19
022425	NDA	MULTAQ	DRONEDARONE HYDROCHLORIDE		60	182
022433	NDA	BRILINTA	TICAGRELOR		62	121
022458	NDA	ELELYSO	TALIGLUCERASE ALFA		0	4
022465	NDA	VOTRIENT	PAZOPANIB HYDROCHLORIDE		61	171
022468	NDA	FOLOTYN	PRALATREXATE		9	18
022474	NDA	ELLA	ULIPRISTAL ACETATE		0	1
022505	NDA	EGRIFTA	TESAMORELIN ACETATE		0	4
022512	NDA	PRADAXA	DABIGATRAN ETEXILATE MESYLATE		1095	3909
022522	NDA	DALIRESP	ROFLUMILAST		101	194
022526	NDA	ADDYI	FLIBANSERIN		0	1
022527	NDA	GILENYA	FINGOLIMOD		112	440
022529	NDA	BELVIQ	LORCASERIN HYDROCHLORIDE		0	0
022535	NDA	ESBRIET	PIRFENIDONE	yes	85	224
022562	NDA	CARBAGLU	CARGLUMIC ACID		1	1
022567	NDA	VIIBRYD	VILAZODONE HYDROCHLORIDE		0	0
022575	NDA	VPRIV	VELAGLUCERASE ALFA		2	5
050786	NDA	PYLERA	BISMUTH SUBCITRATE POTASSIUM; METRONIDAZOLE; TETRACYCLINE		0	0
125141	BLA	MYOZYME	ALGLUCOSIDASE ALFA		0	0
125147	BLA	VECTIBIX	PANITUMUMAB		0	0
125151	BLA	ELAPRASE	IDURSULFASE		0	0
125156	BLA	LUCENTIS	RANIBIZUMAB		0	0
125160	BLA	CIMZIA	CERTOLIZUMAB PEGOL		0	0
125164	BLA	MIRCERA	METHOXY POLYETHYLENE GLYCOL-EPOETIN BETA		0	0
125166	BLA	SOLIRIS	ECULIZUMAB		0	0
125249	BLA	ARCALYST	RILONACEPT		0	0
125261	BLA	STELARA	USTEKINUMAB		0	0
125268	BLA	NPLATE	ROMIPLOSTIM		0	0
125274	BLA	DYSPORT	ABOBOTULINUMTOXINA		0	0
125276	BLA	ACTEMRA	TOCILIZUMAB		0	0
125277	BLA	KALBITOR	ECALLANTIDE		0	0
125288	BLA	NULOJIX	BELATACEPT		0	0
125289	BLA	SIMPONI	GOLIMUMAB		0	0
125291	BLA	LUMIZYME	ALGLUCOSIDASE ALFA		0	0
125293	BLA	KRYSTEXXA	PEGLOTICASE		0	0
125294	BLA	GRANIX	TBO-FILGRASTIM		0	0
125319	BLA	ILARIS	CANAKINUMAB		0	0
125320	BLA	PROLIA	DENOSUMAB		0	0
125326	BLA	ARZERRA	OFATUMUMAB		0	0
125327	BLA	VORAXAZE	GLUCARPIDASE		0	0
125338	BLA	XIAFLEX	COLLAGENASE CLOSTRIDIUM HISTOLYTICUM		0	0
125349	BLA	RAXIBACUMAB	RAXIBACUMAB		0	0

125359	BLA	ERWINAZE	ASPARAGINASE ERWINIA CHRYSANTHEMI			0	0
125360	BLA	XEOMIN	INCOBOTULINUMTOXINA			0	0
125370	BLA	BENLYSTA	BELIMUMAB			0	0
125377	BLA	YERVOY	IPILIMUMAB			0	0
125387	BLA	EYLEA	AFLIBERCEPT			0	0
125388	BLA	ADCETRIS	BRENTUXIMAB VEDOTIN			0	5
125390	BLA	MYALEPT	METRELEPTIN			0	2
125409	BLA	PERJETA	PERTUZUMAB			0	6
125418	BLA	ZALTRAP	ZIV-AFLIBERCEPT			3	10
125422	BLA	JETREA	OCRIPLASMIN			0	2
125427	BLA	KADCYLA	ADO-TRASTUZUMAB EMTANSINE			33	65
125431	BLA	TANZEUM	ALBIGLUTIDE			0	1
125460	BLA	VIMIZIM	ELOSULFASE ALFA			2	34
125469	BLA	TRULICITY	DULAGLUTIDE			5	56
125476	BLA	ENTYVIO	VEDOLIZUMAB			11	46
125477	BLA	CYRAMZA	RAMUCIRUMAB			8	37
125486	BLA	GAZYVA	OBINUTUZUMAB	yes		8	16
125496	BLA	SYLVANT	SILTUXIMAB			1	2
125499	BLA	PLEGRIDY	PEGINTERFERON BETA-1A			4	17
125504	BLA	COSENTYX	SECUKINUMAB			41	197
125509	BLA	ANTHIM	OBILTOXAXIMAB		X		
125511	BLA	NATPARA	PARATHYROID HORMONE			0	1
125513	BLA	STRENSIQ	ASFOTASE ALFA	yes		37	140
125514	BLA	KEYTRUDA	PEMBROLIZUMAB	yes		301	507
125516	BLA	UNITUXIN	DINUTUXIMAB			2	8
125521	BLA	TALTZ	IXEKIZUMAB			8	75
125522	BLA	REPATHA	EVOLOCUMAB			58	734
125526	BLA	NUCALA	MEPOLIZUMAB			8	31
125547	BLA	PORTRAZZA	NECITUMUMAB			3	7
125554	BLA	OPDIVO	NIVOLUMAB	yes		110	462
125557	BLA	BLINCYTO	BLINATUMOMAB	yes		25	121
125559	BLA	PRALUENT	ALIROCUMAB			20	231
125561	BLA	KANUMA	SEBELIPASE ALFA	yes		3	10
200327	NDA	TEFLARO	CEFTAROLINE FOSAMIL			1	1
200603	NDA	LATUDA	LURASIDONE HYDROCHLORIDE			0	5
200677	NDA	SIGNIFOR	PASIREOTIDE DIASPARTATE			0	17
200796	NDA	EDARBI	AZILSARTAN KAMEDOXOMIL			0	9
201023	NDA	JEVTANA KIT	CABAZITAXEL			13	36
201280	NDA	TRADJENTA	LINAGLIPTIN			19	132
201292	NDA	GILOTRIF	AFATINIB DIMALEATE			27	87
201532	NDA	HALAVEN	ERIBULIN MESYLATE			60	106
201699	NDA	DIFICID	FIDAXOMICIN			1	10
202022	NDA	EDURANT	RILPIVIRINE HYDROCHLORIDE			9	9
202067	NDA	ONFI	CLOBAZAM			27	40

202155	NDA	ELIQUIS	APIXABAN	18	106
202192	NDA	JAKAFI	RUXOLITINIB PHOSPHATE	15	88
202276	NDA	STENDRA	AVANAFIL	0	0
202292	NDA	MYTESI	CROFELEMER	0	0
202293	NDA	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	31	102
202324	NDA	INLYTA	AXITINIB	100	221
202379	NDA	ZYTIGA	ABIRATERONE ACETATE	131	282
202429	NDA	ZELBORAF	VEMURAFENIB	135	374
202450	NDA	TUDORZA PRESSAIR	ACLIDINIUM BROMIDE	0	2
202514	NDA	ZIOPTAN	TAFLUPROST	2	8
202535	NDA	PREPOPIK	CITRIC ACID; MAGNESIUM OXIDE; SODIUM PICOSULFATE	2	2
202570	NDA	XALKORI	CRIZOTINIB	212	360
202611	NDA	MYRBETRIQ	MIRABEGRON	18	31
202714	NDA	KYPROLIS	CARFILZOMIB	8	31
202806	NDA	TAFINLAR	DABRAFENIB MESYLATE	72	152
202811	NDA	LINZESS	LINACLOTIDE	0	1
202833	NDA	PICATO	INGENOL MEBUTATE	0	19
202834	NDA	FYCOMPA	PERAMPANEL	4	24
202992	NDA	AUBAGIO	TERIFLUNOMIDE	3	24
203085	NDA	STIVARGA	REGORAFENIB	37	110
203100	NDA	STRIBILD	COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR DISOPROXIL FUMARATE	0	1
203108	NDA	STRIVERDI RESPIMAT	OLODATEROL HYDROCHLORIDE	1	12
203188	NDA	KALYDECO	IVACAFTOR	4	48
203202	NDA	NORTHERA	DROXIDOPA	0	0
203214	NDA	XELJANZ	TOFACITINIB CITRATE	59	231
203314	NDA	TRESIBA	INSULIN DEGLUDEC	28	48
203341	NDA	BOSULIF	BOSUTINIB MONOHYDRATE	12	32
203388	NDA	ERIVEDGE	VISMODEGIB	28	70
203415	NDA	XTANDI	ENZALUTAMIDE	25	186
203441	NDA	GATTEX KIT	TEDUGLUTIDE RECOMBINANT	0	1
203469	NDA	ICLUSIG	PONATINIB HYDROCHLORIDE	19	111
203505	NDA	OSPHENA	OSPEMIFENE	0	0
203567	NDA	JUBLIA	EFINACONAZOLE	0	6
203568	NDA	KYNAMRO	MIPOMERSEN SODIUM	0	0
203585	NDA	SYNRIBO	OMACETAXINE MEPESUCCINATE	0	1
203756	NDA	COMETRIQ	CABOZANTINIB S-MALATE	1	10
203858	NDA	JUXTAPID	LOMITAPIDE MESYLATE	0	2
203971	NDA	XOFIGO	RADIUM RA-223 DICHLORIDE	9	28
203975	NDA	ANORO ELLIPTA	UMECLIDINIUM BROMIDE; VILANTEROL TRIFENATATE	0	0
204026	NDA	POMALYST	POMALIDOMIDE	339	599
204042	NDA	INVOKANA	CANAGLIFLOZIN	20	53

204063	NDA	TECFIDERA	DIMETHYL FUMARATE			52	200
204114	NDA	MEKINIST	TRAMETINIB DIMETHYL SULFOXIDE			59	109
204153	NDA	LUZU	LULICONAZOLE			0	0
204275	NDA	BREO ELLIPTA	FLUTICASONE FUROATE; VILANTEROL TRIFENATATE			1	7
204370	NDA	VRAYLAR	CARIPRAZINE HYDROCHLORIDE			0	0
204384	NDA	SIRTURO	BEDAQUILINE FUMARATE			0	1
204410	NDA	OPSUMIT	MACITENTAN			12	160
204427	NDA	KERYDIN	TAVABOROLE			0	0
204447	NDA	TRINTELLIX	VORTIOXETINE HYDROBROMIDE			0	4
204569	NDA	BELSOMRA	SUVOREXANT			0	4
204629	NDA	JARDIANCE	EMPAGLIFLOZIN			44	149
204671	NDA	SOVALDI	SOFOSBUVIR	yes		22	265
204684	NDA	IMPAVIDO	MILTEFOSINE			3	4
204760	NDA	MOVANTIK	NALOXEGOL OXALATE			0	0
204790	NDA	TIVICAY	DOLUTEGRAVIR SODIUM			4	20
204819	NDA	ADEMPAS	RIOCIGUAT			14	42
204886	NDA	ZONTIVITY	VORAPAXAR SULFATE			0	1
204958	NDA	KENGREAL	CANGRELOR			1	3
205266	NDA	ODOMZO	SONIDEGIB PHOSPHATE			7	12
205353	NDA	FARYDAK	PANOBINOSTAT LACTATE			42	130
205422	NDA	REXULTI	BREXPIPRAZOLE			6	121
205435	NDA	SIVEXTRO	TEDIZOLID PHOSPHATE			1	7
205437	NDA	OTEZLA	APREMILAST			225	694
205494	NDA	CERDELGA	ELIGLUSTAT TARTRATE			1	4
205552	NDA	IMBRUVICA	IBRUTINIB	yes		17	77
205598	NDA	MACRILEN	MACIMORELIN ACETATE		X		
205677	NDA	HETLIOZ	TASIMELTEON			0	0
205718	NDA	AKYNZEO	NETUPITANT; PALONOSETRON HYDROCHLORIDE			0	0
205739	NDA	VELTASSA	PATIROMER SORBITEX CALCIUM			0	2
205750	NDA	CHOLBAM	CHOLIC ACID			0	1
205755	NDA	ZYKADIA	CERITINIB	yes		32	57
205832	NDA	OFEV	NINTEDANIB ESYLATE	yes		62	170
205834	NDA	HARVONI	LEDIPASVIR; SOFOSBUVIR	yes		141	588
205836	NDA	BRIVIACT	BRIVARACETAM			7	17
205858	NDA	ZYDELIG	IDELALISIB	yes		60	136
206038	NDA	ORKAMBI	IVACAFTOR; LUMACAFTOR	yes		147	371
206143	NDA	CORLANOR	IVABRADINE HYDROCHLORIDE			45	132
206162	NDA	LYNPARZA	OLAPARIB			26	81
206192	NDA	COTELLIC	COBIMETINIB FUMARATE			42	97
206256	NDA	BELEODAQ	BELINOSTAT			0	5
206316	NDA	SAVAYSA	EDOXABAN TOSYLATE			0	0
206333	NDA	KYBELLA	DEOXYCHOLIC ACID			0	0

206334	NDA	ORBACTIV	ORITAVANCIN DIPHOSPHATE			0	1
206426	NDA	RAPIVAB	PERAMIVIR			33	46
206488	NDA	EXONDYS 51	ETEPLIRSEN			0	0
206494	NDA	AVYCAZ	AVIBACTAM SODIUM; CEFTAZIDIME			0	0
206500	NDA	VARUBI	ROLAPITANT HYDROCHLORIDE			0	2
206619	NDA	VIEKIRA PAK (COPACKAGED)	DASABUVIR SODIUM ; OMBITASVIR; PARITAPREVIR; RITONAVIR	yes		30	466
206709	NDA	DIACOMIT	STIRIPENTOL		X		
206829	NDA	ZERBAXA	CEFTOLOZANE SULFATE; TAZOBACTAM SODIUM			2	12
206843	NDA	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE			276	529
206940	NDA	VIBERZI	ELUXADOLINE			0	0
206947	NDA	LENVIMA	LENVATINIB MESYLATE			41	89
207078	NDA	LOKELMA	SODIUM ZIRCONIUM CYCLOSILICATE			0	1
207103	NDA	IBRANCE	PALBOCICLIB	yes		139	507
207145	NDA	XADAGO	SAFINAMIDE MESYLATE			3	3
207318	NDA	NUPLAZID	PIMAVANSERIN TARTRATE	yes		7	279
207500	NDA	CRESEMBA	ISAVUCONAZONIUM SULFATE			2	13
207533	NDA	ARISTADA	ARIPIPRAZOLE LAUROXIL			0	0
207561	NDA	GENVOYA	COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE			18	42
207620	NDA	ENTRESTO	SACUBITRIL; VALSARTAN			181	604
207695	NDA	EUCRISA	CRISABOROLE			78	322
207795	NDA	VYZULTA	LATANOPROSTENE BUNOD			0	13
207924	NDA	OLUMIANT	BARICITINIB			53	123
207947	NDA	UPTRAVI	SELEXIPAG			7	93
207953	NDA	YONDELIS	TRABECTEDIN			32	86
207981	NDA	LONSURF	TIPIRACIL HYDROCHLORIDE; TRIFLURIDINE			19	89
207988	NDA	ZURAMPIC	LESINURAD			0	0
207997	NDA	RYDAPT	MIDOSTAURIN	yes		68	133
207999	NDA	OCALIVA	OBETICHOLIC ACID			0	27
208051	NDA	NERLYNX	NERATINIB MALEATE			0	0
208065	NDA	TAGRISSO	OSIMERTINIB MESYLATE	yes		35	76
208073	NDA	XIIDRA	LIFITEGRAST		X		
208078	NDA	FIRDAPSE	AMIFAMPRIDINE PHOSPHATE	yes		2	19
208082	NDA	AUSTEDO	DEUTETRABENAZINE			4	17
208114	NDA	DEFITELIO	DEFIBROTIDE SODIUM			7	20
208169	NDA	XURIDEN	URIDINE TRIACETATE	yes		0	0
208254	NDA	RHOPRESSA	NETARSUDIL DIMESYLATE		X		
208261	NDA	ZEPATIER	ELBASVIR; GRAZOPREVIR	yes		10	48
208325	NDA	PARSABIV	ETELCALCETIDE			11	41
208341	NDA	EPCLUSA	SOFOSBUVIR; VELPATASVIR	yes		28	86
208383	NDA	BEVYXXA	BETRIXABAN		X		
208434	NDA	ALECENSA	ALECTINIB HYDROCHLORIDE	yes		23	54
208447	NDA	ZEJULA	NIRAPARIB TOSYLATE	yes		38	283

208462	NDA	NINLARO	IXAZOMIB CITRATE			104	282
208471	NDA	ADLYXIN	LIXISENATIDE			3	9
208573	NDA	VENCLEXTA	VENETOCLAX	yes		122	245
208610	NDA	BAXDELA	DELAFLOXACIN MEGLUMINE			0	0
208623	NDA	GALAFOLD	MIGALASTAT HYDROCHLORIDE			0	0
208627	NDA	TPOXX	TECOVIRIMAT		X		
208684	NDA	EMFLAZA	DEFLAZACORT			0	0
208700	NDA	LUTATHERA	LUTETIUM DOTATATE LU-177			1	1
208716	NDA	VERZENIO	ABEMACICLIB	yes		8	37
208743	NDA	TYMLOS	ABALOPARATIDE			0	2
208745	NDA	TRULANCE	PLECANATIDE			0	19
208772	NDA	ALUNBRIG	BRIGATINIB	yes		12	17
208794	NDA	XERMELO	TELOTRISTAT ETIPRATE			24	453
208854	NDA	SYMPROIC	NALDEMEDINE TOSYLATE			0	10
208945	NDA	XEPI	OZENOXACIN			0	0
209092	NDA	KISQALI	RIBOCICLIB SUCCINATE	yes		92	201
209115	NDA	RUBRACA	RUCAPARIB CAMSYLATE	yes		16	184
209176	NDA	RADICAVA	EDARAVONE			12	34
209195	NDA	VOSEVI	SOFOSBUVIR; VELPATASVIR; VOXILAPREVIR	yes		5	25
209229	NDA	LUCEMYRA	LOFEXIDINE HYDROCHLORIDE			0	0
209241	NDA	INGREZZA	VALBENAZINE TOSYLATE	yes		4	163
209299	NDA	TAVALISSE	FOSTAMATINIB DISODIUM			0	9
209363	NDA	SOLOSEC	SECNIDAZOLE			0	0
209394	NDA	MAVYRET	GLECAPREVIR; PIBRENTASVIR	yes		11	77
209521	NDA	SEYSARA	SARECYCLINE HYDROCHLORIDE		X		
209531	NDA	SPINRAZA	NUSINERSEN SODIUM			15	63
209570	NDA	BENZNIDAZOLE	BENZNIDAZOLE			0	0
209606	NDA	IDHIFA	ENASIDENIB MESYLATE			14	37
209627	NDA	ANNOVERA	ETHINYL ESTRADIOL; SEGESTERONE ACETATE		X		
209637	NDA	OZEMPIC	SEMAGLUTIDE			1	20
209776	NDA	VABOMERE	MEROPENEM; VABORBACTAM			0	0
209803	NDA	STEGLATRO	ERTUGLIFLOZIN			2	11
209816	NDA	NUZYRA	OMADACYCLINE TOSYLATE		X		
209936	NDA	ALIQOPA	COPANLISIB DIHYDROCHLORIDE			1	4
209939	NDA	PREVYMIS	LETERMOVIR	yes		0	5
210166	NDA	MOTEGRITY	PRUCALOPRIDE SUCCINATE			1	1
210238	NDA	DOPTELET	AVATROMBOPAG MALEATE			0	12
210251	NDA	BIKTARVY	BICTEGRAVIR SODIUM; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE			17	55
210259	NDA	CALQUENCE	ACALABRUTINIB	yes		15	33
210303	NDA	ZEMDRI	PLAZOMICIN SULFATE			0	0
210365	NDA	EPIDIOLEX	CANNABIDIOL		X		
210450	NDA	ORILISSA	ELAGOLIX SODIUM			1	42

210491	NDA	SYMDEKO	IVACAFTOR; IVACAFTOR, TEZACAFTOR	yes		81	226
210493	NDA	AKYNZEO	FOSNETUPITANT CHLORIDE HYDROCHLORIDE; PALONOSETRON HYDROCHLORIDE			0	0
210496	NDA	BRAFTOVI	ENCORAFENIB			0	0
210498	NDA	MEKTOVI	BINIMETINIB			0	0
210589	NDA	OMEGAVEN	FISH OIL TRIGLYCERIDES			0	1
210598	NDA	YUPELRI	REVEFENACIN			0	7
210656	NDA	DAURISMO	GLASDEGIB			12	25
210795	NDA	KRINTAFEL	TAFENOQUINE SUCCINATE	yes		17	28
210806	NDA	PIFELTRO	DORAVIRINE			0	2
210854	NDA	XOFLUZA	BALOXAVIR MARBOXIL			25	352
210861	NDA	VITRAKVI	LAROTRECTINIB	yes		6	8
210867	NDA	MOXIDECTIN	MOXIDECTIN		X		
210868	NDA	LORBRENA	LORLATINIB	yes		65	137
210910	NDA	AEMCOLO	RIFAMYCIN		X		
210922	NDA	ONPATTRO	PATISIRAN SODIUM	yes		15	49
210923	NDA	MULPLETA	LUSUTROMBOPAG			5	7
210951	NDA	ERLEADA	APALUTAMIDE			2	46
211109	NDA	XERAVA	ERAVACYCLINE DIHYDROCHLORIDE			0	0
211155	NDA	COPIKTRA	DUVELISIB			4	24
211172	NDA	TEGSEDI	INOTERSEN SODIUM			0	0
211192	NDA	TIBSOVO	IVOSIDENIB			2	17
211288	NDA	VIZIMPRO	DACOMITINIB			1	3
211349	NDA	XOSPATA	GILTERITINIB FUMARATE			42	85
211651	NDA	TALZENNA	TALAZOPARIB TOSYLATE			9	15
761025	BLA	PRAXBIND	IDARUCIZUMAB	yes		2	10
761029	BLA	ZINBRYTA	DACLIZUMAB			0	7
761032	BLA	SILIQ	BRODALUMAB			3	6
761033	BLA	CINQAIR	RESLIZUMAB			0	0
761034	BLA	TECENTRIQ	ATEZOLIZUMAB	yes		136	285
761035	BLA	EMPLICITI	ELOTUZUMAB	yes		45	88
761036	BLA	DARZALEX	DARATUMUMAB	yes		130	269
761037	BLA	KEVZARA	SARILUMAB			12	37
761038	BLA	LARTRUVO	OLARATUMAB	yes		18	40
761040	BLA	BESPONSA	INOTUZUMAB OZOGAMICIN	yes		22	32
761046	BLA	ZINPLAVA	BEZLOTOXUMAB			0	1
761047	BLA	MEPSEVII	VESTRONIDASE ALFA-VJBK			0	0
761049	BLA	BAVENCIO	AVELUMAB	yes		26	59
761051	BLA	POTELIGEO	MOGAMULIZUMAB-KPKC	yes		6	31
761052	BLA	BRINEURA	CERLIPONASE ALFA	yes		1	4
761053	BLA	OCREVUS	OCRELIZUMAB	yes		88	279
761055	BLA	DUPIXENT	DUPILUMAB	yes		13	179
761061	BLA	TREMFYA	GUSELKUMAB			13	47
761063	BLA	EMGALITY	GALCANEZUMAB-GNLM			210	535

761065	BLA	TROGARZO	IBALIZUMAB-UIYK	yes	X		
761067	BLA	ILUMYA	TILDRAKIZUMAB-ASMN			0	0
761068	BLA	CRYSVITA	BUROSUMAB-TWZA	yes		0	14
761069	BLA	IMFINZI	DURVALUMAB	yes		0	0
761070	BLA	FASENRA	BENRALIZUMAB			4	49
761077	BLA	AIMOVIG	ERENUMAB-AOOE			52	2075
761079	BLA	PALYNZIQ	PEGVALIASE-PQPZ			6	57
761083	BLA	HEMLIBRA	EMICIZUMAB	yes		1	16
761089	BLA	AJOVY	FREMANEZUMAB-VFRM			98	261
761090	BLA	TAKHZYRO	LANADELUMAB (SHP643)	yes		49	88
761092	BLA	REVCOVI	ELAPEGADEMASE-LVLR		X		
761094	BLA	OXERVATE	CENEGERMIN-BKBJ	yes	X		
761097	BLA	LIBTAYO	CEMIPLIMAB-RWLC	yes		24	49
761102	BLA	ASPARLAS	CALASPARGASE PEGOL-MKNL		X		
761104	BLA	LUMOXITI	MOXETUMOMAB PASUDOTOX-TDFK			0	2
761107	BLA	GAMIFANT	EMAPALUMAB-LZSG	yes		0	2
761108	BLA	ULTOMIRIS	RAVULIZUMAB-CWVZ			41	53
761116	BLA	ELZONRIS	TAGRAXOFUSP-ERZS	yes	X		

APPENDIX C: DESCRIPTION OF MATCHING PROCEDURE

Our empirical approach is a difference-in-differences methodology that uses matching to define the treatment and control groups. As described in Section 5.1, matching is used to identify pre-2012 (pre-BTD) treatment and control drugs, such that the most similar and comparable drugs are matched in the pre- and post-2012 periods. Our algorithm matches exactly on the drug's small molecule (vs. biologic) status. We also match coarsely on a drug's access to key FDA review programs (described in detail in Appendix A)—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 firm. Matching on the drug's type, expedited regulatory review programs, known pre-approval safety risks (as measured by boxed warnings), and therapeutic category will minimize key differences across drugs that influence time-to-market and post-approval safety risks. 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.

Notably, we do not use matching to identify control drugs in a contemporaneous sample of drugs – i.e., we do not match post-2012 ("true") BTD drugs with a subset of post-2012 non-BTD drugs to identify the set of contemporaneous control group drugs. Matching on observables, given such non-random determination of a "true" BTD group would be more likely to produce a poor control group, comprised of products that are simply poor comparators (and doing so would bias our estimates upwards). Instead, we identify comparator products by matching on all observables but on a sample of drugs that existed before the BTD was created.

For example, consider an actual BTD drug, approved in 2014 that could be matched to two potential controls, one approved in 2011 and another 2014 (that both benefited from the FDA's Accelerated Approval program, both received Priority Review, were not approved with a boxed warning, and were both commercialized by privately held biotechnology companies). In this case we would match this BTD to the drug that received approval in 2011 because we think that matching to the drug approved in 2014 would give us spuriously large estimates of the BTD program.

Of course, this approach by itself, is insufficient, because there could be general improvements in the quality of medicines or regulatory approval over time (which will look like the BTD program creating these improvements). To remove this source of bias, we crease a control group of non-BTD drugs and find controls for them in the pre-BTD period. This permits a difference-in-differences design for comparing "breakthrough" (and similar) drugs in the pre- and post-periods to non-breakthrough (and similar) drugs in the pre- and post-periods, respectively and using the non-breakthrough drugs as a way to account for any potential differences in outcomes such as adverse-event reporting and R&D practices over time. As long as improvements in these outcomes are the same for drugs with breakthrough designation (true and matched) and for drugs without this designation (true and matched) in the pre-BTD era, then we can identify the causal effect of the breakthroughs program.

Appendix Table C1 describe the final samples of treatment and control groups. The matching algorithm identifies 29 matches for the 60 BTD drugs and 95 matches for the 167 non-BTD drugs. We repeat this matching strategy for the set of 167 non-BTD drugs approved after July 9, 2012 to identify the matched control group for non-BTD drugs. Overall, 31 drugs (eight 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 the pre-2012 treatment or control groups.[1] 45 drugs that were approved 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.

Appendix Table C2 compares drug characteristics across the true and imputed BTD drug samples. Notably, apart from one descriptor, there are no longer statistically significant differences between the two samples.

Table 2 presents summary statistics on the matched sample. As in the unmatched sample, BTD products are associated with faster time-to-approval and higher pre-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 2 (relative to Table

[1] 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.

1), whereas differences between the two groups in both measures of adverse events rates *narrow* in Table 2 (relative to Table 1).

Table C1: Synthetic Treatment and Control Group Counts

	Total (1)	Non-BTD (2)	BTD (3)	Other (4)
Pre-BTD Program	169	95 (Imputed Non-BTD)	29 (Imputed BTD)	45
Post-BTD Program	227	167 (True Non-BTD)	60 (True BTD)	
Total	396	262	89	45

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 C2: Comparing True and Imputed Drugs

	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. BTD Drugs	True		Imputed		
	N = 60		N = 29		
Small Molecule (0/1)	0.57	0.50	0.59	0.50	0.86
Priority Review (0/1)	0.98	0.13	0.97	0.19	0.60
Fast Track (0/1)	0.50	0.50	0.45	0.51	0.65
Accelerated Approval (0/1)	0.35	0.48	0.24	0.44	0.31
Boxed Warning (0/1)	0.23	0.43	0.52	0.51	0.01**
ATC: Cancer (0/1)	0.57	0.50	0.66	0.48	0.43
ATC: Metabolism (0/1)	0.07	0.25	0.00	0.00	0.16
ATC: Antiinfectives (0/1)	0.15	0.36	0.07	0.26	0.28
ATC: Nervous System (0/1)	0.07	0.25	0.07	0.26	0.97
Private Firm (0/1)	0.23	0.43	0.24	0.44	0.93
Panel B. Non-BTD Drugs	True		Imputed		
	N = 167		N = 95		
Small Molecule (0/1)	0.79	0.41	0.89	0.31	0.03**
Priority Review (0/1)	0.49	0.50	0.29	0.46	0.00**
Fast Track (0/1)	0.36	0.48	0.16	0.37	0.00***
Accelerated Approval (0/1)	0.07	0.25	0.04	0.20	0.43
Boxed Warning (0/1)	0.33	0.47	0.40	0.49	0.25
ATC: Cancer (0/1)	0.28	0.45	0.24	0.43	0.56
ATC: Metabolism (0/1)	0.16	0.36	0.20	0.40	0.36
ATC: Antiinfectives (0/1)	0.13	0.34	0.06	0.24	0.08
ATC: Nervous System (0/1)	0.11	0.31	0.16	0.37	0.24
Private Firm (0/1)	0.18	0.39	0.29	0.46	0.03**

Notes: This table compares drug characteristics for true and imputed 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

APPENDIX D: ADDITIONAL ANALYSES AND ROBUSTNESS TESTS

ALTERNATIVE SPECIFICATIONS

In Appendix Tables D4-D5, we probe the robustness of our core results to an alternative functional form, ordinary least squares (OLS). We present results that are very similar to those reported in Table 4. While the results are not directly interpretable as elasticities, we find that at the mean of the data, the BTD designation causes time spent in Phase III to NDA submission to fall by 431 days relative to a mean of 1372 days (31 percent) and time between Phase II to NDA submission declines by 513 days relative to a mean of 2164 days (24 percent). Echoing our findings in Table 5, Appendix Table D5 shows no statistically significant evidence that the BTD was associated with differential subsequent rates of adverse events five months after approval (although somewhat elevated 3-month adverse event rates were seen, as in one specification of Table 5).

CLOSELY-RELATED 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 approved 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 technology). 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 Appendix Table D6, while not statistically significant, are similar in magnitude and direction to those reported in Tables 4. The adverse event results in Appendix Table D7 echo the main findings.

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 this assumption, we perform a placebo test where 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 Tables D8 and D9 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.

Appendix D: Additional Figures and Tables

Table D1: Impact on Adverse Event Levels

	3 Months AE Counts			5 Months AE Counts		
	(1)	(2)	(3)	(4)	(5)	(6)
BTD	0.036	-0.113	-0.479	0.090	-0.065	-0.310
	(0.479)	(0.504)	(0.481)	(0.441)	(0.459)	(0.457)
BTD x Post-2012	1.234**	1.327**	1.670**	0.799	1.079**	1.386**
	(0.545)	(0.552)	(0.511)	(0.520)	(0.514)	(0.509)
NDA		0.086	0.565**		-0.099	0.394
		(0.293)	(0.275)		(0.307)	(0.275)
Priority Review		0.226	0.043		0.089	0.122
		(0.258)	(0.312)		(0.251)	(0.271)
Private Firm		-0.460*	-0.185		-0.445**	-0.178
		(0.235)	(0.250)		(0.223)	(0.244)
Mean	24.25	24.25	24.25	88.70	88.70	88.70
Controls: Drug Characteristics	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y
Observations	351	351	351	351	351	351
log likelihood	-1158	-1157	-1138	-1593	-1592	-1575

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. Columns 1-3 examines the impact on the number of adverse events within 3 months of approval. Columns 4-6 estimates the effect on the number of adverse events within 5 months of approval. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 3 imply that drugs experience an increase in the number of adverse events in the 3 months after receiving BTD designation, on the order of $100 \times (\exp[1.670] - 1) = 431.22\%$, though the effects are not statistically significant. Robust standard errors are in parentheses. *p<0.10, **p<0.05, ***p<0.001

Table D2: Impact on Time-to-Market: No Controls For Manufacturer Type

	Reg Review			Phase III to Reg Review			Phase II to Reg Review		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
BTD	-0.276***	-0.138*	-0.068	-0.304**	-0.171	-0.111	-0.142	-0.094	-0.121
	(0.071)	(0.081)	(0.082)	(0.123)	(0.137)	(0.135)	(0.103)	(0.116)	(0.115)
BTD x Post-2012	0.012	-0.004	-0.052	-0.292*	-0.332**	-0.268*	-0.256*	-0.215*	-0.181
	(0.084)	(0.084)	(0.083)	(0.176)	(0.161)	(0.155)	(0.131)	(0.125)	(0.122)
NDA		-0.095**	-0.113**		0.151**	0.038		0.044	-0.006
		(0.037)	(0.039)		(0.077)	(0.087)		(0.069)	(0.075)
Priority Review		-0.232***	-0.235***		0.022	0.019		0.024	0.078
		(0.047)	(0.045)		(0.103)	(0.104)		(0.078)	(0.081)
Mean	258.32	258.32	258.32	1472.70	1472.70	1472.70	2237.01	2237.01	2237.01
Controls: Drug Characteristics	N	Y	Y	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y	N	N	Y
Observations	351	351	351	331	331	331	302	302	302
log likelihood	-2098	-2084	-2072	-2676	-2659	-2642	-2501	-2491	-2480

Notes: This table report estimates of the effect of the BTD program on time-to-market outcomes in regressions that do not control for manufacturer type. Observations are at the drug-level and estimates are from negative binomial regressions. Columns 1-3 examines the impact on the number of days between NDA submission to approval. Columns 4-6 estimates the effect on the number of days between the start of Phase III to NDA submission. Columns 7-9 shows the effect on the number of days between Phase II to NDA submission. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 4-6 face sample restrictions: there are fewer than 351 observations because we only observe time between the start of Phase III trials and NDA submission for 331 drugs. Columns 7-9 also face sample restrictions: of the 351 drugs in the sample, we only observe time between the start of Phase II trials and NDA submission for 302 drugs. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 4 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 $100 \times (\exp[-0.292] - 1)$ = -25.32%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table D3: Impact on Adverse Event Rates: No Controls For Manufacturer Type

	3 Months AE Rates			5 Months AE Rates		
	(1)	(2)	(3)	(4)	(5)	(6)
BTD	0.178	0.077	-0.312	0.780*	0.415	0.325
	(0.529)	(0.536)	(0.484)	(0.426)	(0.433)	(0.431)
BTD x Post-2012	0.527	0.449	0.729	0.054	0.210	0.463
	(0.606)	(0.601)	(0.552)	(0.515)	(0.510)	(0.485)
NDA		0.319	0.407*		0.386	0.696**
		(0.249)	(0.236)		(0.251)	(0.236)
Priority Review		0.201	0.229		0.562**	0.282
		(0.269)	(0.251)		(0.260)	(0.251)
Mean	2.43	2.43	2.43	3.31	3.31	3.31
Controls: Drug Characteristics	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y
Observations	195	195	195	258	258	258
log likelihood	-356	-354	-332	-520	-515	-495

Notes: This table report estimates of the effect of the BTD program on adverse event rates in regressions that do not control for manufacturer type. Observations are at the drug-level and estimates are from negative binomial regressions. Columns 1-3 examines the impact on adverse event rates within 3 months of approval. Columns 4-6 estimates the effect on adverse event rates within 5 months of approval. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 1-3 face sample restrictions: there are fewer than 351 observations because we only observe 3 month adverse event rates for 195 drugs. Columns 4-6 also face sample restrictions: of the 351 drugs in the sample, we only observe time between 5 month adverse event rates for 258 drugs. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 3 imply that drugs experience an increase in adverse event rates in the 3 months after receiving BTD designation, a statistically significant $100 \times (\exp[0.729] - 1) = 107.3\%$. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table D4: Impact on Time-to-Market: OLS Specification

	Reg Review			Phase III to Reg Review			Phase II to Reg Review		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
BTD	-64.152***	-30.651	-16.522	-284.600**	-225.279	-112.400	-223.160	-153.962	-186.750
	(16.328)	(18.605)	(18.955)	(134.128)	(176.624)	(181.724)	(190.417)	(225.576)	(250.649)
BTD x Post-2012	-2.180	-4.620	-14.782	-404.344**	-392.940*	-430.679*	-572.716**	-528.130**	-513.178**
	(19.775)	(19.890)	(19.759)	(203.920)	(219.417)	(223.202)	(252.998)	(251.819)	(259.705)
NDA		-26.281**	-30.811**		93.235	-1.980		83.713	-8.600
		(10.566)	(10.440)		(110.878)	(116.578)		(158.122)	(164.225)
Priority Review		-61.804***	-61.808***		133.730	144.814		106.682	241.324
		(12.725)	(12.684)		(182.731)	(195.713)		(206.348)	(223.914)
Private Firm		1.968	3.709		408.163**	363.942*		342.212*	340.198*
		(11.926)	(12.118)		(195.447)	(194.175)		(180.103)	(182.438)
Mean	258.32	258.32	258.32	1372.31	1372.31	1372.31	2164.22	2164.22	2164.22
Controls: Drug Characteristics	N	Y	Y	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y	N	N	Y
Observations	351	351	351	331	331	331	302	302	302

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. Columns 1-3 examines the impact on the number of days between NDA submission to approval. Columns 4-6 estimates the effect on the number of days between the start of Phase III to NDA submission. Columns 7-9 shows the effect on the number of days between Phase II to NDA submission. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 4-6 face sample restrictions: there are fewer than 351 observations because we only observe time between the start of Phase III trials and NDA submission for 331 drugs. Columns 7-9 also face sample restrictions: of the 351 drugs in the sample, we only observe time between the start of Phase II trials and NDA submission for 302 drugs. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table D5: Impact on Adverse Event Rates: OLS Specification

	3 Months AE Rates			5 Months AE Rates		
	(1)	(2)	(3)	(4)	(5)	(6)
BTD	0.039	-0.635	-0.747	1.034	0.024	0.374
	(0.418)	(0.733)	(0.656)	(0.811)	(1.071)	(1.081)
BTD x Post-2012	1.786*	1.922*	2.380**	2.540	3.061	3.230
	(1.029)	(1.005)	(1.057)	(1.968)	(1.947)	(2.015)
NDA		0.083	0.623		1.518	2.200**
		(0.734)	(0.792)		(0.990)	(1.069)
Priority Review		0.334	-0.046		1.967*	1.755
		(0.685)	(0.696)		(1.047)	(1.408)
Private Firm		-1.264**	-1.225**		-1.460*	-1.379
		(0.622)	(0.568)		(0.807)	(0.848)
Mean	2.43	2.43	2.43	3.31	3.31	3.31
Controls: Drug Characteristics	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y
Observations	195	195	195	258	258	258

Notes: This table report estimates of the effect of the BTD program on adverse event rates using OLS specifications. Observations are at the drug-level. Columns 1-3 examines the impact on adverse event rates within 3 months of approval. Columns 4-6 estimates the effect on adverse event rates within 5 months of approval. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 1-3 face sample restrictions: there are fewer than 351 observations because we only observe 3 month adverse event rates for 195 drugs. Columns 4-6 also face sample restrictions: of the 351 drugs in the sample, we only observe time between 5 month adverse event rates for 258 drugs. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table D6: Impact on Time-to-Market: Restricted to 2010-2018 Approvals

	Reg Review			Phase III to Reg Review			Phase II to Reg Review		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
BTD	-0.262**	-0.127	-0.008	-0.336**	-0.267*	-0.182	-0.326**	-0.340**	-0.358**
	(0.094)	(0.094)	(0.101)	(0.116)	(0.141)	(0.141)	(0.121)	(0.125)	(0.123)
BTD x Post-2012	-0.002	0.003	-0.103	-0.261	-0.284*	-0.255	-0.072	0.013	0.051
	(0.104)	(0.098)	(0.106)	(0.171)	(0.162)	(0.166)	(0.146)	(0.138)	(0.138)
NDA		-0.094**	-0.120**		0.101	0.010		0.041	0.013
		(0.040)	(0.042)		(0.083)	(0.095)		(0.068)	(0.074)
Priority Review		-0.254***	-0.252***		0.092	0.059		0.046	0.073
		(0.046)	(0.044)		(0.115)	(0.113)		(0.083)	(0.084)
Private Firm		-0.023	-0.027		0.201*	0.140		0.102	0.087
		(0.045)	(0.045)		(0.105)	(0.102)		(0.076)	(0.069)
Mean	259.82	259.82	259.82	1527.77	1527.77	1527.77	2347.97	2347.97	2347.97
Controls: Drug Characteristics	N	Y	Y	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y	N	N	Y
Observations	300	300	300	281	281	281	269	269	269
log likelihood	-1771	-1753	-1740	-2286	-2271	-2259	-2241	-2229	-2220

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. Columns 1-3 examines the impact on the number of days between NDA submission to approval. Columns 4-6 estimates the effect on the number of days between the start of Phase III to NDA submission. Columns 7-9 shows the effect on the number of days between Phase II to NDA submission. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 4-6 face sample restrictions: of the 300 drugs approved between 2010 and 2018, we only observe time between the start of Phase III trials and NDA submission for 281 drugs. Columns 7-9 also face sample restrictions: we only observe time between the start of Phase II trials to NDA submission for 269 drugs. 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 $100 \times (\exp[-0.261] - 1)$ = -22.97%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table D7: Impact on Adverse Event Rates: Restricted to 2010-2018 Approvals

	3 Months AE Rates			5 Months AE Rates		
	(1)	(2)	(3)	(4)	(5)	(6)
BTD	-0.164	-0.329	-0.504	0.985**	0.494	0.340
	(0.604)	(0.521)	(0.476)	(0.482)	(0.458)	(0.470)
BTD x Post-2012	0.868	0.849	0.981*	-0.149	0.092	0.413
	(0.674)	(0.588)	(0.532)	(0.564)	(0.514)	(0.533)
NDA		0.296	0.337		0.364	0.716**
		(0.256)	(0.236)		(0.263)	(0.248)
Priority Review		0.125	0.173		0.781**	0.644**
		(0.291)	(0.264)		(0.291)	(0.259)
Private Firm		-0.789**	-0.904***		-0.752**	-0.855***
		(0.300)	(0.252)		(0.278)	(0.245)
Mean	2.76	2.76	2.76	3.79	3.79	3.79
Controls: Drug Characteristics	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y
Observations	160	160	160	215	215	215
log likelihood	-315	-310	-289	-467	-457	-433

Notes: This table report estimates of the effect of the BTD program on adverse event rates for the sample of drugs approved between 2010 and 2018. Observations are at the drug-level and estimates are from negative binomial regressions. Columns 1-3 examines the impact on adverse event rates within 3 months of approval. Columns 4-6 estimates the effect on adverse event rates within 5 months of approval. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 1-3 face sample restrictions: there are fewer than 300 observations because we only observe 3 month adverse event rates for 160 drugs. Columns 4-6 also face sample restrictions: of the 312 drugs in the sample, we only observe time between 5 month adverse event rates for 215 drugs. Exponentiating the coefficients and differencing from one yield numbers interpretable as elasticities. For example, the estimates in column 3 imply that drugs experience an increase in adverse event rates in the 3 months after receiving BTD designation, a statistically significant $100 \times$ (exp[0.981] - 1) = 166.71%. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table D8: Impact on Time-to-Market: Fast Track as Placebo

	Reg Review			Phase III to Reg Review			Phase II to Reg Review		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Fast	-0.206**	-0.079	-0.059	-0.067	0.016	0.106	-0.091	-0.023	0.024
	(0.081)	(0.082)	(0.085)	(0.092)	(0.095)	(0.096)	(0.085)	(0.087)	(0.085)
Fast x Post-2012	0.102	0.113	0.100	-0.029	-0.082	-0.085	0.010	-0.015	-0.064
	(0.093)	(0.090)	(0.091)	(0.148)	(0.141)	(0.134)	(0.115)	(0.114)	(0.113)
NDA		-0.066*	-0.097**		0.242**	0.117		0.138**	0.094
		(0.039)	(0.041)		(0.076)	(0.086)		(0.064)	(0.068)
Priority Review		-0.271***	-0.257***		-0.056	-0.050		-0.034	-0.003
		(0.047)	(0.047)		(0.094)	(0.094)		(0.068)	(0.068)
Private Firm		0.006	-0.002		0.182*	0.138		0.083	0.087
		(0.046)	(0.047)		(0.098)	(0.090)		(0.070)	(0.067)
Mean	260.75	260.75	260.75	1474.96	1474.96	1474.96	2244.90	2244.90	2244.90
Controls: Drug Characteristics	N	Y	Y	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y	N	N	Y
Observations	341	341	341	321	321	321	298	298	298
log likelihood	-2055	-2036	-2026	-2609	-2586	-2566	-2473	-2458	-2450

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. The sample for this placebo tests consists of 341 drugs. Observations are at the drug-level and estimates are from negative binomial regressions. Columns 1-3 examines the impact on the number of days between NDA submission to approval. Columns 4-6 estimates the effect on the number of days between the start of Phase III to NDA submission. Columns 7-9 shows the effect on the number of days between Phase II to NDA submission. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 4-6 face sample restrictions: of the 341 drugs in the sample, we only observe time between the start of Phase III trials and NDA submission for 321 drugs. Columns 7-9 also face sample restrictions: we only observe time between the start of Phase II trials to NDA submission for 298 drugs. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001

Table D9: Impact on Adverse Event Rates: Fast Track as Placebo

	3 Months AE Rates			5 Months AE Rates		
	(1)	(2)	(3)	(4)	(5)	(6)
Fast	0.606	0.537	0.810**	0.592	0.500	0.296
	(0.416)	(0.408)	(0.389)	(0.373)	(0.376)	(0.393)
Fast x Post-2012	-0.511	-0.457	-0.344	-0.184	-0.359	-0.052
	(0.477)	(0.481)	(0.455)	(0.444)	(0.439)	(0.450)
NDA		0.298	0.353		0.319	0.491**
		(0.242)	(0.224)		(0.248)	(0.243)
Priority Review		0.245	0.153		0.732**	0.523**
		(0.239)	(0.224)		(0.227)	(0.228)
Private Firm		-0.608**	-0.761**		-0.458*	-0.559**
		(0.281)	(0.242)		(0.269)	(0.248)
Mean	2.61	2.61	2.61	3.32	3.32	3.32
Controls: Drug Characteristics	N	Y	Y	N	Y	Y
Controls: Disease	N	N	Y	N	N	Y
Observations	188	188	188	251	251	251
log likelihood	-360	-355	-329	-504	-497	-479

Notes: This table report estimates of the effect of the BTD program on adverse event rates using drugs with Fast Track status as a placebo. The sample for this placebo tests consists of 341 drugs. Observations are at the drug-level and estimates are from negative binomial regressions. Columns 1-3 examines the impact on adverse event rates within 3 months of approval. Columns 4-6 estimates the effect on adverse event rates within 5 months of approval. Additional controls for drug characteristics include: Fast Track status; Accelerated Approval status; and whether the drug is approved with a boxed warning. Columns 1-3 face sample restrictions: there are fewer than 341 observations because we only observe 3 month adverse event rates for 188 drugs. Columns 4-6 also face sample restrictions: of the 396 drugs in the sample, we only observe time between 5 month adverse event rates for 251 drugs. Standard errors are in parentheses, and are clustered at the ATC level. Robust standard errors are in parentheses.
*p<0.10, **p<0.05, ***p<0.001