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Exploring the Impact of the Orphan Drug Act on Rare Disease Drug Development

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ABSTRACT

The Orphan Drug Act (ODA) of 1983 was designed to incentivise pharmaceutical development for rare diseases, which affect small patient populations, less than 200,000 Americans, that are often commercially unviable to treat. Despite this, only around 5% of the nearly 10,000 identified rare diseases have an FDA approved treatment. This paper uses orphan drug approval data from 1983 to 2026, alongside a control set of general drug approvals from 1983 to 2022, to examine the extent to which the ODA contributed to the growth of rare disease drug development. Correlation analysis, continuous trend analysis, interrupted time series and difference-in-differences are used to assess whether the ODA's introduction changed the trajectory of orphan drug approvals. This paper also attempts to isolate this effect from later confounding developments such as the 2012 FDASIA Breakthrough Therapy designation, as well as other broader industry-wide trends. Orphan drug approvals grew sixfold between 1983 and 2022, compared to general drugs growing 1.5 times during that same period. The most significant evidence of impact specific to orphan drugs emerged in 2012, while a comparable shift observed in 2017, following a reduction in the ODA's tax credit, could not be isolated from industry-wide trends. These findings suggest the ODA's market exclusivity provision should be attributed most of the credit for the acceleration in orphan drug development, although this cannot be proven with certainty. This paper contributes an analysis that separates data into distinct time periods and accounts for confounding factors, using statistical methods to evaluate the ODA's impact more precisely.

***Keywords*:** Innovation; New Molecular Entities (NME); Eroom's Law; Marketing Approval; Orphan Drug Designation; Orphan Drug Act; Rare Disease

INTRODUCTION

The Problems of Limited Drug Innovation

Only about 5% of the nearly 10,000 rare diseases that are identified have an FDA approved treatment, with nearly one in ten Americans affected by one of these conditions (GAO, 2024). For the vast majority of these conditions, no treatment has ever been studied in a clinical trial, with as few as 22% of rare diseases having ever been investigated in trials (Kruk, 2019). This gap reflects a lack of investment, not a

lack of scientific capability. For most rare diseases the innovation required to bring a treatment to market has simply never been attempted.

One hypothesis is that the lack of treatments is not because firms lack the ability to develop them, but because they lack the incentive to do so. Investment tends to concentrate where markets are largest and drugs are most commercially viable. This leads to rare diseases, which by definition impact the fewest patients, being consistently overlooked. This paper aims to examine why this is the case, and what policies have been implemented to correct this.

To explore this hypothesis, this paper studies the Orphan Drug Act of 1983 in the US. Data is collected from the FDA on orphan drug approvals from 1983 to 2026, alongside general drug approvals from 1983 to 2022 for comparison. Using descriptive statistics, correlation analysis, continuous trend analysis, interrupted time series and difference-in-differences this paper examines whether the ODA's introduction changed the trajectory of rare disease drug development, while attempting to isolate this effect from later developments such as the FDASIA. This paper found that orphan drug approvals grew sixfold between 1983 and 2022, compared to general drug approvals which grew only 1.5 times during the same period, with clear evidence of orphan-specific acceleration occurring around 2012.

Interestingly, when examining the 2017 reduction in the ODA's tax credit, a comparable shift in both orphan and general drug approvals is observed, suggesting it was caused by an industry wide shift, with limited evidence that the tax credit reduction led to a drop in orphan drug approvals.

These results have implications for which ODA mechanism is most effective to support rare disease drug development. Suggestive evidence shows that market exclusivity had the largest association with the acceleration of orphan drug growth, with tax credits seeming to play a smaller role. This suggests that policies which increase a firms' profit potential, such as extended market exclusivity, may be more effective than those that reduce development costs, such as tax credits.

Understanding whether the Orphan Drug Act has genuinely succeeded in its goal carries direct consequences for millions of Americans affected by rare diseases, the vast majority of which still lack an approved treatment. Understanding the effectiveness of this Act not only is relevant when law makers consider amendments to the Act, but also as other countries look at the ODA as a model for their own policy. Considering the types of incentives included in the ODA may also help inform policies in other areas of drug development or unrelated industries that aim to similarly cultivate increased innovation.

Whether the ODA's incentives came at a justified cost, to the government through grants and tax credits, or to consumers through higher prices, is an important consideration, expanded further later in this paper.

The remainder of this paper is organized as follows. The introduction continues by giving background on the Orphan Drug Act's design, its historical context and a review of existing literature and gaps this paper addresses. The Methods section describes the data and analytical approach this paper uses to evaluate the

ODA's impact. The Results section presents the finding of this analysis and what it means. Finally, the Discussion interprets these findings, considers limitations and discusses policy implications before concluding.

BACKGROUND

Patents: Definitions and Functions

Leading innovation consultants such as McKinsey and IDEO describe innovation as more than just generating new ideas. They define it as the ability to develop, implement and scale new products, services, processes or business models that create value in meaningful ways. Innovation also involves transforming ideas into measurable impacts and applying methods that enable promising concepts to grow successfully (Kent, 2024).

For the healthcare and drug development industry specifically, this innovation primarily takes two forms: the development of entirely new therapeutic compounds or repurposing existing already approved drugs for new therapeutic use.

Patents are one way that governments use to incentivize innovation.

A patent is an exclusive right that is given to the creator of a novel invention. It allows inventor legal protection to prevent the making, selling, using or importing of the patented product, process or composition. Patents have a limited term length and require disclosure of the invention's technical details, a trade off that allows others to learn from and build upon prior inventions once protection expires, serving a broader public purpose of accelerating innovation (WIPO, n.d.; Shear & Kelley, 2003). This exclusivity is crucial in cultivating innovation, as the legal protection it provides encourages greater investment in research and development. The increased profit potential it offers can help offset the costly, time intensive nature of bringing some inventions to market.

On another level, patents provide the necessary legal certainties required to secure funding for high cost sectors with a high risk of failure, such as pharmaceuticals. This allows new technologies to be developed and breakthrough ideas to be brought to market (ICC United Kingdom, 2025). However, the social cost that comes with the patent system must be considered against the benefits which they provide. The main social cost of patents is the temporary monopoly they grant to patent holders, allowing them to charge higher prices than they would under competition and reducing their incentive to innovate further. This may restrict access to the patented products or technology and slow the pace at which others can build upon it. This represents the trade offs that patents cause. The extent to which these benefits outweigh their costs depends heavily on the size and commercial viability of the market a given invention serves.

Why Patents Alone Fail to Incentivise Rare Disease Drug Development

In 1962, the United States Congress passed the Kefauver-Harris Amendment, which mandated that drug manufacturers must prove drugs that are safe and effective before introducing them to the market. The importance of this became apparent when the drug thalidomide, which was sold as a treatment for pregnant women from the late 1950s to early 1960s, led to birth defects and deaths of thousands of children nationally (Gang, 2024). The amendment established the modern Food and Drug Administration (FDA) approval system for therapeutics in the US. The new regulations required pharmaceutical companies to conduct far more rigorous studies in order to gather data and demonstrate that their products were effective and safe. Thus, conducting the study was a vital step in protecting Americans from harmful products. Yet this process has significantly increased the cost of developing drugs (Gang, 2024).

Consequently, many firms have reduced their scope to focus on diseases impacting a large number of people. This was because these drugs would have the biggest market and largest profit potential. This meant that diseases impacting relatively smaller populations, such as Amyotrophic lateral sclerosis (ALS), attracted little attention and/or investment from the industry (Alira Health, 2023). The term ‘orphan disease’ was adopted to describe these conditions. While each orphan drug may have individually impacted a small number of people, there are 6,000 to 8,000 orphan diseases, cumulatively impacting over 25 million Americans (Rhee, 2015).

While patents already grant inventors exclusive rights to profit from their inventions, this exclusivity alone does little to solve the specific problem facing orphan diseases. Even with patent protected market exclusivity, a disease affecting only a few thousand, or even a few hundred, patients rarely generates enough revenue to offset the sharply increased R&D costs imposed by the FDA's post 1962 requirements. Furthermore, patents are typically filed early in a drug's development. This means that a substantial part of the patent's limited term is consumed by lengthy clinical trials and approval process before the drug reaches market. Patents also do not help cover the costly development process, they only provide potential future profit later down the line. For a disease with a small patient population, this combination of eroded exclusivity window, a small addressable market and an absence of upfront support left little commercial incentive for firms to pursue treatment. To combat this the Orphan Drug Act was introduced in 1983.

The Orphan Drug Act

On January 4th 1983, the United States Congress passed the Orphan Drug Act. This act aimed to benefit companies producing ‘orphan drugs’ - which can be defined as any drug targeting disease that impacts fewer than 200,000 people in the US. The law provided several economic incentives including tax credits, fee waivers and extended market exclusivity to firms that produced the drugs. Market exclusivity grants firms seven years during which the FDA cannot approve another company’s version of the same drug for the same rare disease (Cytel, 2024). The Act has since been amended several times. It initially targeted drugs for which there was 'no reasonable expectation' that US sales could support development costs

(Kesselheim, 2010), a standard that proved difficult to assess, while requiring manufacturers to disclose sensitive financial projections. In 1984, Congress replaced this with a threshold defining a rare disease as conditions affecting fewer than 200,000 Americans. A 1985 amendment extended market exclusivity to unpatentable as well as patentable drugs, with a 1988 amendment requiring sponsors to obtain orphan drug designation before submitting marketing application (OIG, 2001). These policies aimed to cut the cost of producing these drugs and increase the potential profit in terms of making the production of orphan drugs commercially viable. Prior to this act, the limited number of affected patients made the development of such drugs unprofitable. Reflecting this lack of commercial incentive, a 1980 congressional study found that of 134 known drugs to treat orphan diseases, only 58 were on the market or under development (Gang 2024), leaving conditions such as Wilson's disease and Tourette's syndrome without any viable treatment (Wallis, 1982).

Companies developing drugs that impact fewer than 200,000 Americans can apply to the FDA for an 'orphan drug designation' for their treatment. Orphan drug designation and FDA approval are two distinct stages: obtaining a designation makes a firm eligible for the ODA's provision, but the drug must still undergo the standard clinical trials and approval process before reaching market (Gang, 2024).

One provision was a tax credit covering a portion of a firm's clinical testing costs. While it was initially set at 50% of the cost of conducting human clinical trials (OIG, 2001), it was later reduced to 25% under the 2017 Tax Cuts and Jobs Act (Briefs, 2025). Patient advocacy groups have argued this change weakens the incentive the ODA originally provided. Firms also benefit from fee waivers, exempting them from the substantial application fee normally charged when submitting a marketing application to the FDA, alongside the potential for accelerated or priority review in some cases. These provisions collectively reduce the cost of developing orphan drugs.

Grants were also made available to firms through the FDA's Office of Orphan Products Development (OOPD), providing funding to support clinical research assessing the safety and effectiveness of treatment for rare diseases. In fiscal year 2001, this grants program was projected to total approximately $12.5 million (OIG, 2001). Unlike tax credits, which reimburse costs only after they have been incurred, these grants provided firms with direct upfront funding, easing the financial burden of conducting costly clinical trials.

However, likely the most impactful provision was market exclusivity. When under a patent, drugs are granted 20 years of market exclusivity from the filing date, much of which is often consumed by the lengthy development, testing and approval process. The market exclusivity offered under the ODA is separate, beginning upon approval and lasting 7 years in which the FDA cannot approve similar drugs. This applies regardless of a drug's patent status and even for repurposed drugs. This delays competition and allows the firm a guaranteed window to recover development cost (Cytel, 2024).

LITERATURE REVIEW

In order to contextualise my own findings, the following section reviews the existing literature on the economics of pharmaceutical innovation and orphan drug policy. It considers prior work on the relationship between patent protection and R&D incentives, as well as studies specific to the Orphan Drug Act's role in rare disease drug development. This literature review identifies what has been achieved by prior research and what gaps are still yet to be filled that this paper can address.

Existing literature has largely established that the ODA has coincided with substantial growth in orphan drug development, typically using FDA orphan drug designations as the primary measure of impact (Kesselheim, 2010; Rodriguez-Monguio et al., 2017; Miller et al., 2021). However, this literature is predominantly descriptive, reporting trends in approvals over time with limited methods designed to isolate ODA's specific causal contribution to the rise in orphan drug approvals. For example, Kesselheim (2010) documents the sharp rise in orphan drug designations and approvals through 2009, yet does not test whether this growth exceeded what would have occurred without the ODA over the same period. This leaves doubt on how much of this growth is genuinely attributable to the ODA itself, instead of broader industry trends. This paper aims to address this gap by using differences-in-differences. There is also limited information on how the impacts of the ODA are felt in relation to newer policies such as FDASIA. As a result, the extent to which observed growth in orphan drug approvals can be attributed to the ODA itself remains insufficiently addressed. Existing work has generally only examined orphan drug growth in isolation, often failing to benchmark it against broader trends in non orphan drug development over the same time period.

The Short and Long Term Impacts

The ODA increased the incentives both to adapt existing drugs to target orphan diseases but also to invest in R&D to develop new drugs for orphan diseases. In the short term the impacts will be limited, this is because there will be a significant time lag before new drugs are able to be developed. According to research from Kesselheim the average time from IND to application was 3.8 years. There is 5.9 years from IND to NDA and 0.7 years until approval, so from IND to approval is 6.6 years. This does not include pre clinical trials before IND which are often roughly 2 years (Nona Biosciences)(Infinix Bio), but sometimes can take up to 6 years (McDowell). This means we can expect a time lag of 8-12 years for the Orphan Drug Act to have an impact. Thus most of the impacts felt in the first few years will be from existing generic drugs being reformulated to target orphan diseases. This was seen in the approval data with 34 approvals in the first 6 years more than doubling to 73 in the following 6 years (FDA), with approvals only increasing after that. Prior to the implementation of the ODA only ten drugs targeting orphan diseases were on the market for patient use (Roberts&Wadhwa, 2023), with only 34 drugs approved from 1967 to 1983 which would have qualified under the ODA (Kesselheim, 2010). In comparison, from when the ODA was introduced in 1983 to 2009 a total of 2,112 drugs have been assigned an orphan drug designation by the OOPD, with 347 (16 percent) of those being approved by the FDA as of the end of 2009 (Kesselheim, 2010).

As of November 28 2023, the FDA granted 6670 orphan drug designations, 1184 of which resulted in FDA approval (Saltonstall et al., 2023). Growth was substantial across the decades, with orphan drug designation more than doubling between the 1980s and 1990s, almost doubling between 1990s and 2000s and almost tripling between 2000s and 2010s (Miller et al., 2021). This period also saw the disappearance of the 'drug lag' that had characterized the 1980s and 1990s, when new drugs were often approved abroad well before reaching American patients. Orphan drugs have since become central to FDA innovation more broadly, now accounting for roughly two thirds of the FDA's most innovative drug approvals, a trend likely to continue (Monge et al., 2021). Recent CDER data directly reflects this shift. Orphan drugs made up 20 of 37 novel drugs approved in 2022, up from 26 of 50 in 2021 (FDA). Many analysts expect orphan drugs to represent a third of the global drug development pipeline in the near future (Senior&Hadjivasiliou, 2022).

However, not all orphan drugs reflect novel drug development. Studies indicate that the number of secondary indication approvals (repurposed drugs) has more than doubled in proportion since the 1980s, from 19% to 47% in the 2010s (Miller&Lanthier, 2018). This shift may reflect the dynamic Eroom's Law describes: the observation that the cost and difficulty of developing new drugs has risen over time (Scannell et al., 2012), pushing firms towards repurposing existing drugs rather than pursuing new drug research. Further research would be required to confirm this link directly.

The ODA has served a vital role in the development of several crucial drugs that would otherwise attract little commercial interest. Infant botulism, a rare neurological disease affecting roughly 100 American children annually, is one such case: too small a patient population to justify private sector investment on its own. The effective treatment that emerged was instead the product of a public sector effort, led by the California Department of Health Services, funded through OOPD grants and developed in close coordination with the FDA (Arnon, 2006). This case illustrates the ODA's grant funding pathway, distinct from the market exclusivity incentives most commonly associated with the Act.

The ODA has had an impact across multiple sections of healthcare. As of 2015 over 3600 drugs have been given an orphan drug designation with over 550 approved by the FDA. These drugs targeted over 277 rare diseases. The largest proportion of drug approvals were cancer therapeutics (31.9%), followed by infectious diseases excluding HIV (8.3%), hemophilia and other bleeding disorders (5.8%), followed by other diseases including growth failure, pulmonary arterial hypertension and transplant related designations (Rodriguez-Monguio et al., 2017).

Alongside this growth, the ODA's incentives have drawn significant criticism. A practice known as 'indication seeking' allows firms to obtain orphan designation for drugs already approved to treat far more common conditions. This allows them to capture exclusivity and tax benefits with limited benefit to rare disease patients. AbbVie's Humira, the best selling drug in history (Norman, 2017), alongside Keytruda, Enbrel and Avastin, have all been cited as examples of this practice. One analysis found that only around 21% of spending on such dual indication drugs went towards their orphan use, with the remainder

attributable to their non orphan indications (Commonwealth Fund, 2025). Orphan drugs have also grown distinctly more expensive : one study found that average annual cost of an orphan drug reached $218,872 per patient, compared to $12,798 for non orphan drugs (Commonwealth Fund, 2025). This raised concerns about affordability and long term sustainability for patients as well as healthcare systems as a whole. These pricing concerns are compounded by the fact that the ODA's tax credit reduced from 50% to 25% in 2017 without legislative hearings to substantiate the change (Saltonstall et al., 2023). This reflects ongoing tension between preserving incentives for genuinely underserved diseases and curbing benefits captured by already profitable drugs. Critics have also pointed to a concentration of orphan drug designation within a small number of therapeutic areas, with more than half of all applicants falling within oncology, neurology, hematology and gastroenterology (Commonwealth Fund, 2025), echoing the disease category imbalance.

While existing research on the ODA has been valuable in establishing broad trends, its largely descriptive nature leaves open questions, which are vital to answer for policy making, that this paper aims to address.

METHODS

Data Source

The primary dataset for this analysis is extracted from the FDA's public 'Search Orphan Drug Designation and Approvals' database (accessdata.fda.gov). Only orphan designated drugs that receive marketing approval were included. For each entry, the generic drug name, designation date and marketing approval date were recorded. To measure the number of approvals per year, the marketing approval date is used. Orphan drug designation and approval data were collected for the period 1983 to 2026. To provide a point of comparison, general drug approval data was also collected from fda.gov, covering the period 1983 to 2022. Where direct comparison between orphan and general drug approval trends are made, the analysis is restricted to the overlapping period of 1983-2022. Both datasets are limited to drugs approved by the FDA, therefore only reflecting the US drug market. In total 1,435 orphan drug approvals were identified across the study period (1983- July 2026).

Defining the Measure of Innovation

This paper measures the ODA's impact using the number of orphan drug approvals per year, encompassing new molecular entities, secondary indications and reformulations. This means the data considers a broad range of forms of innovation, as each of these approval types represents a genuine contribution to expanding treatment availability for rare diseases. Novel compounds and extensions to existing drugs both serve patient populations and provide treatment for rare diseases.

This approach differs from measures such as new molecular entities (NME) counts. An NME is a drug containing a new moiety (the active part of a drug molecule) that has never previously been approved by

the FDA. The use of NME as a measure of innovation helps prevent the double counting of existing drugs that are relaunched with new formulations, dosages or delivery methods due to requiring genuinely new moiety. This makes NME a more precise measure of genuine innovation and would more precisely isolate novel drug development. Yet it was deliberately not used as the primary measure in this analysis, as the paper aims to examine the impact of the ODA on the treatment of rare diseases, which repurposed and reformulated drugs do contribute to. In addition to this, there is a lack of a comprehensive orphan specific NME dataset covering both small molecule and biologic products across the full study period. This will mean however that the analysis presented does not fully separate novel drug development from repurposing.

R&D spend was also considered as an alternative measure of innovation, but was similarly not used. This was due to the effect described by Eroom's Law: the observation that the number of new drugs approved per billion dollars of R&D spending has roughly halved every nine years since the 1950s (Scannel et al., 2012). As a result, increased R&D spend was an unreliable basis for comparison across different time periods of multiple decades. R&D spend also was not used as a supplementary measure of innovation due to the lack of orphan specific R&D spend data.

No measure of innovation is perfect, as none can capture the quality of an innovation or the effort necessary to produce it. However, given the available data, orphan drug approval count remains a reasonable basis for this analysis. This is particularly true given the ODA's goal of increasing the availability of treatments for rare diseases. Thus approval count is a good proxy for this, as even reformulated drugs can be considered innovation as they were not previously used for that particular rare disease, representing an expansion of the treatment options available to patients and the outcome the ODA aimed to achieve. Approval volume is therefore treated throughout this paper as a proxy for growth in treatment availability for rare diseases, rather than a precise measure of scientific novelty.

Time Period Segmentation

Given the limited availability of pre-1983 data on orphan drugs, the analysis period effectively begins with the ODA's introduction in 1983. Approval data is segmented using key legislative and regulatory markers to help isolate the ODA's effects from later confounding developments. The primary periods bounded are 1983-2012, 2012-2017 and 2017-2026 (data for 2026 is only collected until July), corresponding to the ODA's initial implementation, the introduction of the FDASIA Breakthrough Therapy designation in 2012 and the reduction of the ODA's tax credits from 50% to 25% in 2017. Where relevant, these periods are further subdivided or divided differently for specific analysis.

Summary Stats

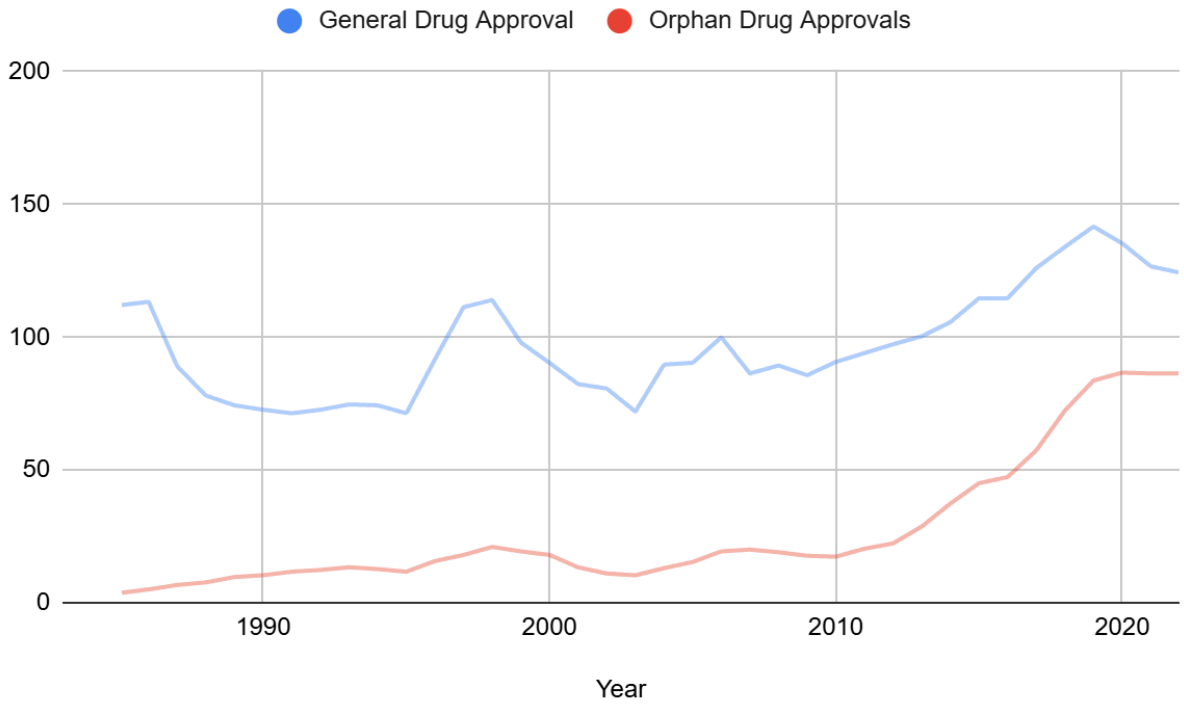

Figure 1. Orphan Drug Approvals compared to General Drug Approvals (Smoothed) 1983-2022 (FDA)

Across the full study period, a total of 1,435 orphan drug approvals were recorded between 1983 and 2026, with 3,921 general drug approvals between 1983 and 2022 used as a control. Orphan drug approvals averaged approximately 33 per year over the full period, compared to approximately 100 per year for general drug approvals. Breaking down these averages we see orphan drugs had large variation, as few as 2 approvals in 1983 to as high as 97 in 2025.

The most notable pattern in the data is a sharp rise in orphan drug approvals from the early 2010s. Average annual orphan drug approvals rose from approximately 14 between 1983 to 2012 to approximately 86 between 2018 and 2022. This was an increase of over 500%, more than 10 times the growth rate of general drug approvals, which grew by only 50% in the same period. This divergence, which is concentrated around a narrow window instead of occurring across the whole study period, motivated the use of period based and breakpoint specific analytical techniques such as difference-in-differences and interrupted time series, with continuous trend analysis used as a contrast to these two models. These models are described further below.

Confound Identification

Several factors beyond the ODA itself may have influenced orphan drug approval trends over the study period. The 2012 introduction of the FDASIA Breakthrough Therapy designation and the 2017 reduction in the ODA's tax credits are both addressed directly through the period boundaries described above, allowing any shifts in approval trends around these events to be examined and compared to understand the impacts attributable to the ODA. Other potential confounding factors in the healthcare industry as a whole such as increased investment in the biotech sector can be partially accounted for by using general drug approvals as a comparison group. Other factors such as advancement in genomic medicine and the reclassification of common diseases into smaller molecular subtypes, are unable to be addressed by this paper and are acknowledged as limitations on the interpretation of the results, further discussed below.

Analytical Approach

Summary statistics alone provide a useful overview of the data but cannot indicate how statistically meaningful these observations are or attribute them to any specific event. Correlation coefficients offer a first step beyond this, providing a simple measure of how closely orphan drug and general drugs move together over time. However, they are unable to establish whether this relationship changed at a specific point or gradually over time. Continuous trend analysis helps test whether the growth of orphan drug approvals follows a smooth linear pattern over time, yet it cannot analyse discrete shifts at specific points. Interrupted time series (ITS) analysis addresses this limitation by testing whether the trend in approvals shifts significantly at a specific break point, while accounting for pre-existing trends. However, ITS alone cannot distinguish whether an observed shift is specific to orphan drugs or reflects a broader, industry-wide trend. Difference-in-differences (DiD) analysis addresses this limitation by comparing orphan drug approvals against a control group (general drug approvals), isolating changes specific to orphan drugs from trends affecting the wider pharmaceutical industry.

Correlation coefficients are additionally calculated between orphan drugs and general drug approvals across the defined time periods. This helps assess the strength and direction of their relationship and how that evolved over time.

Continuous trend analysis is conducted using years since the ODA's introduction as the explanatory variable, allowing the analysis of approval trends as a function of time elapsed since 1983, rather than a categorical before/after comparison. This is estimated using the following formula: $Approvals_{it}=\beta_0+\beta_1(Orphan_i)+\beta_2(YearsSinceODA_t)+\beta_3(Orphan_i\times YearsSinceODA_t)+\varepsilon_{it}$, where β_3 represents the differential growth rate for orphan drugs relative to general drug trends. While less informative in isolation, this analysis complements the other approaches described above, contributing to a more comprehensive understanding of the ODA‘s impact over time.

Interrupted time series (ITS) analysis is applied independently to orphan drug approvals and general approvals at both 2012 and 2017 (Lopez Bernal et al., 2017), assessing whether the trend in each series shifted significantly at these markers. This is estimated using the following formula: $Approvals_t = \beta_0 +$

β_1(YearsCenteredt) + β_2(PostBreakt) + β_3(PostBreakt × YearsCenteredt) +εt, where β_2 represents the level shift at the chosen breakpoint and β3 represents the change in slope following the breakpoint. The results for orphan drugs and general drug approvals are then compared to help distinguish orphan specific trends from broader industry trends.

Difference-in-differences (DiD) analysis is used to compare orphan drug approvals, as the treatment group, against general drug approvals, as the control group (Angrist & Pischke, 2009). General drug approvals are used as the comparison group because they are subject to the same FDA approval process and broader regulatory and macroeconomic environment as orphan drugs, while remaining ineligible for the ODA's own incentives. This is estimated using the following formula: Approvalsit = β0 + β1(Orphani) + β2(Post1990t) + β3(Orphani × Post1990t) + εit, where β3 represents the estimated treatment effect of the ODA.

This analysis relies on the parallel trends assumption: in absence of the ODA, orphan and general drug approvals would have followed similar underlying trends over time. This assumption cannot directly be tested prior to 1983, due to the lack of orphan drug data prior to the ODA's introduction. Notably, the correlation analysis discussed above shows orphan and general drug approvals moving close to independently or at times even in opposite directions, between 1983 to 1989. This divergence would typically weaken confidence in the parallel trends assumption, however this paper instead interprets this divergence as reflecting the ODA's incentives not yet having taken effect during the transitional period. The assumption's validity from 1990 onwards therefore depends on this interpretation being correct. The assumption may also not hold perfectly due to separate factors, as orphan and general drugs may differ in average development times, eligibility for other regulatory pathways such as expedited review programs, and each group's sensitivity to broader biotechnology investment cycles.

1990 is used as the dividing point between pre and post ODA periods. While typically this marker is set at the date a policy is implemented, this was not done in this case due to the time lag in impact of the ODA and the absence of orphan drug data prior to 1983. 1990 was selected on the basis that new orphan drugs were expected to have limited impact within the first seven years of the ODA, due to the 7-10 year time lag in drug development, allowing this period to approximate a pre-treatment baseline. Earlier cutoffs such as 1985 were rejected as too early, since insufficient time would have passed for any ODA driven drug development to plausibly reach approval. Later cutoffs such as 1995 or beyond, were also rejected, as they would allow more time for unrelated confounding developments such as gradual increases in biotechnology investment, to accumulate within the pre-treatment period. This would make it harder to attribute any resulting shift to the ODA. 1990 was chosen as a balance between these two concerns, sitting at the lower bound of estimated development lag and supported by multiple robustness checks.

This approach carries important limitations: by departing from the clean before/after comparison DiD typically required and with the pre-1990 period bearing some impact from the ODA, the analysis may be less reliable. These limitations are discussed further below.

All statistical analysis was conducted in Google Sheets.

Results

RESULTS

Descriptive Numbers

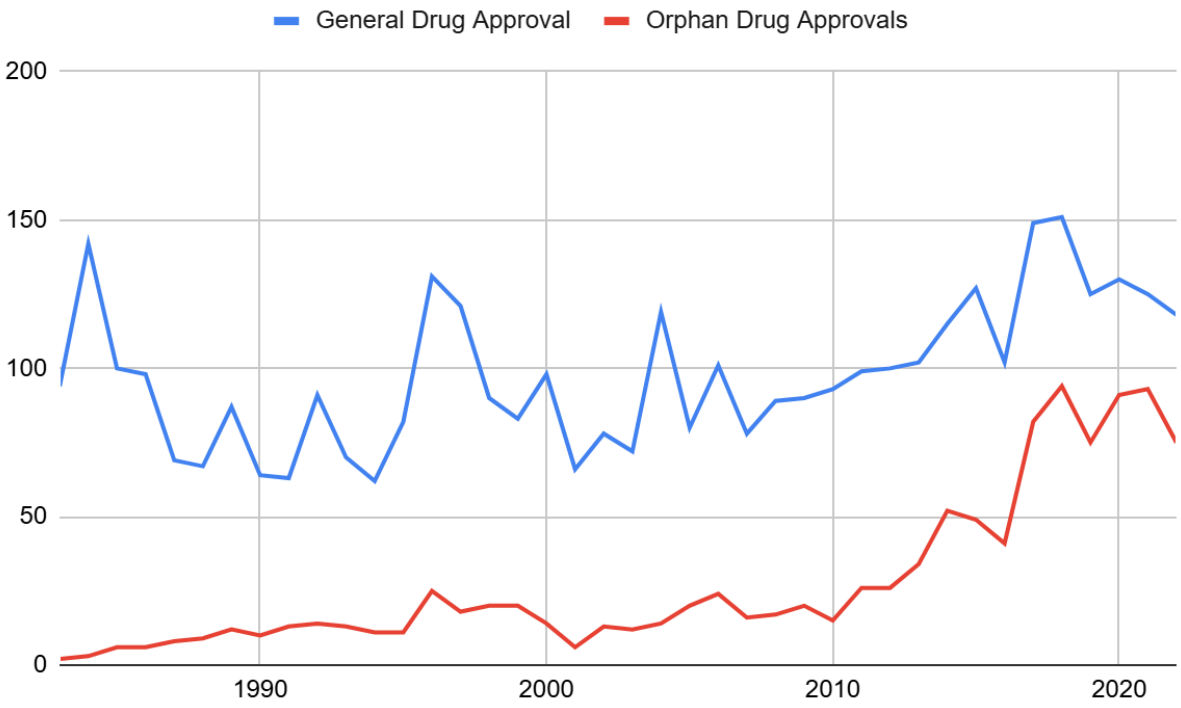

Figure 2. Orphan Drug Approvals compared to General Drug Approvals 1983-2022 (FDA)

Figure 2 shows the annual number of orphan drug approvals relative to general drug approvals from 1983 to 2022.

Orphan drug approvals remained below 9 throughout the mid 1980s, rising gradually to the low double digits by the early 1990s. A significant increase is observed from early to mid 2010s, with approvals rising from 26 in 2012 to 82 in 2017. Approvals then stabilized at a substantially higher range of 75 to 97

approvals from 2018 to 2025. Average annual orphan drug approvals rose from approximately 14 from 1983 to 2012 to approximately 52 between 2013 and 2017 and approximately 86 between 2018 and 2022.

In comparison between 1983 and 2012 general drug approvals rose from approximately 89 to approximately 119 from 2013 to 2017 to approximately 130 from 2018 to 2022. Notably the rise in general drugs was much lower than orphan drugs, with orphan drugs growing sixfold from 1983 to 2022, while general drugs only grew one and a half times in that same time period. This increase is the focus of this paper, and we will explore its behavior and causes in more detail in the analysis section.

Correlation Coefficients

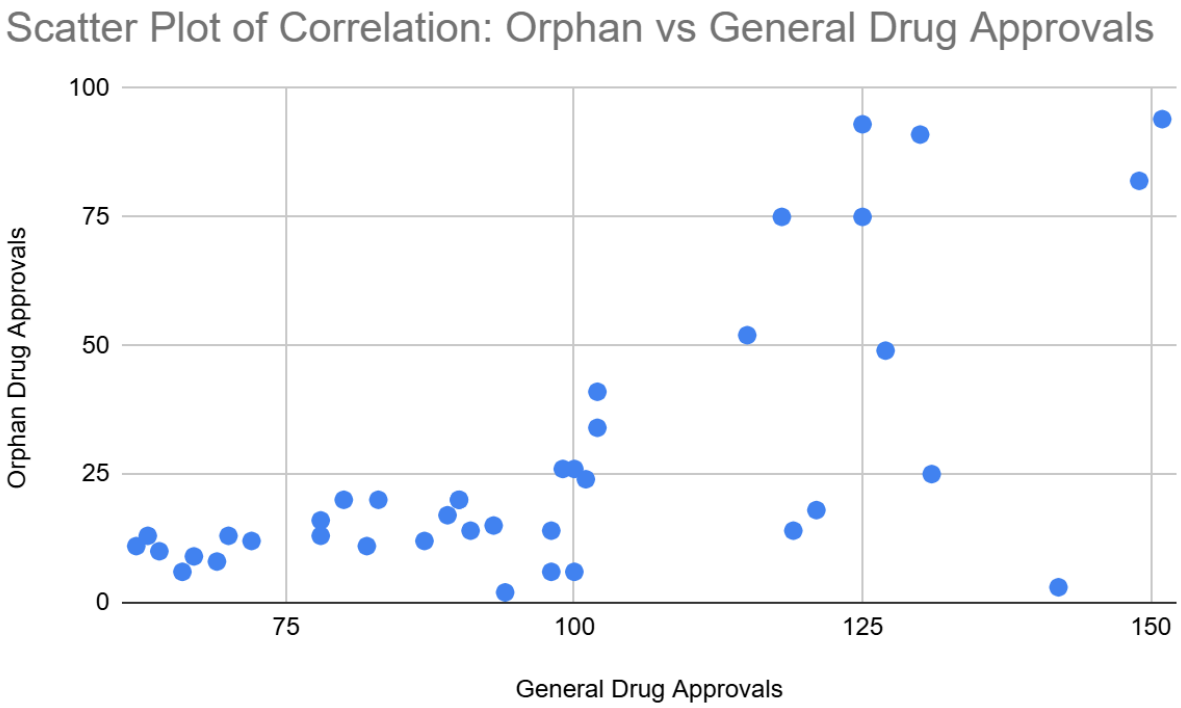

Figure 3. Orphan Drug Approvals vs. General Drug Approvals, 1983–2022 (FDA)

Figure 3 illustrates the overall relationship between orphan drugs and general drug approvals across the study period, with an upward trend visible, which is consistent with the positive correlation below.

Period	**N (Years)**	**Correlation Coefficient**
1983-2022	40	0.69
1983-2009	27	0.15
2010-2022	13	0.87
1983-1989	7	-0.61
1990-2009	20	0.64

Table 1. Correlation Coefficient between Orphan Drugs and General Drugs across Time Periods
Table 1 shows the correlation coefficient between orphan drug approvals and general drug approvals. The overall correlation is calculated using data from 1983 to 2022, with sub-period correlations (1983-1989, 1990-2009, 2010-2022) calculated within this same range.

The overall correlation coefficient between orphan and general drug approvals across the full study period is 0.69, indicating that a substantial share of the variation in orphan drug approvals is associated with variation in general drug approvals. This relationship strengthens considerably in later periods. The correlation from 2010 onwards is 0.87, indicating that orphan drugs and general drugs moved closely together over this period. In contrast, the correlation between 1983 and 2009 is significantly lower at 0.15, indicating orphan drugs moved largely independently, from general drugs during this period. Looking closer we can see that between 1983 to 1989 the correlation is negative at -0.61, indicating orphan drugs and general drugs moved in the opposite direction during this period. Later on from 1990 to 2009 the correlation rose to 0.64, indicating they moved generally in the same direction.

The negative correlation observed between 1983 and 1989 is consistent with the development lag discussed earlier in the paper: given a 7-10 year period typically required to bring a new drug to market, the ODA's incentives would not be expected to meaningfully affect approval trends until the early 1990s. This decoupling may reflect the conditions of the orphan drug market prior to the ODA (pre-1983), in which limited commercial viability left orphan drug development largely disconnected from broader industry trends. These conditions may have led to the introduction of the ODA. The subsequent rise from the 1990s onwards and particularly strong correlation observed from 2010, is consistent with the possibility that orphan drug development became increasingly responsive to the same broader industry trends affecting general drugs. This may indicate that during this period orphan drugs may have begun to become as commercially viable as general drugs. However, the correlation alone cannot establish that it was the ODA that caused this shift.

Continuous Trend Analysis

Coefficient	SE	t	R^2
0.67	0.54	1.24	0.866

Table 2. Continuous Trend Analysis Estimates 1983-2009

A continuous trend regression, using years since the ODA's introduction and an orphan/general drug interaction term was conducted with data from 1983 to 2009 in order to separate impacts from later developments such as FDASIA (2012) and the tax credit reduction (2017). This analysis produced an interaction coefficient of 0.67. What this means is that orphan drugs grew approximately 0.67 more per year, relative to general drug approvals, for each additional year since 1983. However this estimate falls below the general bar for statistical significance (t=1.24).

The continuous trend analysis did not find a statistically significant difference in the growth rate of orphan drug approvals relative to general drug approvals over time. This contrasts somewhat with the correlation results discussed above and DiD results discussed later, which suggest a meaningful shift in orphan drug approvals following the ODA's introduction. This discrepancy may reflect the different way each method models change. The continuous trend analysis assumes a smooth, linear relationship between orphan drug growth and time, whereas the actual pattern shown in Figure 2 may be more consistent with a discrete shift around a specific period. As such, the result being not statistically significant may be considered as evidence that the simple linear trend line does not fully capture the pattern in the data instead of as being contradictory to the DiD, ITS or correlation findings.

Interrupted Time Series (ITS)

Breakpoint	Group	Coefficient	Value	SE	t	R^2
2012	**Orphan**	**Level shift (β_2)**	15.30	5.18	2.96	0.936
2012	**Orphan**	**Slope change (β_3)**	4.71	0.57	8.25	0.936
2012	**General**	**Level shift (β_2)**	21.10	13.39	1.58	0.406
2012	**General**	**Slope change (β_3)**	2.48	1.93	1.29	0.406
2017	**Orphan**	**Level shift (β_2)**	48.98	5.34	9.17	0.945
2017	**Orphan**	**Slope change (β_3)**	0.33	0.97	0.34	0.945
2017	**General**	**Level shift (β_2)**	49.49	15.52	3.19	0.429

2017	**General**	**Slope change (β_3)**	-6.97	4.62	-1.51	0.429

Table 3. Interrupted Time Series Estimates: Orphan and General Drug Approvals

This set of analysis uses data from 1983 to 2025 for orphan drugs, however when general drugs are used as control the period used is 1983 to 2022 due to data limitations.

Interrupted time series analysis was conducted with 2012 as the breakpoint due to the introduction of the FDASIA during that year. The analysis found a statistically significant level shift of 15.30 additional approvals immediately following 2012 (t = 2.96), alongside statistically significant pre-2012 upward trend of 0.53 approvals per year (t = 2.92). The growth rate itself increased significantly after 2012, with an additional 4.71 approvals per year beyond the pre-existing trend (t = 8.25). This model explained a substantial proportion of the variation in orphan drug approvals ($R^2 = 0.936$).

To assess the robustness of the 2012 breakpoint, the ITS was repeated using 2011 and 2013 as alternate breakpoints. The estimated slope change and pre-existing trend remained statistically significant and stable throughout all three breakpoints, providing strong evidence that orphan drug approval growth accelerated considerably around this period. On the contrary, the estimated level shifts grew larger and more significant moving from 2011 to 2013, from not very significant (t = 1.95) to very significant (t = 4.46).

This pattern is consistent with the timing of the FDASIA's introduction in mid 2012, legislation introducing expedited review for drugs targeting serious conditions. This policy is a very plausible explanation for the increase in orphan drug approvals. Considering this in addition to the breakpoint data makes 2012 a suitable breakpoint for this analysis.

The same ITS analysis was conducted on general drug approvals for comparison. Unlike the orphan drug results, none of the coefficients reached statistical significance. The pre-2012 trend (t = -0.02), the level shift (t = 1.58) and slope change (t = 1.29) all were not very statistically significant. This model also explains a smaller portion of variation in general drug approvals ($R^2 = 0.406$), compared to orphan drug approvals ($R^2 = 0.936$).

There is a very notable contrast between the orphan and general drug ITS trend. If FDASIA's Breakthrough Therapy designation had driven approval growth industry-wide, a similarly significant result would be expected between orphan drugs and general drugs. Since this was not the case, the data may indicate that orphan drugs and general drugs were not influenced by this policy to the same degree, for one of several possible reasons. One explanation may be that the existence of the ODA provided conditions that the impact of the FDASIA could be greater in orphan drugs than general drugs. On the other hand, it may be the case that the FDASIA disproportionately affects orphan drugs simply because

many drugs treating life threatening conditions, a requirement for Breakthrough Therapy designation under the FDASIA, happen to also be orphan drugs.

Interrupted time series analysis was also conducted with 2017 as the breakpoint, corresponding to the reduction in ODA's tax credit from 50% to 25%. For orphan drugs, the analysis found a statistically significant level shift of 48.98 additional approvals immediately following 2017 (t = 9.17), alongside a statistically significant pre-2017 upward trend of 0.93 approvals per year (t = 7.06). Unlike the 2012 result, the growth did not significantly change after 2017 (0.33, t = 0.34). This means approvals continued growing at approximately the same pace before and after this breakpoint. The model explains a substantial proportion of the variation in orphan drug approvals ($R^2 = 0.945$). The same analysis applied to general drug approvals also found a statistically significant level shift at 2017 (49.49, t = 3.19), nearly identical magnitude to the orphan drug shift. The pre-2017 trend (t = 1.35) and the slope change (t = -1.51) were not statistically significant.

The 2017 results present patterns quite different to 2012. While orphan drug approvals showed a large, significant level shift at this breakpoint, this coincided with a comparably large significant shift in general drug approvals. This suggests 2017 level shifts reflect an industry-wide event rather than an effect specific to orphan drugs. This finding also appears to be counterintuitive as 2017 marked a reduction in the ODA's tax credit from 50% to 25%, which should have decreased the incentive to produce orphan drugs. These findings suggest there were confounding industry-wide factors which caused the increase in drug approvals during this time period, however there doesn't seem to be sufficient evidence to suggest the reduction in the ODA's tax credit caused a reduction in orphan drug innovation. One plausible candidate for this industry-wide shift is the 21st Century Cures Act, which was signed into law in December 2016 and implemented throughout 2017. This legislation was designed to accelerate approval of new medical products through relaxing FDA standards by allowing treatment for priority health conditions to be approved with fewer supporting studies (Kaplan et al, 2023).

Difference in Differences (DiD)

Breakpoint	Group	Coefficient	Value	SE	t	R^2
2012	**Orphan**	**Level shift (β_2)**	15.30	5.18	2.96	0.936
2012	**Orphan**	**Slope change (β_3)**	4.71	0.57	8.25	0.936
2012	**General**	**Level shift (β_2)**	21.10	13.39	1.58	0.406
2012	**General**	**Slope change (β_3)**	2.48	1.93	1.29	0.406
2017	**Orphan**	**Level shift (β_2)**	48.98	5.34	9.17	0.945

2017	**Orphan**	**Slope change (β_3)**	0.33	0.97	0.34	0.945
2017	**General**	**Level shift (β_2)**	49.49	15.52	3.19	0.429
2017	**General**	**Slope change (β_3)**	-6.97	4.62	-1.51	0.429

Table 4. Difference-in-Differences Estimates (1983–2009)

For difference-in-differences analysis data was used from 1983 to 2009 with 1990 as the dividing point between pre and post ODA periods, this was done to focus on the ODA's impact rather than confounding factors during later periods. An estimated treatment effect of 16.44 ($t = 1.73$) additional orphan drug approvals per year following 1990 relative to the trend expected based on general drug approvals over the same time period was produced. This estimate falls just short of the $p < 0.05$ threshold which is typically used to assess statistical significance. The analysis was repeated using earlier cutoff years as a robustness check. Using 1989 as the dividing point produced a larger estimated effect of 18.29 ($t = 1.88$), using 1988 instead produced an estimated effect of 25.14 ($t = 2.41$), reaching statistical significance at $p < 0.05$, with the t value increasing further as the cutoff date reduced.

This result should be interpreted with several considerations in mind. The cutoff period of 1990 was chosen based on the estimated 7-10 year time lag in drug development. The estimated treatment effect based on this cutoff period falls just short of conventional statistical significance; this marginal significance may itself partially reflect the deliberate choice of the 1990 cutoff while an earlier cutoff may have produced a more statistically significant, but less logically defensible result. However earlier cutoffs (1989 and 1988) produce progressively larger and more statistically significant estimates. This trend does require skepticism as moving the cutoff period earlier does substantially shrink the pre-period sample, to as low as 5 years for a 1988 cutoff year. This leaves the pre-period average more sensitive to individual outliers and a less reliable measure of orphan drug approval trends. This pre-period is also likely to include some repurposed or reformulated drugs that reached market within 7 years of the ODA's implementation. Furthermore, the 7-10 year time lag for novel compounds is only an average, thus there are likely multiple faster moving drug developments influenced by the ODA also occurring in this period. These factors will introduce further noise in the pre-treatment period. As such, while the 1988 and 1989 results may suggest the true treatment effect is understated by the 1990 cutoff, they may just reflect the increased noise and reduced reliability of a smaller pre-period baseline. 1990 is used as this paper's primary DiD estimate due to the larger pre-period and the evidence that the 7 year time lag is appropriate, the earlier cutoffs therefore can serve simply as a robustness check.

DISCUSSION

Summary of Key Findings

Taken together, the results of this analysis provide moderate to strong evidence that orphan drug approvals meaningfully accelerated following the ODA's introduction, though the strength of evidence varies across different methods used. The correlation analysis shows orphan drugs and general drugs not very correlated in the years immediately following the ODA's passage, consistent with the market's early lack of responsiveness due to development time lags. From there, once the Act's incentives began to take effect, approvals of orphan drugs and general drugs began to converge into a much stronger positive correlation from the 1990s onwards. The DiD analysis using the 1990 cutoff, based on a theoretical development lag of 7 years, produces a positive but only marginally statistically significant result of the ODA's impact. While robustness checks indicate earlier cutoff dates show the impact to be more significant, this may not be very reliable due to the increased noise with such a small pre-period. The clearest evidence of an orphan-specific shift comes from the interrupted time series analysis. When analysing 2012 as the breakpoint, a statistically significant accelerating rise unique to orphan drug approvals was found. This however does coincide with the FDASIA, meaning this analysis cannot distinguish what is attributable to the ODA, its interaction with the FDASIA, or other factors specifically impacting orphan drugs. In contrast 2017 as the breakpoint showed comparable shifts between orphan and general drug approvals despite the reduction in ODA tax credit. The continuous trend analysis, conversely, found no significant linear difference in growth rates over time. This indicates that a more discrete shift around a specific period was more likely than a smooth and continuous acceleration. Collectively, these findings suggest the ODA's incentives, potentially interacting with later regulatory developments, were associated with meaningful, often orphan-specific, growth in rare disease drug development. While nothing provides definitive proof of a causal relationship, there is meaningful evidence consistent with such a link, with the strength of data varying considerably across periods and methods.

Limitations

These findings should be interpreted with several limitations.

First, the core measure of innovation used in this paper includes repurposed drugs alongside new compounds. This means the sixfold increase in orphan drug approvals may partly reflect an increase in repurposing and reformulations, rather than solely reflecting the ODA's impact on genuinely novel drug development.

Second, approvals measure the quantity of drugs reaching the market, but not their quality or impact on patient population. While, by design, orphan drugs will impact far smaller patient populations than general drugs, this analysis will be restricted to quantity rather than quality.

Third, the difference-in-difference analysis departs from the clean pre/post design DiD typically necessitates. Using 1990 as opposed to 1983, was necessary given the absence of pre-1983 data.

However, the pre-1990 period likely includes drugs already influenced by the ODA through reformulations and repurposed drugs, which likely understates its estimated effect. This limitation should be weighed carefully when interpreting the DiD results.

Fourth, this analysis lacks a counterfactual. While the data shows orphan drug approvals rose after the ODA's introduction, it is not possible to know what would have happened in its absence. There still may be other factors independent of the ODA that caused the increase, while most factors likely are controlled for using general drugs as a comparison and using period markers, there are likely other factors that we are unable to control for. Similarly, the DiD analysis relies on the parallel trends assumption mentioned above. This assumption cannot be tested given the limited pre-1983 data, and may not fully hold given orphan drugs and general drugs are subject to different regulatory pathways and R&D dynamics.

Fifth, limited data availability prior to 1983 makes it difficult to observe the orphan drug market before the ODA's introduction. The negative correlation observed between 1983 to 1989, discussed above, is consistent with the market's continued unresponsiveness in the years immediately following the Act's passage. However, the lack of comparison to the actual pre-ODA baseline remains a limitation of this paper.

Sixth, the annual approval count data used throughout this analysis is likely subject to autocorrelation, in that approval counts in a given year are correlated with counts in preceding years rather than statistically independent. Ordinary least squares (OLS) regression, which is used in DiD ITS and continuous trend models, assumes independent errors. When the assumption is violated, the standard error reported can understate the true uncertainty in these estimates, causing the statistical significance to be overstated in many cases.

Seventh, this analysis was unable to analyse the 2017 tax credit reduction in isolation, as broader industry-wide shifts occurred during this period. While comparing the difference in trends between general and orphan drug approvals allowed me to determine whether the impact of the reduction was felt in orphan drugs, the inability to isolate the tax credit's effect from these broader shifts limits what conclusions can be drawn about this specific mechanism.

Eighth, this analysis measures orphan drug approvals rather than designations, meaning it does not capture innovation that reached the designation stage that did not result in an approved drug. A substantial share of orphan drug designations historically have not led to approval, for example only around 16% of designations granted between 1983 and 2009 had been approved by the end of that period (Kesselheim, 2010). This means genuine R&D investment and innovation prompted by the ODA's incentives may have been understated by this analysis.

Finally, while this paper's period-based and comparative analysis aims to go beyond purely descriptive analysis, it should be understood as an exploration of the ODA's association with rare disease drug development, rather than a definitive causal estimate.

Policy Implications

These findings carry several implications for how the ODA's incentive structure might be refined, as well as for the broader design of policies aimed at stimulating drug development in commercially unviable markets.

The evidence this paper presented suggests that market exclusivity had more of a contribution to the acceleration in orphan drug development than tax credits. The absence of any observable decrease following the 2017 tax credit reduction indicates that at that point in the Act's maturity tax credits that reduced development costs had limited impact on orphan drug development, instead that market exclusivity may have been the primary reason for the ODA's success.

The 2012 findings, which withstood a robustness check across multiple breakpoints and were specific to orphan drugs, show that orphan drugs benefited disproportionately from FDASIA's Breakthrough Therapy designation relative to general drugs. However, this analysis is unable to fully disentangle whether this reflects the ODA's own cumulative effect interacting with the FDASIA, the FDASIA's eligibility criteria disproportionately capturing orphan drugs or a combination of the two. What can be said with a level of confidence is that by 2012, orphan drugs appear to have become sufficiently integrated into the broader regulatory and commercial landscape to meaningfully benefit from complementary developments aimed at serious or life threatening conditions.

Provided that this analysis could not confidently isolate the individual impact of the 2017 tax credit reduction, this specific policy change warrants further evaluation before any definitive conclusions are drawn about its impacts. Furthermore, given this change was made once the Act had already matured after being in place for many decades, it is plausible that such tax credits were necessary in initially making orphan drugs commercially viable, although this has not been tested. Thus policymakers should be cautious about underestimating the impact of tax credits on rare disease drug development.

The Act's design, combining extended exclusivity, targeted tax incentives and direct grant funding to address market failure driven by a small consumer base and high upfront costs, may offer a useful template for policies beyond rare diseases. Industries facing the same issues, in the pharmaceutical industry or beyond, could plausibly benefit from a comparable incentive structure, especially given the evidence that such incentives could meaningfully accelerate development in otherwise commercially unattractive markets.

Given this analysis is limited to the US market, the extent to which similar incentive structures would have been effective abroad has not been tested in this paper. Research has been done using comparative analysis of orphan drug policies across countries, yet further research would represent a valuable contribution to understanding how best to design policies for similar legislation abroad.

CONCLUSION

This paper set out to examine the extent to which the Orphan Drug Act contributed to the growth of rare disease drug development, aiming to examine evidence of a causal relationship between the ODA and the growth of orphan drug approvals independent from other confounding factors. The evidence this paper presented is substantial, yet not conclusive. Orphan drug approvals grew over 500% in the period of 1983 to 2022, compared to only around 50% for general drug approvals in the same period. ITS provided the clearest evidence of an orphan-specific effect linked to the ODA emerging in 2012, though it coincided with introduction of the FDASIA and cannot be fully attributable to the ODA alone, while the DiD analysis offered a directionally consistent, yet falling just below the bar of statistical significance, support for the ODA's overall impact. The 2017 findings using ITS illustrate the difficulty of isolating the ODA's impacts from other confounding factors.

Taken together, this analysis suggests that the ODA has played a meaningful role in addressing the market failure which was present in the rare disease drug market. This suggests that, primarily through its market exclusivity provision, but also through its other schemes, the policy appears to have made meaningful progress towards the goals it set out to achieve. This paper's contribution is not conclusively settling this question with certainty or offering definitive proof of causation. Instead this paper moves beyond descriptive methods, using quantitative analysis to provide clearer evidence of in which conditions the ODA's effects were felt most significantly.

For the millions of Americans affected by rare diseases, the vast majority of which still lack an approved treatment, understanding whether targeted incentive structures like the ODA are effective may determine whether or not they will be able to get treatment for their disease. This paper's findings offer support for continued and refined use of such incentives, while highlighting specific mechanisms and policy changes such as the 2017 tax credit reduction that warrant further evaluation to understand future policy implications.

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