

Cutting Tax Incentives for Orphan Drug Development: Effects on Innovation and Sponsor Composition

Simona Gamba* and Laura Magazzini**

Abstract

We investigate how fiscal incentives affect innovation by exploiting the 2017 US reform that halved the Orphan Drug Tax Credit. We analyze orphan drug designations using a multiple-intervention interrupted time-series model that accounts for changes in orphan drug policies across pharmaceutical markets. We examine heterogeneous responses according to sponsors' ability to benefit from the incentive, proxied by whether they had obtained at least one product approval from the Food and Drug Administration in the previous ten years. The results indicate that tax credits stimulate orphan drug research. The reform significantly reduced orphan drug innovation, with heterogeneous effects across sponsors. The decline was concentrated among sponsors with at least one previously approved product, whose designations decreased progressively after 2017. Consistently, the probability that a designation was filed by such a sponsor fell significantly. These findings suggest that reduced tax-credit generosity lowered investment in orphan drug and altered the composition of sponsors undertaking research.

* University of Milan, Milan, Italy

** Sant'Anna School of Advanced Studies and L'EMbeDS, Pisa, Italy

I. Introduction

Rare diseases are generally defined as conditions affecting a small share of the population, although the specific prevalence thresholds used for regulatory purposes vary across jurisdictions. In the United States, a disease is considered rare when it affects fewer than 200,000 individuals, whereas in the European Union the threshold is set at five cases per 10,000 inhabitants.¹ Beyond these regulatory definitions, the concept of an orphan disease refers more broadly to conditions for which the expected market returns are insufficient to stimulate adequate private investment in the development of treatments, diagnostic and prevention tools.

While each rare disease affects only a limited number of individuals, their aggregate impact is far from negligible. Current estimates suggest that between 6,000 and 8,000 rare diseases have been identified worldwide, collectively affecting approximately 300 million people.² In the European Union alone, rare diseases are estimated to affect between 27 and 36 million individuals, while in the United States more than 30 million people are believed to live with a rare condition.³ Moreover, many rare diseases are severe, chronic, progressive, or life-threatening, often imposing substantial burdens on patients, families, and healthcare systems.⁴

Despite remarkable advances in biomedical research over recent decades, progress has not been evenly distributed across therapeutic areas. Private pharmaceutical innovation is largely driven by market size⁵, making firms less likely to invest in research when expected economic returns are limited.⁶ Consequently, conditions characterised by small patient populations (e.g., rare diseases), high scientific uncertainty (e.g., Alzheimer's disease and other dementias), or limited purchasing power (e.g., neglected tropical diseases) are particularly prone to persistent unmet medical needs. This uneven distribution of innovation reflects a broader misalignment between private research and

¹ United States Congress, *Orphan Drug Act*, Pub. L. No. 97-414, 96 Stat. 2049 (1983); European Parliament and Council, *Regulation (EC) No. 141/2000 of 16 December 1999 on Orphan Medicinal Products*, Official Journal of the European Communities L18 (2000): 1–5.

² World Health Assembly, *Rare Diseases: A Global Health Priority for Equity and Inclusion*, WHA78.11, May 27, 2025; Stéphanie Nguengang Wakap et al. “Estimating Cumulative Point Prevalence of Rare Diseases: Analysis of the Orphanet Database.” *European Journal of Human Genetics* 28, no. 2 (2020): 165–173.

³ European Commission, *Commission Staff Working Document on Rare Diseases* (Brussels: European Commission, 2008); U.S. Food and Drug Administration, *Developing Products for Rare Diseases & Conditions* (Silver Spring, MD: FDA, accessed June 2026).

⁴ Stéphanie Nguengang Wakap et al., *supra* note 2.

⁵ Daron Acemoglu and Joshua Linn, “Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry,” *The Quarterly Journal of Economics* 119, no.3 (2004): 1049–1090.

<https://doi.org/10.1162/0033553041502144>; Pierre Dubois et al., “Market size and pharmaceutical innovation,” *The RAND Journal of Economics* 46, no. 4 (2015): 844–871.

⁶ Toshiaki Iizuka, T. and Gyo Uchida, “Promoting innovation in small markets: Evidence from the market for rare and intractable diseases,” *Journal of Health Economics* 54, (2017): 56–65, <https://doi.org/10.1016/j.jhealeco.2017.03.006>

development (R&D) incentives and public health.⁷ The limited availability of effective treatments has long been interpreted as the manifestation of a market failure in pharmaceutical innovation, whereby research projects with high social value may not generate sufficient expected returns to justify private investment.

The economic challenges associated with pharmaceutical innovation are well documented. Developing a new medicine requires substantial investments in R&D, lengthy development timelines, and entails considerable scientific and regulatory uncertainty. A large proportion of drug candidates fail during the development process, often because they do not demonstrate adequate safety or efficacy in preclinical or clinical testing. On average, bringing a new medicine from the initial synthesis of an active compound to market authorization takes approximately 12–13 years.⁸ Estimates suggest that the average R&D cost per approved medicine—accounting for the costs of unsuccessful development programmes and the opportunity cost of capital over the extended development period—exceeds US\$2 billion.⁹ Human clinical trials constitute the most resource-intensive phase of the innovation process, accounting for approximately two-thirds of total drug development expenditures, as they require large-scale patient recruitment, extensive monitoring, and compliance with stringent regulatory standards.¹⁰ These challenges are amplified in the context of rare diseases. Because potential patient populations are small, expected revenues are often insufficient to justify the costs of development, even when the health benefits generated by successful therapies are potentially large. Furthermore, patient recruitment may be particularly difficult, clinical evidence may be harder to generate, and fixed development costs must be recovered from a relatively limited market.¹¹ These economic barriers contribute to substantial unmet clinical needs: fewer than 10% of identified rare

⁷ Evidence suggests that also governments do not always allocate biomedical research funding in ways that maximise social welfare, and that public funding decisions may themselves reflect political considerations. In the United States, Hegde finds that research institutions in the constituencies of certain congressional appropriators received more funding. Lichtenberg also finds that public biomedical R&D was more responsive to the health needs of men and white people. Frank R. Lichtenberg, “The Allocation of Publicly Funded Biomedical Research,” in *Medical Care Output and Productivity*, ed. David M. Cutler and Ernst R. Berndt (Chicago: University of Chicago Press, 2001), 565–90. Deepak Hegde, “Political Influence behind the Veil of Peer Review: An Analysis of Public Biomedical Research Funding in the United States,” *Journal of Law and Economics* 52, no. 4 (2009): 665–90.

⁸ [the-pharmaceutical-industry-in-figures-2024.pdf](#)

⁹ Joseph A. DiMasi et al., “Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs,” *Journal of Health Economics* 47 (2016): 20–33.

¹⁰ Joseph A. DiMasi et al., “The price of innovation: new estimates of drug development costs,” *Journal of Health Economics* 22, (2003): 151–185.

¹¹ Erik Tambuyzer, “Rare diseases, orphan drugs and their regulation: questions and misconceptions,” *Nature Reviews Drug Discovery* 9, no.12 (2010): 921–929.

diseases have an approved therapy.¹² An efficiency-based rationale for public intervention arises when the expected social returns to additional R&D exceed its costs but the expected private returns do not. If equal health gains are assigned equal social value across patients, the expected aggregate benefit of a treatment depends on both the number of patients who could benefit and the health gain per patient, which is shaped by disease severity and treatment efficacy.¹³ Another rationale for public intervention may be the disparity in treatment availability between rare and more common diseases, which raises concerns about inequality.¹⁴ An equality-of-opportunity perspective offers a related justification, since whether an individual develops a rare disease is beyond their control.¹⁵ Public support may also be warranted by knowledge spillovers: research on rare diseases can generate insights useful for treating other conditions.¹⁶ Taken together, these economic and equity considerations help explain why policymakers have introduced dedicated incentives to stimulate R&D for rare diseases. These incentives can be broadly classified into two categories. Push incentives reduce private costs associated with pharmaceutical R&D, thereby lowering the resources firms must commit before a product reaches the market. Because support is provided before the outcome of development is known, these incentives shift some of the financial risk from firms to the public sector. Pull incentives, by contrast, increase the expected returns to successful innovation by enhancing the revenues that can be generated following regulatory approval, while leaving the development risk with private firms.

The concern that “some promising orphan drugs will not be developed” without measures to reduce R&D costs and provide financial incentives, together with Congress’s finding that “it is in the public interest to provide such changes and incentives”,¹⁷ motivated the enactment of the Orphan Drug Act (ODA) in 1983 and the introduction of dedicated incentives for orphan drug development in the United States. The legislation introduced a combination of push and pull incentives: tax credits for clinical testing expenditures, research grants, regulatory assistance, fee waivers, and a period of market exclusivity following approval. The apparent success of the ODA subsequently inspired the adoption of orphan drug legislation in several other jurisdictions, including Japan (1993), Australia

¹² Irena Melnikova, “Rare diseases and orphan drugs,” *Nature Reviews Drug Discovery* 11, no.4 (2012): 267-268.

¹³ Kyle, Margaret K. “The Alignment of Innovation Policy and Social Welfare: Evidence from Pharmaceuticals.” *Innovation Policy and the Economy* 20 (2020): 95–123.

¹⁴ McCabe, C., K. Claxton, and A. Tsuchiya. “Orphan Drugs and the NHS: Should We Value Rarity?” *BMJ* 331, no. 7523 (2005): 1016–19.

¹⁵ Roemer, J. *Equality of Opportunity*. Harvard University Press, 1998.

¹⁶ Rodwell, C., and S. Aymé. “Rare Disease Policies to Improve Care for Patients in Europe.” *Biochimica et Biophysica Acta (BBA) – Molecular Basis of Disease* 1852, no. 10 (2015): 2329–35.

¹⁷ *Orphan Drug Act*, Pub. L. No. 97-414, § 1(b)(5)–(6), 96 Stat. 2049 (1983) (congressional findings).

(1997), the European Union (2000),¹⁸ Taiwan (2000), and South Korea (2003). While the specific design of these frameworks differs across countries, they all combine economic and regulatory incentives intended to encourage the development of orphan medicinal products.

In the more than four decades after the introduction of the ODA, the number of orphan drug designations (ODDs) and approvals has increased dramatically, and rare diseases have become an increasingly important area of pharmaceutical R&D.¹⁹ Despite the relatively limited empirical evidence, a number of studies have assessed the extent to which orphan drug policies have stimulated research activity and orphan drug development.²⁰ However, focusing exclusively on average effects may obscure substantial heterogeneity in policy responses. The economic barriers targeted by orphan drug policies vary considerably across diseases and development projects, while firms differ substantially in terms of resources, capabilities, and financial constraints. Consequently, incentives that appear effective on average may generate markedly different responses depending on the characteristics of the diseases being targeted and the firms undertaking the development effort. Understanding these heterogeneous responses is essential for assessing the achievements of existing orphan drug frameworks and for informing future policy reforms.

By exploiting the 2017 reduction in the US orphan drug tax credit, this chapter provides new evidence on the role of fiscal incentives in stimulating pharmaceutical innovation and on the extent to which their effectiveness depends on firms' ability to benefit from them.

¹⁸ The European Union also invoked equity as a rationale for intervention (McCabe, Christopher, Karl Claxton, and Aki Tsuchiya. "Orphan Drugs and the NHS: Should We Value Rarity?" *BMJ* 331, no. 7523 (2005): 1016–19). Recital 2 of Regulation (EC) No 141/2000 states that "patients suffering from rare conditions should be entitled to the same quality of treatment as other patients".

¹⁹ Marlene E. Haffner, "Adopting Orphan Drugs—Two Dozen Years of Treating Rare Diseases," *New England Journal of Medicine* 354, no. 5 (2006): 445–447; Katherine L. Miller and Marc Lanthier, "Investigating the Landscape of US Orphan Product Approvals," *Orphanet Journal of Rare Diseases* 13, no. 1 (2018): 183.

²⁰ M. Miles Braun et al., "Emergence of Orphan Drugs in the United States: A Quantitative Assessment of the First 25 Years," *Nature Reviews Drug Discovery* 9, no. 7 (2010): 519–22, <https://doi.org/10.1038/nrd3160>. Frank R. Lichtenberg and Joel Waldfogel, "Does Misery Love Company? Evidence from Pharmaceutical Markets before and after the Orphan Drug Act," *Michigan Telecommunications and Technology Law Review* 15 (2009): 335–57. Wesley Yin, "Market Incentives and Pharmaceutical Innovation," *Journal of Health Economics* 27, no. 4 (2008): 1060–77; Committee for Orphan Medicinal Products and European Medicines Agency Scientific Secretariat, "European Regulation on Orphan Medicinal Products: 10 Years of Experience and Future Perspectives," *Nature Reviews Drug Discovery* 10, no. 5 (2011): 341–49, <https://doi.org/10.1038/nrd3445>

II. Institutional Background

The modern framework for orphan drug regulation originated in the United States with the enactment of the ODA in 1983. Prior to its adoption, the development of treatments for rare diseases was widely perceived as commercially unattractive, particularly following the regulatory changes introduced by the Kefauver–Harris Amendments of 1962, which strengthened requirements concerning the demonstration of drug safety and efficacy and contributed to increasing development costs. Patient advocacy groups, most notably the National Organization for Rare Disorders (NORD), played a central role in bringing attention to the limited availability of therapies for rare conditions and in mobilizing political support for legislative intervention.²¹

The ODA sought to address the economic barriers associated with orphan drug development through a combination of incentives designed both to reduce development costs (push incentives) and to increase expected returns (pull incentives). Under the Act, sponsors may obtain an ODD for products intended to treat diseases affecting fewer than 200,000 individuals in the United States, or for diseases for which there is no reasonable expectation that development costs can be recovered through future sales. Once the ODD has been granted, sponsors become eligible for several benefits, including tax credits for qualified clinical testing expenditures, research grants, protocol assistance, fee reductions, and seven years of market exclusivity following regulatory approval.²²

Among the pull incentives introduced by the ODA, market exclusivity has traditionally been regarded as the most important component of the legislation. Unlike patent protection, orphan exclusivity is indication-specific and begins upon regulatory approval, preventing the approval of competing products for the same indication during the exclusivity period unless clinical superiority can be demonstrated. Tax credits and grants instead lower the financial burden associated with clinical development. Unlike grants, which may support different stages of development, the orphan drug tax credit is limited to qualified human clinical testing expenditures incurred during the clinical development phase, which typically accounts for a substantial share of total pharmaceutical R&D expenditures. The credit is available to the taxpayer that incurs qualified clinical testing expenditures for an orphan-designated drug and on whose behalf the clinical testing is conducted, regardless of its legal form. Any unused credit may be carried back for one year or carried forward for up to 20 years. In the original legislation, tax credits allowed taxpayers to claim a credit equal to 50 percent of qualified clinical testing expenditures. A major modification to this framework was introduced in

²¹ Marlene E. Haffner, “Orphan Products: Origins of the Orphan Drug Act,” *Drug Information Journal* 28, no. 2 (1994): 291–297.

²² United States Congress, *Orphan Drug Act*, Pub. L. No. 97–414, 96 Stat. 2049 (1983).

through the Tax Cuts and Jobs Act (TCJA), which was adopted on December 22nd 2017 and entered into force on January 1st, 2018. Among its numerous fiscal provisions, the legislation reduced the orphan drug tax credit from 50 percent to 25 percent of qualified clinical testing expenditures.²³ The reform emerged within a broader effort to simplify the tax system and reduce federal tax expenditures. Although the credit was preserved, the reduction represented the most substantial change to the financial incentives established by the ODA since its enactment. From an economic perspective, the reform created a valuable opportunity to examine the extent to which firms rely on fiscal incentives when making orphan drug development decisions.

During the 1990s and early 2000s, several other jurisdictions introduced orphan drug legislations providing economic and regulatory incentives for drugs obtaining an ODD. Japan established a dedicated orphan drug program in 1993, Australia in 1997, while the European Union adopted Regulation (EC) No. 141/2000 on orphan medicinal products, creating a common framework across Member States. Taiwan (2000) and South Korea (2003) implemented similar policies. While all frameworks rely on a combination of push and pull incentives, important differences emerge in the relative emphasis placed on individual policy instruments. For example, among the major orphan drug legislations, only the United States, Japan, and Taiwan include tax incentives specifically targeted at orphan drug development, while Australia and South Korea do not. Similarly, the European orphan drug framework does not provide tax credits among its incentives, as taxation remains within the competence of individual Member States. Differences emerge also in the eligible expenditures qualifiable for tax credits: qualified clinical testing expenditures (Phases I–III and certain clinical development costs) in the United States; R&D expenditures including clinical and non-clinical costs in Japan.²⁴ Table 1 summarizes the main features of orphan drug legislation in selected jurisdictions.

Several other jurisdictions, including Canada, China and India, have introduced policies or regulatory measures addressing rare diseases or orphan drugs. However, unlike the jurisdictions reported in Table 1, they have not adopted a comprehensive orphan drug legislative framework providing dedicated innovation incentives comparable to those established under the ODA.

²³ Other provisions of the Tax Cuts and Jobs Act included the reduction of the corporate income tax rate and changes to the taxation of foreign earnings. Changes to the taxation of foreign earnings may have affected multinational firms' liquidity and investment decisions, but their effect on orphan-drug R&D was likely less direct than that of the reduction in the Orphan Drug Tax Credit. We cannot rule out, however, that they contributed to the observed changes in orphan drug designations.

²⁴ In Taiwan, the eligible expenditures and the applicable tax benefits were specified in implementing regulations and evolved over time.

Table 1. Characteristics of orphan drug legislation in selected jurisdictions

Jurisdiction	Legislation	Rare disease threshold	Push incentives	Pull incentives
United States	Orphan Drug Act (1983)	<200,000 patients in US or not profitable	Tax credits (50% of qualified clinical testing expenditures until 2017; 25% since 2017), research grants, protocol assistance, fee waivers	7-year market exclusivity
Japan	Orphan Drug Program (1993)	<50,000 patients in Japan	Tax credits (6% R&D expenditures), research grants, protocol assistance	10-year re-examination period
Australia	Orphan Drug Policy (1997)	<5 per 10,000 inhabitants	Fee waivers, protocol assistance	Regulatory exclusivity mechanisms
European Union	Regulation (EC) No. 141/2000	≤5 per 10,000 inhabitants OR both not profitable & life-threatening	Protocol assistance, fee reductions	10-year market exclusivity
Taiwan	Rare Disease and Orphan Drug Act (2000)	<1 per 10,000 population	Research grants, protocol assistance, fee reductions, tax incentives	10-year market exclusivity, priority review
South Korea	Orphan Drug Guideline (2003); Pharmaceutical Affairs Act	<20,000 patients (or diseases designated by the Ministry of Food and Drug Safety)	Fee reductions, protocol assistance, accelerated review, research support	Market exclusivity (6 years), expedited approval procedures

III. Literature review

Since its enactment, the US ODA has attracted considerable attention from scholars interested in the relationship between market incentives and pharmaceutical innovation. A first group of studies evaluates the aggregate impact of orphan drug legislation by asking whether the introduction of dedicated incentives increased research activity and drug development for rare diseases. Overall, this literature provides evidence that the ODA contributed to expanding innovation directed at orphan conditions. Yin, for example, studies the effect of the ODA on the flow of new clinical trials for a large set of rare diseases and finds that the Act generated a significant and sustained increase in clinical development activity, particularly among relatively more prevalent rare diseases. Importantly, Yin also provides evidence that tax credits can stimulate R&D by lowering the effective cost of clinical development and thereby encouraging firms to undertake projects that would otherwise be unprofitable.²⁵ Lichtenberg and Waldfogel provide evidence that the ODA contributed to an increase in the number of drug approvals for orphan diseases relative to non-orphan conditions, highlighting the role of market size and policy incentives in shaping pharmaceutical innovation.²⁶ Descriptive evidence points in the same direction: Braun et al. provide a quantitative assessment of orphan designations and approvals during the first twenty-five years of the ODA, documenting the emergence of orphan drugs as a substantial component of pharmaceutical development in the United States.²⁷ Evidence from Europe is broadly consistent with this pattern. Westermarck et al., reviewing the first ten years of the EU Regulation on orphan medicinal products, document a substantial increase in orphan designations and approvals following the adoption of the European framework.²⁸

While Yin provides some evidence that the response to orphan drug incentives is stronger among relatively more prevalent rare diseases, the literature has generally focused on average treatment effects. Gamba, Magazzini and Pertile are the first to place heterogeneity at the centre of the analysis by developing a theoretical framework and testing explicitly whether the impact of orphan drug legislation differs across diseases with different prevalence.²⁹ Their starting point is that

²⁵ Wesley Yin, *supra* note 20.

²⁶ Frank R. Lichtenberg and Joel Waldfogel, *supra* note 20.

²⁷ Miles M. Braun et al., *supra* note 20.

²⁸ Committee for Orphan Medicinal Products and European Medicines Agency Scientific Secretariat, *supra* note 20.

²⁹ Simona Gamba et al., “R&D and Market Size: Who Benefits from Orphan Drug Legislation?” *Journal of Health Economics* 80 (2021): 102522.

orphan diseases are not homogeneous in terms of market size. Some conditions affect patient populations close to the regulatory threshold for orphan designation, whereas others are ultra-rare and involve only a handful of known cases. Since expected revenues increase with the number of potential patients, incentives that are formally available to all orphan diseases may nevertheless generate stronger responses for less rare conditions.

Gamba, Magazzini and Pertile develop a theoretical model to study how push and pull incentives affect R&D decisions at both the extensive and intensive margins. The extensive margin concerns whether a disease attracts any R&D investment at all; the intensive margin concerns the amount of R&D effort conditional on investment taking place. The model shows that both push incentives, which reduce development costs, and pull incentives, which increase expected returns after approval, may interact with disease prevalence in ways that favour diseases with comparatively larger patient populations. This theoretical result is particularly important because it implies that orphan drug legislation may reduce inequality between rare and common diseases while simultaneously increasing inequality within the class of rare diseases.

The empirical analysis combines data on ODDs granted by the FDA with information on disease characteristics from Orphanet. ODDs are used as a proxy for R&D effort, since designation is typically obtained before sponsors can access the incentives provided by orphan drug legislation. The unit of analysis is the disease-year, and the dependent variable is the yearly number of FDA ODDs associated with each disease. The authors distinguish between diseases with different prevalence levels and exploit the staggered introduction of orphan drug regulations across jurisdictions to assess whether incentives changed the allocation of R&D effort within the orphan disease space.

Methodologically, the paper estimates a zero-inflated count model, which is well suited to the structure of the data because many rare diseases receive no orphan designation in a given year. The zero-inflated component captures the probability that a disease receives no R&D investment, while the count component models the intensity of R&D effort among diseases that do attract activity. This empirical strategy mirrors the theoretical distinction between extensive and intensive margins and allows the authors to examine whether the effect of orphan drug policies differs across prevalence classes.

The results indicate that the increase in R&D effort following the strengthening and international diffusion of orphan drug incentives was concentrated mainly among less rare orphan diseases. In the baseline specification, the difference between the predicted number of ODDs for

diseases in the highest and lowest prevalence classes became substantially larger over time: after 2008, it was estimated to be 5.6 times larger than in the period 1983–1992. These findings support the idea that orphan drug incentives, while successful in stimulating research for rare diseases as a whole, may have disproportionately benefited conditions with relatively larger market potential. The policy implication is that uniform incentives based on a single orphan threshold may be poorly targeted if the objective is to promote innovation also for the rarest conditions. In such a setting, more differentiated incentive schemes, including greater reliance on push mechanisms or prevalence-dependent support, may be needed to avoid widening the gap between more and less rare diseases.

An important dimension of heterogeneity remains unexplored in the existing literature: how the effectiveness of ODA may vary across firms. This issue is particularly relevant for push incentives such as tax credits, whose value depends not only on the characteristics of the development project but also on the financial position of the sponsoring firm. Unlike market exclusivity, which increases expected returns following successful approval, tax credits reduce development costs only to the extent that firms are able to offset eligible expenditures against their tax liabilities. Consequently, firms with limited or no taxable income—such as many small biotechnology companies operating at a loss during the early stages of drug development—may benefit less from tax-based incentives than established firms with products already on the market. The following section builds on this intuition by examining the reduction in the orphan drug tax credit introduced by the TCJA of 2017. Exploiting this policy change, we investigate the effectiveness of fiscal incentives in stimulating innovation and whether the response to cost-reducing incentives differs according to firms' financial capacity, thereby extending the analysis of heterogeneity from disease characteristics to firm characteristics.

IV. Data description

The analysis relies on a dataset built by the authors, that combines information on candidate drugs receiving ODDs, used as a proxy for innovation, with information on approved drugs, which we use as a proxy for sponsors' ability to benefit from orphan drug tax credits.

The list of candidate drugs receiving ODDs in the US has been retrieved from the FDA website.³⁰ Fine-grained information is available for each ODD, including the company sponsoring

³⁰ The list of ODDs has been extracted from <https://www.accessdata.fda.gov/scripts/opdlisting/oodpd/>, accessed on March 18th, 2026.

the trial and its location, the name of the molecule under scrutiny, the designation date and the (eventual) approval date, and targeted rare disease indication(s). An ODD is granted to a molecule for a specific indication. We selected the 7,943 ODDs granted from 1983 up to December 31, 2025, comprising information on 5,722 compounds, each receiving on average 1.4 rare disease indications (see Table 2).

Tax credits can only generate their full economic value for organizations that expect to generate sufficient taxable income against which the credit can be claimed. Because information on taxpayers' taxable income is unavailable, we proxy their ability to benefit from tax credits using data on drug approvals. Specifically, we assume that entities with at least one drug already on the market are more likely to generate sufficient taxable income to benefit from orphan drug tax credits. For this reason, ODDs data have been integrated with information on drugs approvals, retrieved from the Drugs @FDA database and the Purple Book.³¹ Drugs@FDA reports drugs approved for human use in the US since 1939. The database includes approvals for small molecule drugs (new drug applications, NDA), generic products (abbreviated new drug applications, ANDA), and biological products (biological license applications, BLA) approved by the Center for Drug Evaluation and Research (CDER). Information on FDA-approved biologics regulated by the Center for Biologics Evaluation and Research (CBER), such as vaccines, allergenic products, blood and blood products, plasma derivatives, cellular and gene therapy products, have been complemented using the Purple Book. All product approved from 1939 to 2025 have been considered.

Sponsor's names were harmonized across the three sources and were used to merge them. To be more specific, for each ODD we matched, based on the sponsor's name, the information on approvals obtained by that sponsor available from Drugs@FDA and the Purple Book. ODDs filed by different subsidiaries, legal entities or divisions of the same parent company (e.g., Pfizer Ireland and Pfizer Laboratories) were consolidated and attributed to the corresponding corporate group.

Sponsors are classified according to their probability to benefit from the tax credit: sponsors with at least one pharmaceutical product approved by the FDA during the previous ten years, and sponsors without. This classification does not reflect legal eligibility for the orphan drug tax credit, which is available irrespective of the sponsor's prior approval history. Rather, it is intended to proxy for differences in sponsors' ability to monetize the credit and, consequently, in its expected net present value. Sponsors with a recent FDA-approved product may be more likely to have an established

³¹ The Drugs@FDA dataset can be downloaded from: <https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files> (accessed on March 18th, 2026). Purple Book is available at <https://purplebooksearch.fda.gov/index.cfm?event=downloads> (accessed on July 9th, 2026).

revenue stream and generate taxable income against which the credit can be used. By contrast, for sponsors without previously approved products, the ability to monetize the credit may depend more heavily on carrying it forward until sufficient tax liability arises, for example following the successful approval and commercialization of the orphan-designated product or another product in their pipeline. Licensing agreements with larger firms, including upfront or milestone payments, may also enable these sponsors to use the credit if the resulting revenues contribute to sufficient taxable income. An acquisition may also create opportunities to use previously accrued credits, although this depends on the transaction structure and is subject to restrictions on the use of credits after a change in ownership. The timing and actual utilization of the credit are therefore more uncertain for these sponsors, potentially reducing its expected net present value. We use a ten-year look-back period on the assumption that products approved within the preceding decade are more likely to remain protected by intellectual property rights and generate revenues that may translate into taxable income, thereby increasing the sponsor's ability to monetize the tax credit.

Our proxy for sponsors' ability to benefit from the tax credit does not account for changes in corporate ownership during the study period. Firms that were independent at the beginning of the period are treated as independent throughout. For example, Genentech is treated as a separate entity even after it became part of the Roche Group in March 2009. This approach does not capture ownership changes affecting approximately 20% of the entities in our dataset. It may therefore classify some sponsors as less likely to benefit from the credit even when, at the time of designation, they belonged to a corporate group with taxable income. To the extent that this occurs, our main estimates represent a lower bound, understating the difference between the two groups of sponsors. As a robustness check, we repeat the analysis using the corporate group structure observed in 2025; under this alternative classification, Genentech is treated as part of Roche throughout the study period. For this robustness check, we reclassify each sponsor according to whether any member of the corporate group to which it belonged in 2025 had obtained an FDA product approval in the preceding ten years.³²

Table 2 presents descriptive statistics on ODDs by sponsors' market experience. Only 206 sponsors (6% of all sponsors) had at least one approved product in the ten years preceding the designation. Despite their limited number, these sponsors account for 1,908 ODDs (24% of all designations), suggesting that they are substantially more active in orphan drug development than

³² Information on corporate group affiliations in 2025 was collected through targeted Google searches, supplemented by queries to Google Gemini and ChatGPT. We then manually reviewed the information obtained to assess its accuracy.

sponsors without previously approved products. At the same time, the fact that 94% of sponsors had no approved products in the preceding ten years suggests that orphan drug research is predominantly undertaken by sponsors without an established commercial product portfolio. On average, sponsors with a previous approval also receive more ODDs per marketed product (1.68 versus 1.32; the difference is statistically significant at the 1% level). Table 2 also shows that the vast majority of sponsors are companies: of the 3,292 sponsors in the sample, 3,109 are corporate entities, while the remaining sponsors include individuals, hospitals, universities, not for profit entities, and research foundations.

Table 2. Descriptive statistics on the composition of the ODDs sample, partitioning the sponsors according to the presence of at least one approved product in the ten years before the designation

Approved product(s) in the 10 years before designation	Number of ODDs (%)	Number of sponsors (%)	Number of companies (%)	Average number of orphan designation by product
No	6,035 (76%)	3,086 (94%)	2,904 (93%)	1.32
Yes	1,908 (24%)	206 (6%)	205 (7%)	1.68
Total	7,943 (100%)	3,292 (100%)	3,109 (100%)	1.39

Table 3 reports the main characteristics of ODDs according to the intended use of the designated product and its therapeutic area. Information on the intended use was retrieved from the ODD through a keyword search. Nearly all ODDs were granted for products intended to treat a rare disease (95.9%), whereas designations for disease prevention (4.3%) and diagnosis (1.3%) are comparatively uncommon.³³ In addition, more than one-third of all ODDs (34.5%) target rare cancers. Some differences emerge across sponsors. ODDs sponsored by entities with a previous approved product are more likely to target rare cancers (37.7% versus 33.5%) and to concern disease treatment (96.5% versus 95.1%), while they are less likely to involve diagnostic products (0.7% versus 1.5%). These differences are statistically significant, whereas no significant difference is observed for products intended for disease prevention.

³³ 1.0% of ODDs were granted for products with more than one intended use (e.g. treatment and prevention).

Table 3. Characteristics of designated indications (N=7,943); partitioning the sponsors according to the presence of at least one approved product in the ten years before the designation (*p*-value of the test of no difference among the proportions).

Approved product in the 10 years before designation	ODDs targeting cancer (%)	New treatment (%)	Prevention method (%)	Diagnostic tool (%)
No	0.334	0.951	0.044	0.015
Yes	0.382	0.965	0.037	0.007
Total	0.345	0.954	0.043	0.013
p- value (chi-squared test)	<0.001	0.007	0.185	0.005

V. Empirical analysis

Throughout the descriptive and econometric analyses, we focus on the main milestones in the evolution of orphan drug legislation. Following Gamba, Magazzini, and Pertile³⁴, we restrict attention to reforms implemented in the largest pharmaceutical markets (US, Japan and the EU). This choice is motivated by the fact that Australia and South Korea did not introduce tax credits, so the main economic incentive provided by their orphan drug legislation is market exclusivity, whose value depends critically on market size. Accordingly, we do not consider the introduction of orphan drug legislation in Australia (1997) or South Korea (2003), while Taiwan's legislation is contemporaneous with the European reform. We therefore identify five major milestones: (i) the enactment of the US Orphan Drug Act in January 1983; (ii) the introduction of Japan's orphan drug programme in April 1993; (iii) the entry into force of Regulation (EC) No. 141/2000 in the European Union in January 2000 (coinciding with the introduction of Taiwan's orphan drug legislation); (iv) the introduction of the joint FDA–EMA application procedure in June 2008; and (v) the reduction of the US orphan drug tax credit in December 2017, which became effective in January 2018. The first four milestones are included to account for major institutional changes in the orphan drug landscape, with the fourth

³⁴ Simona Gamba et al., *supra* note 29.

representing the introduction of a common form to allow sponsors to file parallel requests for ODD, thus reducing sponsors' paperwork. Finally, the last milestone (v) represents the policy intervention examined in this study.

The empirical analysis proceeds in three steps. We first examine the evolution of ODDs over time, comparing trends for sponsors with and without a previous approval during the previous ten years (as a proxy for the probability to be eligible for the tax credit). This descriptive evidence provides a first assessment of whether the reduction in the tax credit was associated with differential changes in orphan drug development across the two groups of sponsors. We then complement the descriptive analysis with two econometric approaches. First, an interrupted time series analysis is used to evaluate changes in the evolution of the number of ODDs following the 2017 reform. Second, we estimate whether the 2017 reform affected the probability that an ODD was filed by a sponsor with a previously approved product rather than a sponsor without a previously approved product.

A. Descriptive evidence

Figure 1 illustrates the evolution of the annual number of ODDs. The number of designations increased steadily over most of the sample period, particularly after the early 2000s. Following the 2017 reform, however, the upward trend appears to slow, with the number of ODDs declining in 2018 and 2019 before resuming modest growth in subsequent years. Because ODDs are typically granted during the clinical development phase³⁵, when sponsors incur qualified clinical testing expenditures eligible for the orphan drug tax credit, any reduction in the generosity of the credit could reasonably be expected to affect sponsors' R&D decisions with relatively little delay. In particular, lower tax incentives may reduce the expected profitability of projects at the clinical stage, leading sponsors to discontinue or postpone the development of marginal candidates.

The overall pattern remains virtually unchanged when the analysis is restricted to corporate sponsors (Figure 2), suggesting that the observed dynamics are not driven by the relatively small number of non-corporate sponsors included in the sample.

³⁵ For ODDs granted by the European Medicines Agency (EMA), the dataset includes information on the stage of development at the time of designation. The data show that most ODDs are granted during Phase II clinical trials, indicating that sponsors typically seek orphan status relatively early in the clinical development process.

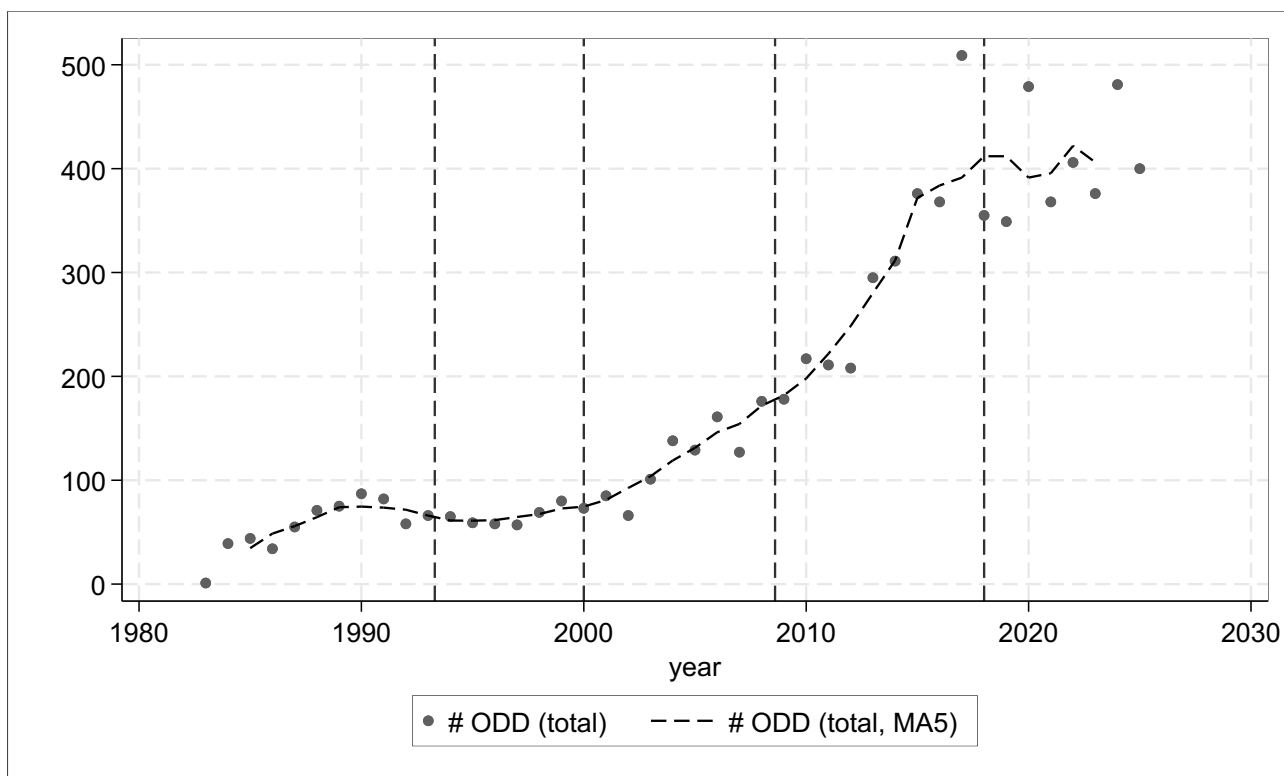


Figure 1 – Evolution in the annual number of ODDs (all institutions). Vertical dashed lines indicate the timing of the policy milestones included in the analysis.

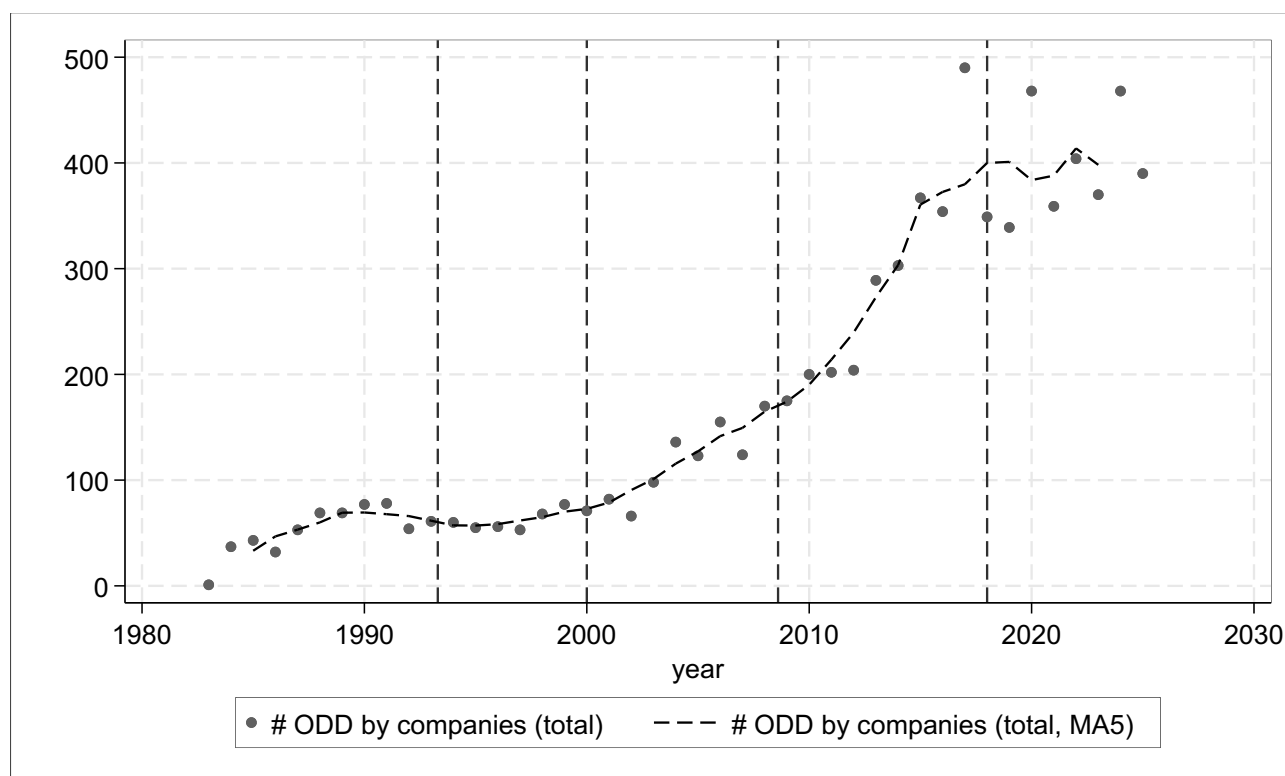


Figure 2 – Evolution in the annual number of ODDs (companies only). Vertical dashed lines indicate the timing of the policy milestones included in the analysis.

Interestingly, this pattern appears to be specific to orphan drug development. As shown in Figure 3, the number of commercial Investigational New Drug (IND) applications—the regulatory applications submitted to the FDA to obtain authorization to begin clinical testing of a new drug candidate in humans with the ultimate goal of commercial marketing and large-scale public distribution — does not exhibit a comparable slowdown following the 2017 reform. This suggests that the observed change is unlikely to reflect a broader decline in pharmaceutical innovation and may instead be specific to orphan drug development.

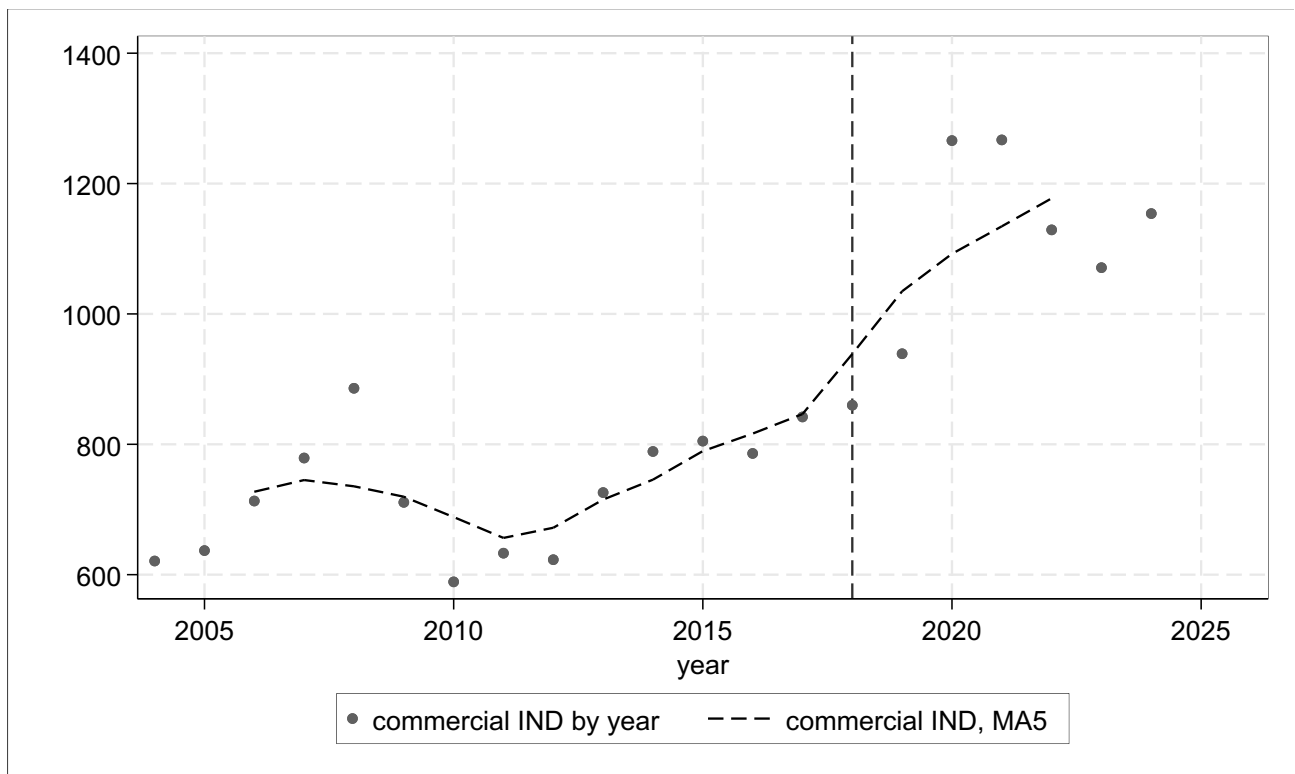


Figure 3 – Evolution of the annual number of commercial IND. Vertical dashed lines indicate the timing of the policy milestones included in the analysis (source: FDA website).

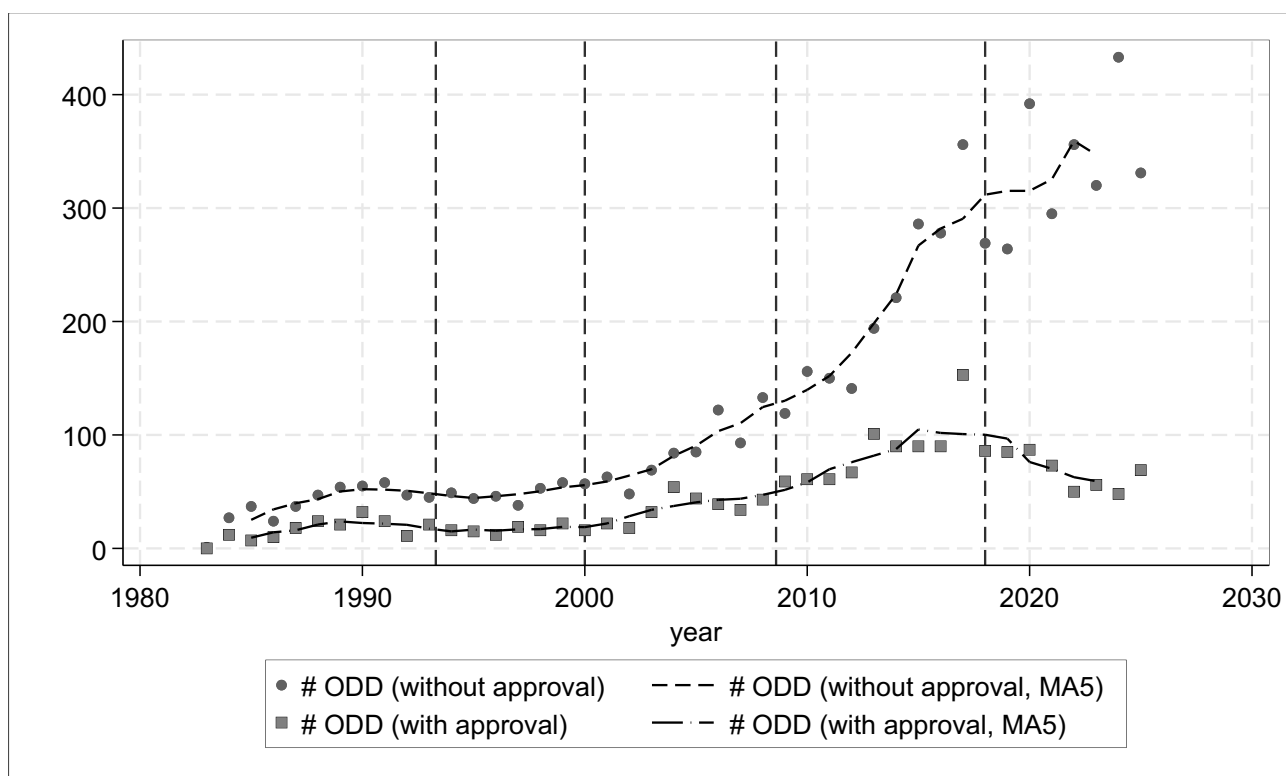


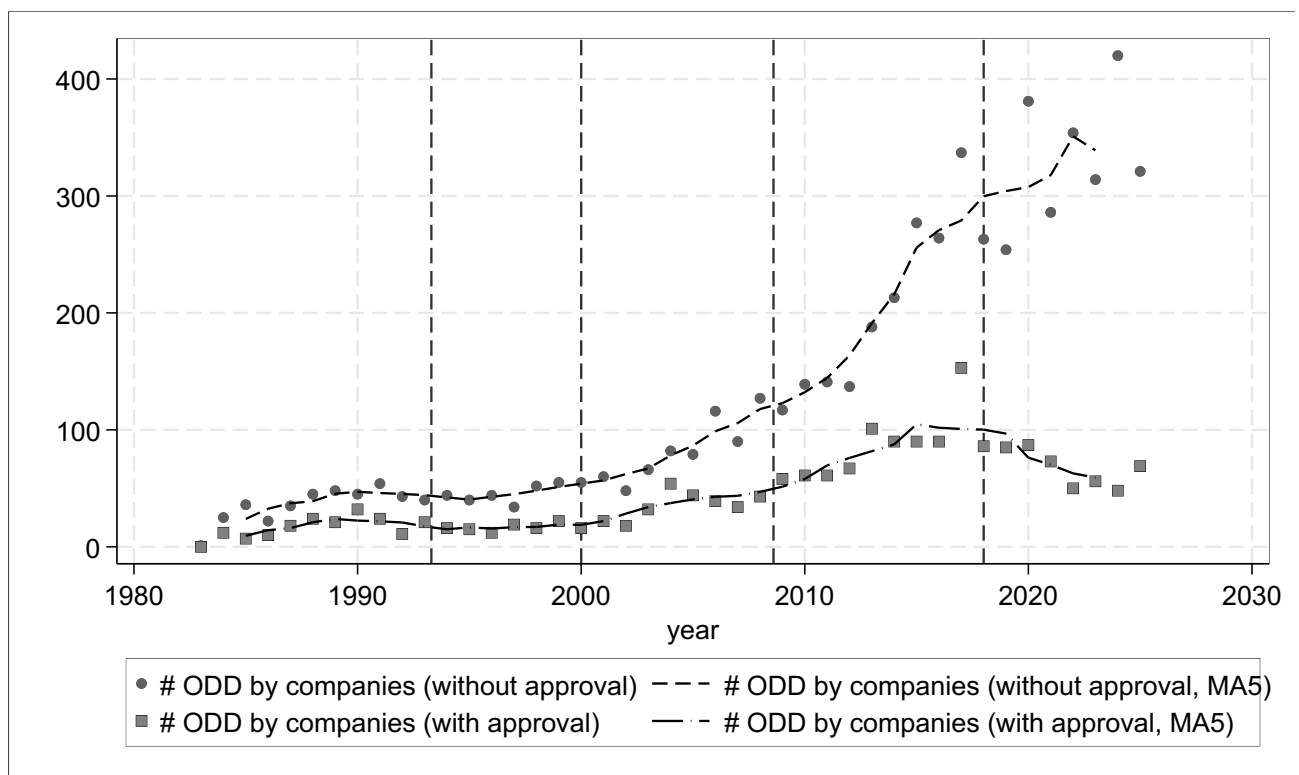
Figure 4. Evolution of the annual number of ODDs (all institutions) by sponsor's status.
Vertical dashed lines indicate the timing of the policy milestones included in the analysis.

Figure 4 reports the annual number of ODDs separately for sponsors with and without a previously approved product. Throughout the sample period, sponsors without a previously approved product account for the majority of ODDs and continue to exhibit an upward trend after 2017, showing no evidence of a structural break. The prominent role of sponsors without a previously approved product is consistent with evidence that smaller firms make a substantial contribution to orphan drug development. For example, Lincker et al. found that 61% of orphan-designated medicines in their European sample originated in small and medium-sized enterprises.³⁶ Several factors may help explain why sponsors without a previously approved product continue to pursue orphan drug designations. Orphan drug projects have a revenue-generating potential as great as non-orphan drugs and their profitability is higher when considered in the full context of developmental drivers including government financial incentives.³⁷ Moreover, orphan drug designations have been associated with higher investor valuations and greater access to external

³⁶ Lincker, Helene, Constantinos Ziogas, Melanie Carr, Nuria Porta, and Hans-Georg Eichler. "Where Do New Medicines Originate from in the EU?" *Nature Reviews Drug Discovery* 13, no. 2 (2014): 92–93.

³⁷ Meekings, Kiran N., Cory S. M. Williams, and John E. Arrowsmith. "Orphan Drug Development: An Economically Viable Strategy for Biopharma R&D." *Drug Discovery Today* 17, nos. 13–14 (2012): 660–64.

finance for biotechnology firms, while orphan-designated products can also contribute to the value of firms acquired before commercialization.³⁸ While sponsors without a previously approved product continue to exhibit an upward trend after 2017, ODDs sponsored by entities with a previously approved product exhibit a marked and persistent decline. This descriptive evidence is consistent with the intuition that the 2017 reform primarily affected sponsors with the capacity to claim the orphan drug tax credit, a hypothesis that is formally tested in the econometric analysis. The results remain virtually unchanged when the analysis is restricted to companies only, indicating that the small number of non-corporate sponsors does not drive the observed patterns (Figure 5).



³⁸ Miller, Kathleen L. "Do Investors Value the FDA Orphan Drug Designation?" *Orphanet Journal of Rare Diseases* 12 (2017): 114. Gorry, Philippe, and Diego Useche. "Orphan Drug Designations as Valuable Intangible Assets for IPO Investors in Pharma-Biotech Companies." In *Economic Dimensions of Personalized and Precision Medicine*, edited by Ernst R. Berndt, Dana P. Goldman, and John Rowe, 305–34. Chicago: University of Chicago Press, 2019. Michaeli, Daniel Tobias, Hasan Basri Yagmur, Timur Achmadeev, and Thomas Michaeli. "Valuation and Returns of Drug Development Companies: Lessons for Bioentrepreneurs and Investors." *Therapeutic Innovation & Regulatory Science* 56, no. 2 (2022): 313–22.

Figure 5. Evolution of the annual number of ODDs (companies only) by sponsor's status.
Vertical dashed lines indicate the timing of the policy milestones included in the analysis.

B. Interrupted time series analysis

To assess the impact of the 2017 reform on innovation for orphan diseases, we consider the time series data on the monthly number of ODDs and estimate an interrupted time series (ITS) model. As in Gamba, Magazzini, and Pertile,³⁹ the total number of ODDs is assumed to follow a Poisson distribution. Given that the dependent variable is a non-negative count, the model is estimated using a generalized linear model (GLM) with a log link function. As discussed above, the specification accounts for the major milestones in the evolution of orphan drug legislation that may have affected the overall level of orphan drug development. The model allows both the level and the slope of the time trend to vary across policy periods, thereby distinguishing short-run discontinuities from longer-term changes in the trajectory of orphan drug development. We also account for the possibility of autocorrelation in the number of ODDs granted over time. Analysis is performed using the *itsa* command in Stata, which allows estimation of single and multiple interrupted time series models.⁴⁰

Table 4 and Figure 6 report the results of the interrupted time series analysis. As shown in Figure 6, orphan drug designations spiked sharply in June 2017. This reflects the FDA's clearance of a backlog of ODD requests, rather than a sudden increase in underlying innovation activity. To assess whether this administrative event influences our estimates, columns 2 and 3 of Table 4 present a robustness analysis excluding June 2017 from the estimation. Columns 2 and 3 also exclude observations prior to October 1984. Originally, the ODA definition of orphan was any disease or condition occurring “infrequently” in the United States without reasonable expectations of profits. The Health Promotion and Disease Prevention Amendments of October 30th 1984 specified the prevalence requirement.⁴¹ Consequently, the early months following the enactment of the ODA represent a transition period during which applications may have been delayed, contributing to the large number of zero observations in the monthly series (see Figure 6).

Across all alternative specifications and levels of temporal aggregation, the estimated baseline trend is positive and highly significant, indicating that the number of ODDs increased steadily over time. When the full sample is considered, the 1993 policy milestone appears to be associated with a

³⁹ Simona Gamba et al., *supra* note 29.

⁴⁰ Ariel Linden, “Conducting Interrupted Time-Series Analysis for Single- and Multiple-Group Comparisons,” *Stata Journal* 15, no. 2 (2015): 480–500.

⁴¹ Matthew Herder, “What is the purpose of the orphan drug act?,” *PLoS medicine* 14.1 (2017): e1002191.

significant downward shift in both the level and the trend of US ODDs (columns 1). However, this result is not robust to the exclusion of observations prior to October 1984. The large number of zero observations during the initial implementation period affects the estimated baseline trend and, consequently, the estimated change in trend associated with the 1993 policy milestone. Once this transition period is excluded, the estimated effect on the trend of the 1993 intervention is no longer statistically significant. By contrast, the introduction of the European orphan drug legislation in 2000 is not associated with a statistically significant immediate change in the level of designations, but it is followed by a significant increase in the underlying trend. This suggests that, while the number of designations did not increase immediately following the introduction of the European framework, the long-run growth trajectory became steeper thereafter. The 2008 milestone does not appear to have significantly affected either the level or the trend of ODDs. Across all specifications, the reduction in the orphan drug tax credit, introduced by the 2017 reform, is associated with a statistically significant decrease in both the level and the trend of ODDs. The negative coefficients remain highly significant regardless of whether seasonality is controlled for through monthly fixed effects. These findings indicate that the reform produced both an immediate reduction in orphan drug development activity and a persistent slowdown in its subsequent growth. This result is consistent with the hypothesis that the reduction in the orphan drug tax credit weakened the expected profitability of orphan drug development and, consequently, sponsors' incentives to invest in this area.

Table 4. Estimates from the ITS analysis on all sponsors (standard errors in brackets)

	(1)	(2)	(3)
Constant (level at baseline)	.7993***	1.3798***	1.3547***
	(.2774)	(.1752)	(.1870)
Time trend (baseline)	.0106***	.0055**	.0055*
	(.0035)	(.0028)	(.0028)
04/1993 (Δ level)	-.5387**	-.3699**	-.3592*
	(.2180)	(.1792)	(.1846)
04/1993 (Δ trend)	-.0078**	-.0026	-.0028
	(.0038)	(.0031)	(.0032)
01/2000 (Δ level)	-.0483	-.0483	-.0388
	(.1107)	(.1107)	(.1153)
01/2000 (Δ trend)	.0062***	.0062***	.0063***

	(.0022)	(.0022)	(.0023)
06/2008 (Δ level)	-.1167	-.0804	-.0789
	(.1122)	(.1063)	(.1092)
06/2008 (Δ trend)	.0011	.0002	.0002
	(.0017)	(.0016)	(.0016)
01/2018 (Δ level)	-.3008***	-.2376***	-.2254***
	(.0894)	(.0803)	(.0822)
01/2018 (Δ trend)	-.0082***	-.0073***	-.0074***
	(.0016)	(.0014)	(.0014)
<i>Observations</i>	516	494	494
Month dummy	NO	NO	YES
Exclude 06/2017	NO	YES	YES
Exclude 01/83-10/84	NO	YES	YES

Statistical significance: *** $p < 0.01$; ** $p < 0.05$; * $p < 0.10$. In parenthesis, SE computed using the Newey-West formula with 12 lags.

Figure 6 reports the observed monthly number of ODDs together with the values predicted by the ITS model presented in column 1 of Table 4. The figure suggests a clear structural break following the 2017 reform. The interruption is particularly striking because it follows almost a decade of sustained and accelerating growth in ODDs. From January 2018 onwards, this strong upward trajectory is interrupted. The reform is associated not only with an immediate reduction in the level of ODDs but also with a marked flattening of the long-run growth trend, indicating that the effect persisted beyond the initial years following the policy change.

Figure 6. Observed and predicted ODDs from the ITS model (M1). Vertical dashed lines indicate the timing of the policy milestones included in the analysis.

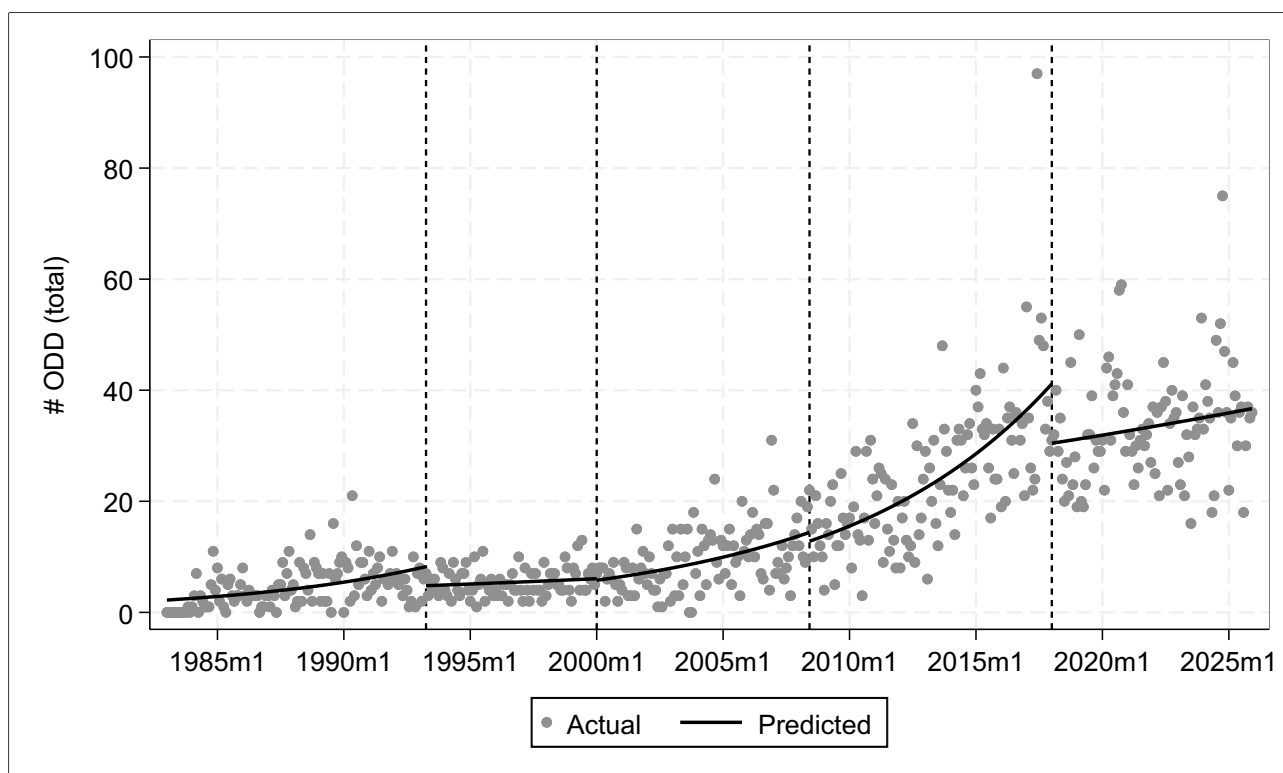


Table 5 and Figure 7 investigate whether the effect of the reform differs according to sponsors' probability to benefit from the orphan drug tax credit. For sponsors without a previously approved product, the post-2018 period is characterized by a significant reduction in the level of ODDs and a flattening of the growth trend (columns 1 to 3, Table 5), although the trend remains positive (see Figure 7). When compared with sponsors with a previously approved product, results show no difference in the immediate reduction in the number of ODDs across the two groups (the coefficient for “01/2018 (Δ level, Δ with approvals)” is not significant). However, the post-reform period is characterized by a steepest negative change in the time trend (the coefficient for “01/2018 (Δ trend, Δ with approvals)” is negative and significant), exhibiting a progressive decline of ODDs over time (see Figure 7). This finding is consistent with the interpretation that the reduction in the generosity of the orphan drug tax credit gradually translated into lower investment in orphan drug development, mainly among firms that were most likely to benefit from the incentive. Three factors may explain why sponsors without a previously approved product also responded to the reduction in the tax credit. First, the credit could still have value to these sponsors if they expected to generate taxable income in the future, even though its expected net present value may be lower. Second, the reduction in the

tax credit may have made these sponsors less attractive to potential acquirers, to the extent that an acquirer expected to benefit from the credit. Third, as discussed in Section IV, our main classification does not account for changes in corporate ownership during the study period. Some sponsors classified as having no previously approved product may therefore have joined a corporate group with an approved product. If the group generated taxable income, they may have been better positioned to benefit from the credit. This misclassification could understate the difference in responses between the two groups, so the magnitude of that difference is likely to be a lower bound. To examine this possibility, column 4 repeats the analysis using the corporate group structure observed in 2025. With this classification, the post-reform reduction in the level of ODDs among sponsors without a previously approved product is no longer statistically significant, while the change in trend remains negative and significant. This exercise also has a limitation: applying the 2025 group structure to the entire study period may overstate a sponsor's ability to benefit from the credit before it joined a group, particularly if the acquisition occurred near the end of the period.

***Table 5 – Estimates from the ITS monthly data analysis accounting for sponsor' status
(standard errors in brackets)***

	Monthly data	Monthly data	Monthly data	Monthly data (parent)
	(1)	(2)	(3)	(4; parent)
Constant (level at baseline)	.4783*	1.0605***	1.0353***	.4171**
	(.2839)	(.1738)	(.1860)	(.1948)
Time Trend (baseline, without approval)	.0102***	.0049*	.0049*	.0072**
	(.0035)	(.0027)	(.0027)	(.0031)
Baseline level (Δ with approval)	-.9690**	-.9749***	-.9746***	.4442*
	(.4102)	(.2867)	(.2871)	(.2594)
Time trend (Δ baseline, with approval)	.0015	.0020	.0020	-.0031
	(.0053)	(.0048)	(.0048)	(.0043)
04/1993 (Δ level, without approval)	-.4426**	-.2666	-.2559	-.3973
	(.2080)	(.1706)	(.1747)	(.2798)

04/1993 (Δ trend, without approval)	-.0078**	-.0025	-.0027	-.0011
	(.0038)	(.0031)	(.0031)	(.0044)
04/1993(Δ level, Δ with approval)	-.3479	-.3715	-.3712	.0796
	(.3574)	(.3196)	(.3246)	(.3387)
04/1993(Δ trend, Δ with approval)	.0005	-.0001	-.0001	-.0040
	(.0060)	(.0056)	(.0056)	(.0055)
01/2000 (Δ level, without approval)	-.0512	-.0512	-.0415	-.0435
	(.1205)	(.1206)	(.1260)	(.1908)
01/2000 (Δ trend, without approval)	.0061**	.0061**	.0063**	.0023
	(.0025)	(.0025)	(.0026)	(.0045)
01/2000 (Δ level, Δ with approval)	.0115	.0115	.0112	-.0038
	(.2378)	(.2379)	(.2404)	(.2250)
01/2000 (Δ trend, Δ with approval)	-.00004	-.00004	-.00003	.0086*
	(.0044)	(.0044)	(.0045)	(.0051)
06/2008 (Δ level, without approval)	-.0859	-.0614	-.0598	-.0720
	(.1509)	(.1476)	(.1468)	(.1670)
06/2008 (Δ trend, without approval)	.0019	.0013	.0012	.0022
	(.002)	(.0019)	(.0020)	(.0022)
06/2008 (Δ level, Δ with approval)	-.1025	-.0608	-.0615	-.0076
	(.2711)	(.2666)	(.2701)	(.2233)
06/2008 (Δ trend, Δ with approval)	-.0026	-.0036	-.0036	-.0050

	(.0039)	(.0036)	(.0037)	(.0031)
01/2018 (Δ level, without approval)	-.2428**	-.2005**	-.1881*	-.1626
	(.0951)	(.0968)	(.0980)	(.1011)
01/2018 (Δ trend, without approval)	-.0068***	-.0062***	-.0063***	-.0064***
	(.0018)	(.0018)	(.0018)	(.0019)
01/2018 (Δ level, Δ with approval)	-.1854	-.1097	-.1100	-.1451
	(.1882)	(.1615)	(.1618)	(.1371)
01/2018 (Δ trend, Δ with approval)	-.0086**	-.0076**	-.0076**	-.0077***
	(.0035)	(.0031)	(.0032)	(.0028)
<i>Observations</i>	1032	988	988	988
<i>Monthdummy</i>	NO	NO	YES	YES
<i>Exclude 06/2017</i>	NO	YES	YES	YES
<i>Exclude 01/83-10/84</i>	NO	YES	YES	YES

Statistical significance: *** $p < 0.01$; ** $p < 0.05$; * $p < 0.10$. In parenthesis, SE computed using the Newey-West formula with 12 lags. Interpretation of estimated coefficients: Δ level/ Δ trend, without approval: change in level/trend as compared to baseline for sponsors without previously approved products; Δ level/ Δ trend, Δ with approval: change in level/trend for sponsors with previously approved products as compared to baseline and compared to sponsors without approvals.

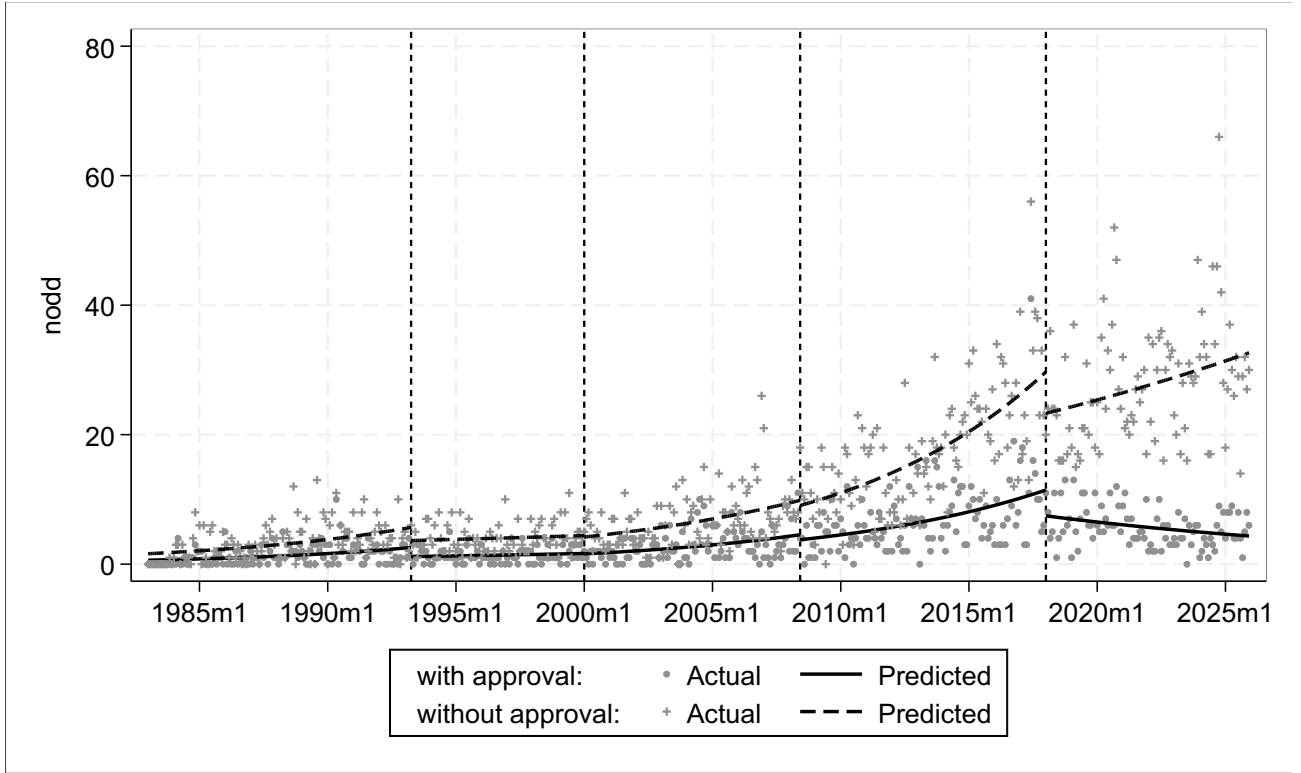


Figure 7. *Observed and predicted ODDs from the ITS model (Model 1 in Table 5) for sponsors with and without a previously approved product. Vertical dashed lines indicate the timing of the policy milestones included in the analysis.*

C. ODD-level analysis

We next examine whether the 2017 reform affected the composition of orphan drug innovation by estimating its impact on the probability that an ODD is filed by a sponsor with a previously approved product. Specifically, we estimate the following probit model:

$$\Pr ODD (with\ approval = 1)_{it} = \Phi\left(\alpha + \sum_{j=1}^4 \beta_j Period_{jit} + \gamma X_{it} + \delta D2018_{it}\right)$$

where the dependent variable is a binary indicator equal to one if ODD i filed at time t is sponsored by an entity with a previously approved product, and zero otherwise. $Period\ j$ captures the time periods defined by the five major institutional changes (US ODA, 1983; Japan, 1993; the European Union/Taiwan, 2000; and the FDA–EMA joint application procedure, 2008; tax-credit cut, 2018), with the dummy $Period_4$ (period 2008–2017) representing the baseline. The coefficient of primary interest is β_5 , which measures the effect of the 2017 reform on the probability that an ODD is filed by a sponsor with a previously approved product with respect to the baseline period. The vector X

includes a set of controls capturing the characteristics of the designated product. Specifically, we control for whether the ODD targets an oncological indication (*DCancer*), whether the designation concerns a diagnostic product (*DDiagnosis*), a preventive product (*DPrevention*), or a therapeutic product (*DTreatment*).

Table 6 reports the average marginal effects from the probit model. The probability that an ODD is filed by a sponsor with a previously approved product does not differ significantly across the pre-reform periods. In contrast, a substantial and statistically significant decline emerges after the reduction of the orphan drug tax credit. Relative to the 2008–2017 period, this probability falls by approximately 11.2 percentage points in 2018-2025 (column 1). The estimated effect is robust to the inclusion of controls for the characteristics of the designated product (column 2). The estimated decline is also stable when we vary the starting year of the sample (columns 3–5) and when we classify sponsors using the corporate group structure observed in 2025 (column 6). To limit potential misclassification from applying the 2025 corporate group structure to earlier years, we restrict this specification to ODDs granted from June 2008 onward (column 6). Regarding product characteristics, the probability that an ODD is filed by a sponsor with a previously approved product is significantly higher for oncology products, suggesting that orphan drug development in oncology is relatively more common among established sponsors. No statistically significant differences emerge for the other product characteristics.

Table 6. Average marginal effects from probit estimation.

	All periods	All periods	From 04/93	From 01/00	From 06/08	From 06/08 (parent)
	(1)	(2)	(3)	(4)	(5)	(6)
Period ₁ (01/83- 03/93)	.125	.0265				
	(.0211)	(.0216)				
Period ₂ (04/93- 12/99)	-.0266	.0202	.0206			
	(.0226)	(.0228)	(.0229)			
Period ₃ (01/00- 05/08)	.0133	.0147	.0150	.0148		

		<i>(.0171)</i>	<i>(.0171)</i>	<i>(.0172)</i>	<i>(.0172)</i>		
Period ₄	(06/08-12/17)	(omitted)	(omitted)	(omitted)	(omitted)	(omitted)	(omitted)
Period ₅	(01/18-12/25)	-.1123***	-.1120***	-.1126***	-.1127***	-.1130***	-.1772***
		<i>(.0108)</i>	<i>(.0108)</i>	<i>(.0108)</i>	<i>(.0108)</i>	<i>(.0109)</i>	<i>(.0117)</i>
DCancer			.0399***	.0382***	.0351***	.0269**	.0588***
			<i>(.0100)</i>	<i>(.0102)</i>	<i>(.0105)</i>	<i>(.0111)</i>	<i>(.0119)</i>
DDiagnosis			-.1589*	-.1013	-.0712	-.0586	.0196
			<i>(.0717)</i>	<i>(.0833)</i>	<i>(.0894)</i>	<i>(.1068)</i>	<i>(.1134)</i>
DPrevention			-.0440	-.0502	-.0386	-.0393	-.0860
			<i>(.0485)</i>	<i>(.0602)</i>	<i>(.0676)</i>	<i>(.0872)</i>	<i>(.0954)</i>
DTreatment			.0004	.0159	.0255	.0266	.0087
			<i>(.0548)</i>	<i>(.0663)</i>	<i>(.0732)</i>	<i>(.0924)</i>	<i>(.1010)</i>

Figure 8 plots the estimated coefficients for the period indicators in the probit models underlying the average marginal effects reported in Table 6. The pre-reform coefficients are not statistically different from zero, providing no evidence that the probability of an ODD being filed by a sponsor with a previously approved product differed from the June 2008–December 2017 reference period. By contrast, the coefficient for 2018–2025 is negative and statistically significant, including when sponsors are classified according to the corporate group structure observed in 2025. This finding reinforces the evidence that the reduction in the orphan drug tax credit substantially altered the composition of orphan drug innovation, reducing the share of ODDs sponsored by entities more likely to benefit from the tax incentive.

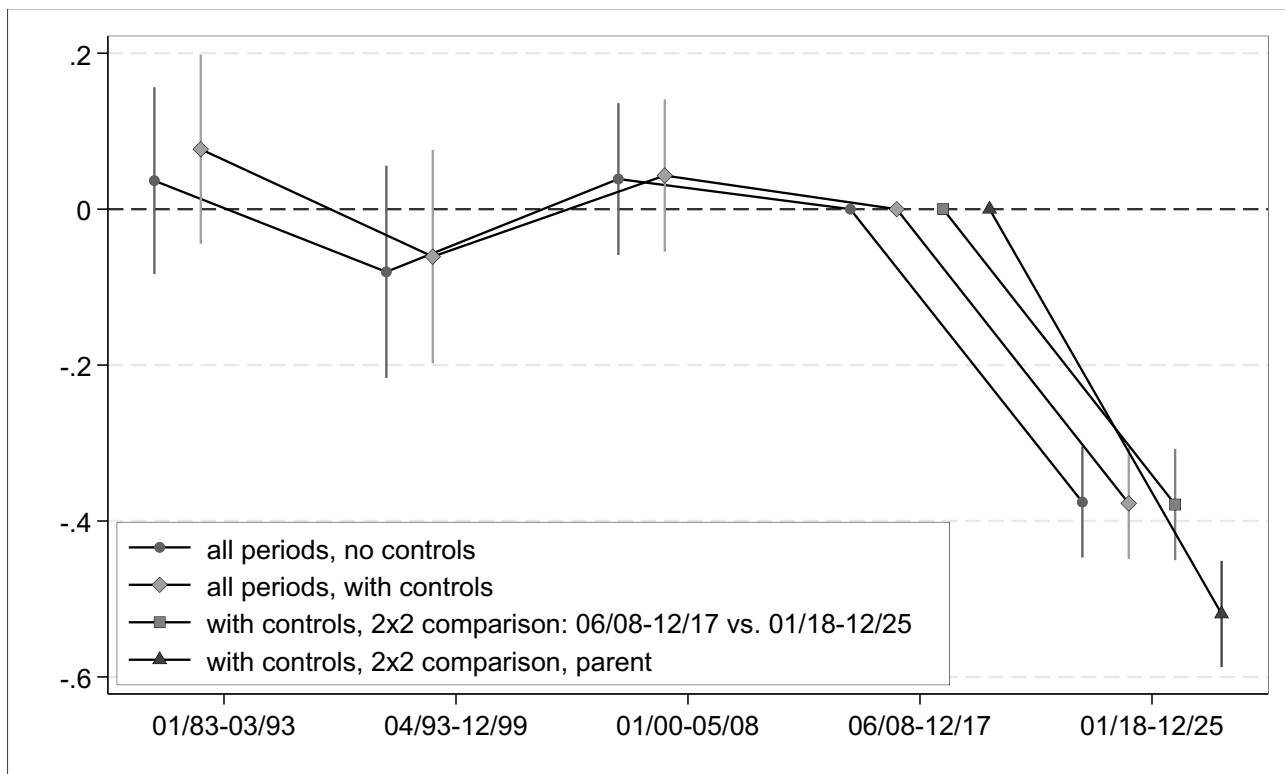


Figure 8. Estimated time coefficients from probit estimation.

VI. Concluding remarks

More than four decades after the enactment of the US ODA, orphan drug policies remain one of the most prominent examples of innovation policies designed to address market failures in pharmaceutical research. By combining push and pull incentives, the ODA fundamentally changed the economics of rare disease drug development and contributed to a substantial increase in ODDs and approvals. Nevertheless, despite its apparent success, relatively little attention has been devoted to understanding the contribution of individual policy instruments and whether their effects differ across firms.

This chapter has focused on one of the most distinctive components of the American orphan drug framework—the clinical trial tax credit—and exploited the reduction introduced by the TCJA of 2017 to assess its long-term impact on orphan drug development. The reform provides a unique opportunity to isolate the role of a specific financial incentive within an otherwise stable regulatory framework.

The empirical evidence suggests that tax credits play a meaningful role in stimulating orphan drug research. Following the reduction in the tax credit, the number of ODDs declined significantly. Importantly, this decline was not uniform across sponsors. The reduction was concentrated among sponsors with a previously approved product, while the response among sponsors without a previously approved product was considerably smaller. Consistent with these findings, the probability that an ODD was submitted by a sponsor with a previously approved product also decreased after the reform.

These findings contribute to a broader understanding of how fiscal incentives influence pharmaceutical innovation. Rather than affecting all innovators equally, tax incentives appear to have heterogeneous effects depending on sponsors' ability to benefit from them. Consequently, evaluating innovation policies solely on the basis of their average effects may overlook important distributional consequences across different types of innovators.

From a policy perspective, these results carry several implications. First, they suggest that fiscal incentives remain an important component of orphan drug policy even in the presence of powerful pull mechanisms such as market exclusivity. Second, they highlight that changes to individual incentives may alter not only the overall level of innovative activity but also the composition of entities undertaking research. Finally, they underscore the importance of considering the interaction between policy design and innovators' characteristics when reforming innovation incentives. A policy instrument that appears fiscally efficient in aggregate may disproportionately affect the small subset of innovators that is most responsive to financial support.

More generally, this analysis illustrates the importance of moving beyond evaluations of orphan drug legislation as a single policy package. Disentangling the respective effects of single incentives—and understanding how these effects vary across different types of firms, technologies, and diseases—represents an important step for both research and policy. Such evidence would help policymakers design more targeted and cost-effective innovation policies while preserving incentives to develop treatments for patients affected by rare diseases. Indeed, as governments continue to revise pharmaceutical innovation policies in response to increasing budgetary pressures, identifying which incentives matter, for whom, and under what circumstances will become increasingly important.