The impact of inflation reduction act on rare diseases and orphan drugs

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INTRODUCTION

- Orphan drugs, defined under the United States (US) Orphan Drug Act (ODA) of 1983, target rare diseases affecting fewer than 200,000 individuals in the United States (US).[1]
- The ODA was established to promote innovation in rare disease treatments by offering, tax incentives, financial grants, and market exclusivity, thereby encouraging sponsors to seek orphan drug designation from the the US Food and Drug Administration (FDA).[1]
- The Inflation Reduction Act (IRA) of 2022, designed to lower the prescription drug costs by its Drug price Negotiation Program (DPNP) explicitly exempts orphan drugs with only a single approved indication from negotiation. However, if an orphan drug receives a second orphan designation or approval to treat additional conditions, it will lose its exemptions to price negotiations.[1]
- The Orphan Drug Tax Credit (ODTC) in the US, allowed pharmaceutical companies to claim a 25% tax credit for clinical research costs for orphan drugs.[2] These incentives from ODA may not benefit manufacturers anymore due to changes in policy and price pressure from IRA.
- The limited DPNP orphan drug exemption creates risk in the already challenging arena of drug development and could disincentivize manufacturer from pursuing rare treatments.[1]

OBJECTIVES

- To qualitatively evaluate the potential impact of the IRA on orphan drugs and drug development strategies in rare diseases. This research aims to offer meaningful insights for industry stakeholders and policymakers as they adapt to the changing landscape influenced by the IRA.

METHODS

- Desk research was conducted for policy analysis and to identify previous policy analyses
- MEDLINE and EMBASE were searched in a targeted manner to identify published literature on impacts of IRA orphan drug exemption on drug development. Professional Society for Health Economics and Outcomes Research (ISPOR) was also searched to identify relevant posters

RESULTS

IRA price negotiation conditions for orphan drugs[3]

Eligibility for price negotiation	Eligibility for exclusion	Eligibility for renegotiation
Drugs designated for >1 rare disease or condition	Drugs with single orphan drug designation with indication only for the same	Not available
Single source drugs post 9 years of FDA approval	• Plasma derived products • New formulations	Until a generic or biosimilar is launched
Single source biologics post 13 years of FDA approval	Drugs below expenditure of $200 million annually (total Part B and Part D)	Not available

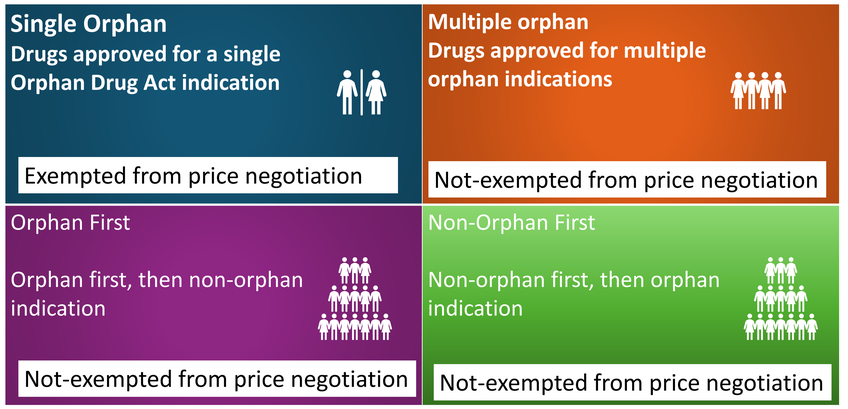
Impact of IRA

Reduction in subsequent indications:

- Orphan drugs are exempt from price negotiation only if they are designated for a single rare disease. If a drug gains approval for multiple indications—even if each is an orphan disease—it becomes subject to pricing controls. This disincentivizes pharmaceutical companies from expanding the use of existing orphan therapies to additional rare diseases, limiting therapeutic options for underserved patients.

RESULTS

Figure 1: Orphan drug categorization in IRA context



We identified Chambers et al. (2023) assessed follow-on indications of treatment options from 2003-2022.[4] We utilized this data and analyzed FDA orphan drug database from 2022 to 2025 April for further understanding.

Orphan Drug Approval landscape:

- Chambers et al. reported that 282 novel orphan drugs were approved by the FDA between 2003 and 2022.[4] We identified six additional approvals between 2022 and April 2025, bringing the total to 288 novel orphan drugs.
- Cumulatively of these 288, 66 (23%) drugs received at least one follow-on indication, including 30 (10%) with multiple follow-ons between 2003-2025 April.
- Chambers et al. (2023) also noted, between 2003 and 2022, 92 (61%) out of 152 total follow-on indications, were for orphan conditions.[4]
- Drugs with multiple indications are more likely to be subject to price negotiations under the Inflation Reduction Act (IRA), provided they generate over $200 million in annual revenue per drug under Medicare Parts B or D. Had the IRA implications been there between 2012-21, 12 sole orphan drugs would have been eligible for price negotiation.[5] For subsequent indication, early revenue forecasting becomes essential. A minimum of 40% revenue increase from subsequent indication may cover the losses due to price negotiation.[6]

Reduced research and development:

Drug development for rare diseases faces challenges like small sample sizes, limited understanding, and complex FDA trial requirements. While the 1983 ODA incentivizes, IRA restrictions on multiple indications for exemptions reduce Return on Investment (RoI), prompting disinvestment.

Reports indicate manufacturers are already halting rare disease projects.[1]

1. AstraZeneca and Soliris

AstraZeneca noted that its drug Soliris, initially developed for one rare disease, later gained approvals for others. Under the IRA's framework, such expansion would trigger price negotiations.[7]

2. Alnylam Pharmaceuticals and Amvuttra

In a real-world example of IRA-related consequences, Alnylam Pharmaceuticals canceled a Phase III trial of its drug Amvuttra for Stargardt disease, a rare eye condition. Although Amvuttra is already approved for hereditary ATTR amyloidosis, pursuing a second indication would have exposed it to IRA pricing negotiations.[8]

RESULTS

Impact of maximum fair price

The IRA's maximum fair prices could be up to 80% lower than current Medicare prices. Given the small patients' size of <200,000 in the U.S., such steep price reductions may render many orphan drugs financially unsustainable.[1]

However, manufacturers have limited recourse—refusing to accept the IRA's pricing can trigger an escalating excise tax ranging from 185% to 1,900% of the drug's daily revenue, potentially resulting in millions in daily penalties.[1]

Delayed launch or non-availability:

Close to 33% drugs would be approved for subsequent indication after they are eligible for price negotiation.[9] Manufacturers may prioritize launching orphan drugs in markets like Europe, and Japan, shifting away from the US-first approach and limiting access to innovative medicines for Americans.[10] Alternatively, manufacturers might prioritize high burden disease areas as first indication to offset price negotiation. Additionally, if companies focus on US, they may launch these drugs with initial high price with patent protect to protect their return on investment on these molecules.

Impact on indications in same disease:

A 2024 article indicated that the Centers for Medicare & Medicaid Services (CMS) may consider multiple orphan indications within the same disease area when evaluating eligibility for the orphan drug exemption. The upcoming 2025 price negotiation for TAGRISSO® (osimertinib) will be a key case to watch, as it holds four approved indications for specific NSCLC mutations and is projected to generate over $1.2 billion in revenue.[11] It remains unclear if line or age-specific indications will count as subsequent indications. The decision on treatments like Tagrisso, approved for multiple non-small cell lung cancer indications, needs to be observed.

CONCLUSION

Orphan drugs, developed to treat rare diseases affecting fewer than 200,000 individuals, often carry high prices due to limited patient populations and the absence of economies of scale. Approximately 60% of these therapies are developed for a single rare disease, with cost per treatment rising as rarity increases.[1] While the IRA aims to curb overall drug spending, its current exemption for sole orphan drugs from Medicare price negotiations may unintentionally discourage manufacturers from pursuing additional indications. This creates a strategic incentive to limit development to single-use orphan drugs, undermining the innovation incentives intended by the Orphan Drug Act and potentially reducing access to treatments for patients with unmet needs.

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