Assessing the Impact of US IRA Regulations on Investment Incentives for Orphan Disease Drug Development

HPR55

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BACKGROUND AND OBJECTIVES

- The Orphan Drug Act of 1983 incentivized orphan drug development in the United States (US) through the accelerated approval pathway (AAP), priority review, and fast-track designation.
- Orphan drugs often have high prices, sometimes maintained even after subsequent indications are approved. The Inflation Reduction Act (IRA) of 2022 introduced Centers for Medicare & Medicaid Services (CMS) price negotiations, affecting high-expenditure drugs, including orphan drugs with subsequent indications.
- This study examined the potential effects of the IRA price negotiations on manufacturers' orphan drug development incentives.

METHODS

Landscape Assessment

- Using the Center for Drug Evaluation and Research database published by the Food and Drug Administration,[1] key factors associated with each AAP submission between 2005 and 2023 were collected (e.g., drug, indication, approval date, and conversion/withdrawal dates, as applicable). For each indication, population size was identified from published sources.
- The collected data were used to identify drugs initially approved for an orphan indication 12+ years ago via the AAP that later received approval for an additional indication.
- One such drug was selected for a case study.

Economic Modeling for Assessing Potential Impact of IRA Pricing Negotiations

- An Excel model was developed and populated with historical approval timing, population size (adjusted to assume 50% market share), and pricing data for the selected case study drug to approximate the net present value (NPV) of revenues over an 18-year period.
- Drug prices at multiple timepoints were obtained from publicly available sources. Using these data, annual prices were interpolated for years between the timepoints, assuming linear change.
- To assess the potential impact of IRA provisions – specifically, negotiating a drug price discount 9 years after approval of the first indication – NPVs (assuming an annual discount rate of 3%) were compared under alternative clinical development scenarios.
- The NPV as of the initial approval date was estimated, assuming an IRA price negotiation 9 years later. Additionally, the NPV as of the initial approval date was estimated using a hypothetical scenario that assumed the initial indication was delayed to coincide with the subsequent indication (Figure 1), which also delayed the IRA pricing negotiation.
- NPVs were compared with analyzed trade-offs among price, volume, and time to first sales.

Figure 1. Model Schematic for NPV Calculator

Figure 1a: NPV Calculation With and Without IRA Price Negotiation

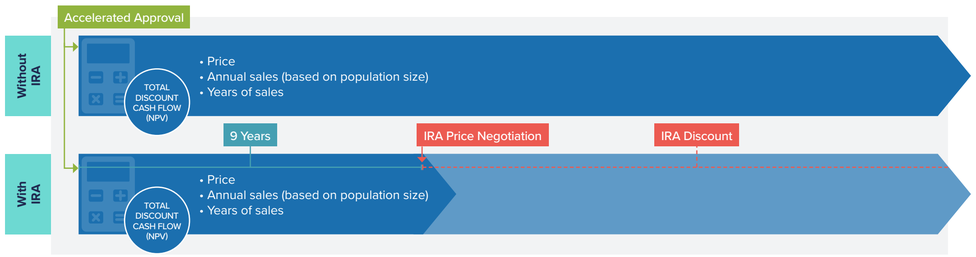
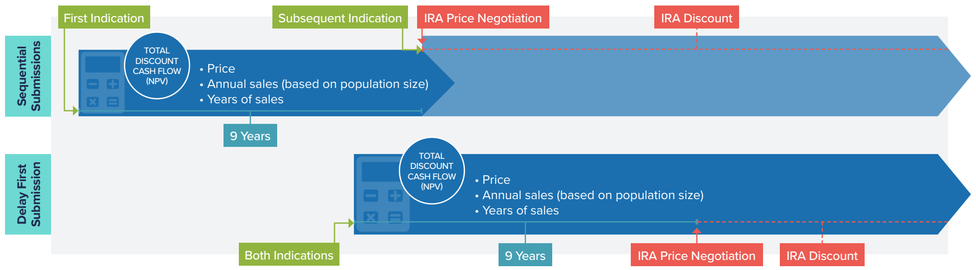


Figure 1b: NPV Calculations Under 2 Submission Strategies With the IRA Price Negotiation



RESULTS

Landscape Assessment

- Among 219 AAP submissions reviewed, 134 (61%) were for the drug's first indication; 147 (67%) involved orphan indications, 48 of which had additional indications submitted via the AAP (Table 1).
- Most AAP submissions since 2005 were in oncology (Table 1).[1]

Table 1. Summary of AAP Submissions 2005-2023

2005-2023	N	%
Number of submissions	**219**	**100%**
First AAP submissions for the drug (i.e., not line extensions)	134	61%
Line extension AAP submissions	85	39%
Orphan designation	147	67%
With additional indications	48	32.7% of 147
Indications		
Oncology	169	77%
Hematology (non-oncology)	17	7.8%
Infectious diseases (e.g., HIV, tuberculosis, anthrax, Chagas disease)	14	6.4%
Other conditions	19	8.7%

Case Study Selection

- From the 48 orphan designation AAP submissions with additional indications, 4 drugs were identified that were approved for 2+ indications via AAP, with 12+ years after approval of the first indication, enabling simulation of the IRA pricing negotiations' impact 9 years after approval of the first indication (Table 2).
- Nilotinib (approved in 2007 for an ultra-orphan population [n ≈ 650] and in 2010 for a broader indication [n ≈ 8,500]) was selected for a case study.

Table 2. Drugs With Multiple AAP Submissions, With First Indication Approved Before 2012

Generic name	Indication	Approval date
Dasatinib	CML resistant or intolerant to prior therapy, including imatinib	28 Jun 2006
	Ph+ chronic-phase CML	28 Oct 2010
Nilotinib	Ph+ CML resistant or intolerant to existing therapies	29 Oct 2007
	Newly diagnosed Ph+ CML	17 Jun 2010
Deferasirox	Chronic iron overload due to blood transfusions	2 Nov 2005
	Chronic iron overload in nontransfusion dependent thalassemia	23 Jan 2013
Everolimus	Subependymal giant cell astrocytoma associated with TSC (adults)	29 Oct 2010
	Renal angiomyolipoma and TSC not requiring immediate surgery	26 April 2012
	Subependymal giant cell astrocytoma associated with TSC (pediatrics)	29 Aug 2012

CML = chronic myeloid leukemia; Ph+ = Philadelphia chromosome positive; TSC = tuberous sclerosis complex.

Nilotinib Case Study Analyses

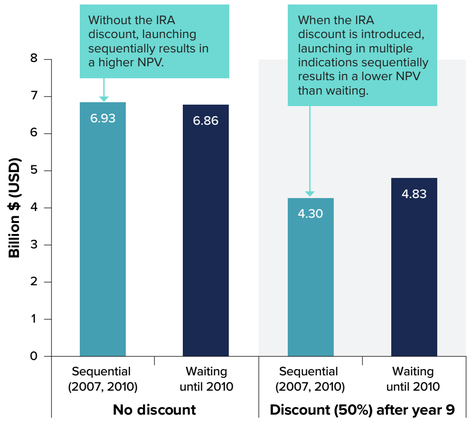
Drug Pricing

- Historical prices for nilotinib in the US were obtained from multiple sources ($6,140 in 2007 and $7,010 in 2014 from the Memorial Sloan Kettering Cancer Center,[2] and $20,042 in 2024 from Red Book[3]). Using the 3 data points, prices for years 2008-2013 and 2015-2023 were estimated by assuming a linear growth trend.

Results

- When nilotinib was approved for the 2 indications sequentially, assuming no IRA discount, the submissions yielded an NPV of $6.93 billion (2007 US dollars [USD]).
- Without the IRA price discount, if the company were to delay the launch for the first indication and choose to launch both indications in 2010 simultaneously, the NPV would decrease to $6.86 billion (2007 USD).
- A hypothetical 50% IRA price discount after year 9 reduced the NPV for both strategies. Delaying the initial approval to 2010 mitigated the loss from 38% to 30%, resulting in NPV of $4.3 billion to $4.83 billion (USD) (Figure 2).

Figure 2. Base Case Discounted NPV of Revenue From Nilotinib Over 18 Years (in 2007 Billion $ [USD])



- Sensitivity analyses were performed to evaluate the effects on the difference in NPV resulting from changes in the IRA discount and population sizes.
  - The higher the IRA discount, the more advantageous the delaying strategy is regarding the NPV (Figure 3).
  - Similarly, the larger the population size, the more advantageous the delaying strategy is regarding the NPV (Figure 4).

Figure 3. Effects of Price Discount Size on NPV of the Revenue Stream (in 2007 Billion USD)

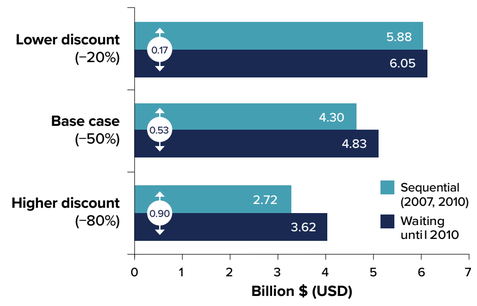
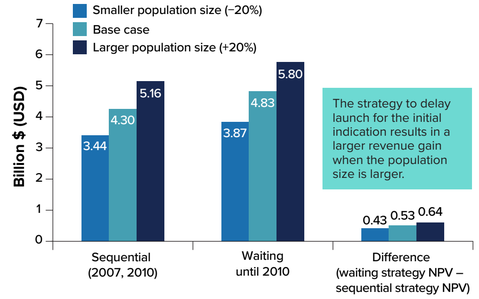
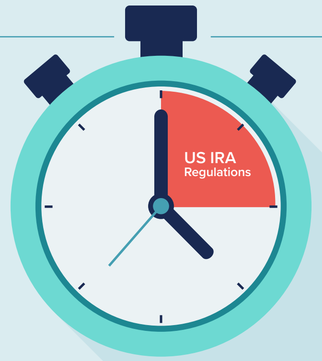


Figure 4. Effects of Population Sizes on NPV of the Revenue Stream (in 2007 Billion $ [USD])



CONCLUSIONS

- Our calculator demonstrated that drug pricing negotiations under the IRA may reduce the NPV of a revenue stream when a company launches a drug with a smaller indication early, with a plan to broaden the indications subsequently.



- This finding may suggest an incentive for manufacturers to shift focus on investment toward clinical development programs for broader populations.
- Further policies are needed to balance cost containment with timely developments for rare serious diseases.

References

1. FDA. Dec 2023. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approvals.
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3. Micromedex Solutions. 31 Oct 2024. https://www.micromedexsolutions.com/.

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The power of **knowledge**
The value of **understanding**

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