Investments in Research and Development for Supplemental Drug Indications—Implications for Drug Price Negotiations

Vokinger, Kerstin N ; Perényi, Gellért ; Wouters, Olivier J

DOI: https://doi.org/10.1001/jamahealthforum.2023.2798

JAMA Health Forum™

Viewpoint

Investments in Research and Development for Supplemental Drug Indications —Implications for Drug Price Negotiations

Kerstin N. Vokinger, MD, JD, PhD; Gellért Perényi, BSc; Olivier J. Wouters, PhD

Author affiliations and article information are listed at the end of this article.

The high costs of brand-name drugs in the US are a major public health concern.[1] In August 2022, the Inflation Reduction Act was signed into law, allowing Medicare to negotiate the prices of a small number of medicines beginning in 2026.[2] In March 2023, Medicare published a memorandum to provide guidance regarding how such negotiations ought to be conducted[3]; the agency published a revised memorandum in June 2023.[4] Medicare Part D net prices or average sales prices of therapeutic alternatives for the selected drugs will serve as a starting point for developing initial price offers. Medicare will consider additional factors, including the extent to which manufacturers have recouped investments in research and development (R&D).[4] If a manufacturer has not recouped its R&D investments, Medicare may adjust the preliminary price upwards and vice versa.[4] In this Viewpoint, we compared the R&D investments for a drug's first indication with those for supplemental indications, demonstrating that the costs associated with gaining approval for supplemental indications may be substantially lower than those associated with the initial indication. This pattern changes the picture of R&D investments for drugs and demonstrates the importance of considering the whole life cycle of a drug when evaluating R&D investments.

The scale of investment by companies needed to bring 1 new drug to market has been the focus of multiple studies. One study estimated the mean R&D investment per product to be $3.2 billion (in 2022 US dollars), based on confidential data supplied by manufacturers.[5] A more recent study arrived at a lower estimate of $1.8 billion (in 2022 US dollars), using publicly available data.[6] In the latter study, the investments for developing cancer drugs were found to be higher than for drugs in other disease areas, related primarily to lower clinical trial success rates with cancer drugs.

These estimates did not capture investments needed to obtain approvals for supplemental indications for the same drug. After the initial approval of a novel therapeutic agent, a company may seek authorization for the agent to be used to treat other conditions or illnesses or for the drug to be used to treat a larger target population for the same disease (eg, any newly diagnosed acute myeloid leukemia cases instead of only relapsed cases). For example, pembrolizumab (Keytruda) was first approved for the treatment of advanced melanoma and subsequently approved for more than 30 supplemental indications by the US Food and Drug Administration (FDA) and more than 15 supplemental indications by the European Medicines Agency (EMA). Similarly, nivolumab (Opdivo) was first approved for the treatment of non–small cell lung cancer before being granted more than 20 supplemental indications by the FDA and more than 10 by the EMA.

This trend is likely to continue given advancements in medicine, notably the growth of immunotherapies and gene therapies, which may be used to target multiple conditions. For example, monoclonal antibodies, such as brentuximab vedotin (Adcetris), bind to specific targets on cells. These targets can be located on cells in different organs, which may enable treatment of several disorders. Such targets are especially common in the treatment of cancers. The approval of subsequent supplemental indications results in larger markets for manufacturers (**Table**).[7] This pattern has implications for drug pricing negotiations in the US. Because the Inflation Reduction Act[2] shields new drugs from negotiation for the first 9 years (and 13 years for biologics) on the market, some of these drugs will likely have been approved for more than 1 indication by the time they become eligible for price negotiations.

Differences in R&D investments can be observed for initial indications vs supplemental indications. The Table shows 4 selected drugs for which R&D data are publicly available from reports filed by companies with the US Securities and Exchange Commission.[8] In these examples, the investments associated with supplemental indications were often substantially lower than for the initial indication.[7] For instance, the R&D investments associated with gaining approval for the initial indication for brentuximab vedotin were estimated to be $2.4 billion (in 2022 US dollars), compared with $443 million for the first supplemental indication, $149 million for the second, $905 million for

Table. Estimated Research and Development Costs for First and Supplemental Indications of Selected Drugs Approved by the US Food and Drug Administration[a]

Approval No.	Indication (summary)	R&D spending (millions), $	Estimated spending on failed trials (millions), $	Cost of capital (millions), $	Total (millions), $
Ravulizumab (Ultomiris)					
First approval	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria	332.8	381.3	110.1	824.1
Second approval	Treatment of adult and pediatric patients with atypical hemolytic uremic syndrome	167.4	80.0	15.2	262.5
Ivosidenib (Tibsovo)					
First approval	Treatment of adult patients with relapsed or refractory acute myeloid leukemia	234.8	1240.0	584.0	2058.9
Second approval	Treatment of newly diagnosed acute myeloid leukemia	131.7	240.9	76.2	448.7
Rucaparib (Rubraca)					
First approval	Treatment of patients with advanced ovarian cancer who have been treated with 2 or more chemotherapy treatments	634.8	233.3	115.5	983.5
Second approval	Maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	309.0	204.2	126.3	639.4
Third approval	Treatment of metastatic castration-resistant prostate cancer	397.4	255.9	107.7	761.0
Brentuximab vedotin (Adcetris)					
First approval	Treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or of at least 2 prior chemotherapy treatments; treatment of patients with systemic anaplastic large cell lymphoma after failure of at least 1 prior chemotherapy treatment	779.1	1132.5	534.0	2445.7
Second approval	Treatment of patients with classical Hodgkin lymphoma at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation consolidation	175.2	123.6	143.6	442.5
Third approval	Adult patients with primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides who have received prior systemic therapy	68.8	46.8	33.8	149.3
Fourth approval	Treatment of previously untreated stage III or IV classical Hodgkin lymphoma, in combination with chemotherapy	376.6	273.3	255.5	905.3
Fifth approval	Treatment of previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphoma, in combination with cyclophosphamide, doxorubicin, and prednisone	254.3	182.0	126.7	563.0

Abbreviation: R&D, research and development.

[a] Research and development costs were extracted from reports filed by companies with the US Securities and Exchange Commission.[7] Spending on failed trials and cost of capital were estimated using the same methods as in a previous study.[6] If trials for multiple supplemental indications (for the same drug) were conducted concurrently, costs were allocated proportionally based on patient enrollment figures.

the third, and $563 million for the fourth. Investments in R&D for the other 3 drugs followed similar patterns. The Table also includes estimated spending on failed trials and cost of capital.

None of the manufacturers conducted additional phase 1 trials to gain their supplemental indications. Instead, they relied on the phase 1 data for the initial indication as evidence of safety, which is common practice for supplemental indications.[9] Ivosidenib (Tibsovo) was the only product for which a new phase 2 trial was conducted for a supplemental indication. The other supplemental indications were based solely on phase 3 trials. This was a key driver of the lower R&D investments for supplemental indications compared with the respective first-approved indications.

In the coming years, the number of drugs approved for supplemental indications will likely increase, especially for treatments of cancers. Whether and how R&D investments should be considered in price negotiations is subject to much debate.[10] Nevertheless, at present, Medicare is set to consider such investments under the Inflation Reduction Act.[2] In its guidance document, Medicare highlighted that a drug's clinical benefit can vary across indications, and the agency may therefore adjust its initial offers based on benefits associated with individual indications.[3,4] If R&D investments are to be considered, it will be important to apply a similar logic and evaluate the whole life cycle of a drug, including supplemental indications.[3,4]

ARTICLE INFORMATION

Published: September 1, 2023. doi:10.1001/jamahealthforum.2023.2798

Corresponding Author: Kerstin N. Vokinger, MD, JD, PhD, Faculty of Law and Faculty of Medicine, University of Zurich, Ramistrasse 74, 8001 Zurich, Switzerland (lst.vokinger@rwi.uzh.ch).

Author Affiliations: Faculty of Law and Faculty of Medicine, University of Zurich, Zurich, Switzerland (Vokinger, Perényi); Department of Health Policy, London School of Economics and Political Science, London, United Kingdom (Wouters).

Conflict of Interest Disclosures: Dr Vokinger reported grants from Swiss National Science Foundation during the submitted work and Swiss Cancer Research Foundation outside the submitted work. No other disclosures were reported.

Funding/Support: Partial funding was provided by the Swiss National Science Foundation (grant, PCEGP1_194607) and the Swiss Cancer Research Foundation (Krebsforschung Schweiz).

Role of the Funder/Sponsor: The funder had no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Rome BN, Egilman AC, Kesselheim AS. Trends in prescription drug launch prices, 2008-2021. *JAMA*. 2022;327(21):2145-2147. doi:10.1001/jama.2022.5542

2. HR 5376—Inflation Reduction Act of 2022. 117th Congress (2021-2022). Accessed July 31, 2023. https://www.congress.gov/bill/117th-congress/house-bill/5376

3. US Centers for Medicare & Medicaid Services. Medicare Drug Price Negotiation Program 2023. Accessed March 21, 2023. https://www.cms.gov/files/document/medicare-drug-price-negotiation-program-initial-guidance.pdf

4. US Centers for Medicare & Medicaid Services. Medicare Drug Price Negotiation Program: revised guidance, implementation of sections 1191-1198 of the Social Security Act for initial price applicability year 2026. June 2023. Accessed July 3, 2023. https://www.cms.gov/files/document/revised-medicare-drug-price-negotiation-program-guidance-june-2023.pdf

5. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ*. 2016;47:20-33. doi:10.1016/j.jhealeco.2016.01.012

6. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *JAMA*. 2020;323(9):844-853. doi:10.1001/jama.2020.1166

7. Vokinger KN, Glaus CEG, Kesselheim AS, Serra-Burriel M, Ross JS, Hwang TJ. Therapeutic value of first versus supplemental indications of drugs in US and Europe (2011-20): retrospective cohort study. *BMJ*. 2023;382:e074166. doi:10.1136/bmj-2022-074166

8. US Securities and Exchange Commission. EDGAR company filings. 2022. Accessed September 7, 2022. https://www.sec.gov/edgar/searchedgar/companysearch.html

9. Dhodapkar M, Zhang AD, Puthumana J, Downing NS, Shah ND, Ross JS. Characteristics of clinical studies used for US Food and Drug Administration supplemental indication approvals of drugs and biologics, 2017 to 2019. *JAMA Netw Open*. 2021;4(6):e2113224. doi:10.1001/jamanetworkopen.2021.13224

10. Garrison LP, Towse A. The IRA's request for product-specific R&D cost information: short-sighted and irrelevant. Health Affairs Forefront. June 5, 2023. Accessed July 31, 2023. https://www.healthaffairs.org/content/forefront/ira-s-request-product-specific-r-d-cost-information-short-sighted-and-irrelevant