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Implications of the Inflation Reduction Act on Post-Approval Research & Development of Biopharmaceutical Medicines

Summary: This study found that exploration of the clinical benefits of pharmaceuticals frequently continues beyond initial FDA approval, and this further research leads to new indications that benefit additional patients.

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Background

Research and development of prescription medicines typically continues well beyond a product's initial FDA approval, paving the way for many important advances in patient care. For example, post-approval research and development can determine whether a medicine can be used to treat different conditions or additional subgroups of patients, such as pediatric and rare disease populations. These advancements, which are generally the result of clinical trials, necessitate supplemental applications to the FDA and are held to the same rigorous FDA review and approval standards as the initial approved application. Post-approval research and development involves a substantial amount of resources and investment from biopharmaceutical companies, with no guarantee of success.

The recently passed Inflation Reduction Act ("IRA") includes provisions that require the government to set prices for certain medicines in Medicare. Medicines may be eligible for government price setting after they have been approved for 7 years (for small molecule drugs) or 11 years (for biologics), with the government-set prices going into effect in the second year after selection (year 9 or 13, since approval, respectively).[1] Under these timeframes, government price setting would occur long before many critically important post-approval advancements are realized. Given it can take several years to conduct the clinical trials for new indications and that for most innovative prescription medicines and that research and development doesn't stop with initial FDA approval, the timing of eligibility for price setting under the IRA threatens to upend the current post-approval research and development process and risks the loss of important new uses or indications that could benefit patients.

This study sought to assess how the timeline for price setting of a medicine under the IRA would impact R&D investment decisions and likely lead to significant reductions in post-approval advances that are meaningful to patients. We looked at new medicines (small molecule and biologics) initially approved by the FDA between 2010 and 2012 and investigated the number and timing of additional FDA approvals for new uses or indications. We also calculated the share of post-approval indications that occurred 7 or more years after a drug's initial FDA approval to assess the potential impact of requiring the government to select medicines for price-setting as early as 7 years post approval.

Findings

- Post-approval indications comprised over half of all indications for medicines in this study.
    - This study identified 88 small molecule and biologic medicines that received original FDA approval from 2010-2012.
    - There were 209 total indications identified for these medicines (88 original approvals and 121 post-approval indications).
    - Post-approval indications comprised 58% of the 209 total indications.
- Additional indications were common throughout the life of the medicines studied, with a large share occurring many years after initial approval.

- Out of a total of 121 post-approval indications observed in this study, 53 indications (44%) were approved 7+ years after the initial approval. (Figure 1)

- 47 (53%) of the 88 medicines included received at least one additional indication after the initial approval.
  - 29 medicines (62%) received a new indication 7+ years after initial FDA approval. (Figure 2)
  - 18 medicines (38%) had at least 3 additional indications after initial approval. (Figure 3)

- Receiving additional indications beyond the first is especially common within oncology medicines (both small molecule and biologics), with 13 of 21 therapies (62%) having more than one indication. Of these, 8 received a new indication 7+ years after the initial approval. (Figure 2)

- Post-approval indications were similarly prevalent for small molecule and biologic medicines. Ten out of 17 biologics (59%) and 37 out of 71 small molecules (52%) received at least one additional indication. (Figure 2)

Figure 1: Timing of new indications approved following initial FDA approval among all medicines initially approved from 2010 to 2012 (n=121 new indications)

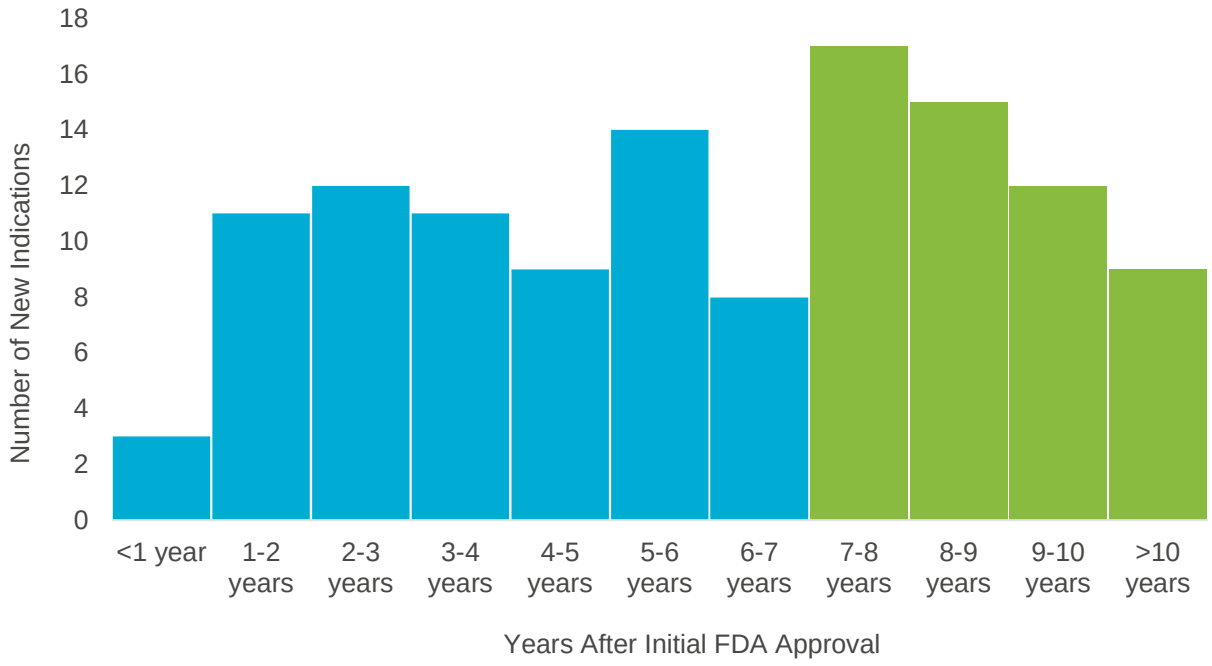


Figure 2: Timing of additional approvals among medicines receiving initial FDA approval from 2010 to 2012

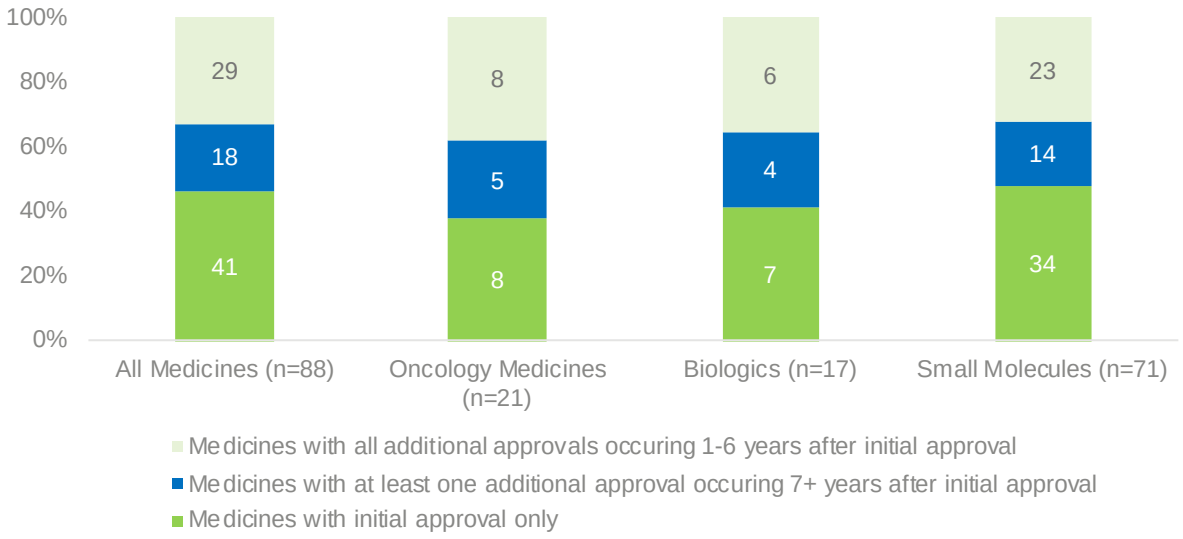
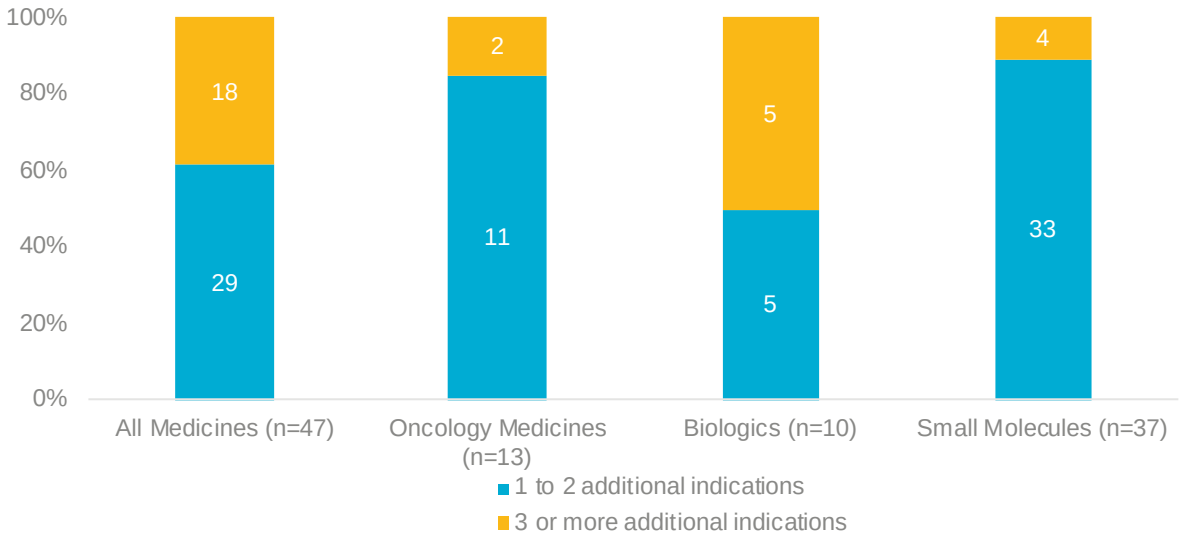


Figure 3: Number of additional approvals among medicines receiving at least 1 additional approval after initial FDA approval from 2010 to 2012



Discussion

Progress against disease does not usually come in the form of a single dramatic breakthrough. More often, significant progress is realized as advances in scientific knowledge build upon each other over time. Our findings demonstrate that innovator biopharmaceutical companies frequently pursue additional FDA-approved indications after a medicine's initial approval, with more than half of the sample having one or more indications added to its label in subsequent years. These indications represent important new medical advances and treatment options for different patient populations and diseases beyond the medicines' original uses. This was especially true for the cancer medicines included in our sample, with nearly two-thirds receiving approval for subsequent uses or indications. These additional indications spanned different cancer types (i.e., solid and hematologic), cancer sites (e.g., breast, prostate, colorectal), different patient subgroups (e.g., HER2+, treatment naïve, early stage), and either as monotherapy or in combination with other therapies.

The important research that occurs after a medicine's initial FDA approval can provide new treatment options for patients, with benefits such as increased survival rates, better health outcomes, and improved quality of life. In cancer, researchers typically begin by testing the medicine in narrowly defined patient populations with an unmet medical need or among those who have failed other treatment options, for ethical, scientific, and practical reasons. For some cancer medicines, subsequent indications show even greater efficacy when administered to patients earlier in the progression of their disease.[4]

This analysis demonstrates that recently enacted government policies threaten the continuation of these critical post-approval R&D innovations by requiring the government to select medicines for price setting as early as 7 years post-approval, before many of the innovations in our sample would have been realized. The work to address unmet patient needs and advance science takes time and significant investment. Subjecting medicines to government price setting so soon after they are first approved, especially for small molecule medicines, reduces the incentive to invest more and puts this much needed continuing research and development at risk. Ongoing work on an expanded cohort will consider implications of the Inflation Reduction Act on small and large molecule development as well as in different diseases.

Methods

For this analysis, we compiled a list of all brand prescription large and small molecule medicines that received an initial FDA approval between 2010 and 2012.[2] Of the 90 medicines initially considered (72 small molecules and 18 biologics), we eliminated 2 medicines that were later removed from the market. We then searched the product labels, FDA approval supplement categories, and approval types on the Drugs@FDA website for the remaining 88 medicines to determine (1) whether additional indications (e.g., changes in patient population treated) had been approved and (2) the date when they were approved and included in the product label.[3]

Limitations

This study did not seek to assess whether these medicines would be on an initial list for government price setting rather the intent was to assess how the timeline for consideration price setting would impact R&D investment decisions. The sample size for this analysis was limited to medicines receiving initial approval between 2010 and 2012. While we strived to ensure the most complete data were captured, not all package inserts and approval letters were available on the Drugs@FDA website. It is possible that some indications may have been missed. To alleviate this concern, package inserts for the time periods immediately before and after any missing inserts were checked for differences. Furthermore, this study did not consider post-approval advances such as new dosage forms or routes of administration, which may improve patient adherence. Thus, our results do not reflect all forms of post-approval innovation.

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1. The Inflation Reduction Act of 2022. Available at: https://www.congress.gov/bill/117th-congress/house-bill/5376/text

2. Brown DG, Wobst HJ. A Decade of FDA-Approved Drugs (2010–2019): Trends and Future Directions. *J Med Chem*. 2021;64(5):2312-2338. doi:10.1021/acs.jmedchem.0c01516

3. U.S. Food and Drug Administration. Approval Date(s) and History, Letters, Labels, Reviews. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

4. Sweeney N, Goss T. The Value of Innovation in Oncology: Recognizing Emerging Benefits Over Time. Boston Healthcare Associates, Inc. 2015.