PHAR Partnership for Health Analytic Research

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Implications of the Inflation Reduction Act Price Setting Provisions on Post-approval Indications for Small Molecule Medicines

Prepared for: The Pharmaceutical Research and Manufacturers of America

Executive Summary

Post-approval research and development (R&D) involves evaluating the safety and efficacy of an approved medicine for new uses, including the treatment of different conditions, different stages of disease, or different patient populations. Post-approval research is disincentivized under the Inflation Reduction Act (IRA), most notably for small molecule drugs which can now be selected for government price setting just seven years after approval.

This study describes the role of post-approval R&D in the life cycle of small molecule drugs, demonstrating that a large and diverse number of clinically important indications are approved after a drug's initial approval by the U.S. Food and Drug Administration (FDA), often many years later. Under the IRA, incentives to develop these later indications will be significantly reduced.

Key findings include:

- Of all the small molecule medicines approved from 2006 through 2012, **more than half** received at least one additional indication after the initial FDA approval.
- **52%** of all indications awarded for these small molecule medicines were post-approval indications, that is, they were awarded to a medicine after its initial approval.
- **45%** of these post-approval indications were approved seven or more years after initial approval. **63%** were approved five or more years after approval.
- Post-approval indications represent important advances for patients:
    - **32%** of post-approval indications expanded a medicine's use to new age groups.
    - **25%** of post-approval indications were for new disease targets.
    - Other important advances included new combination therapies (9**%**), earlier disease intervention (5**%**), new standalone therapies (4**%**), and new genetic targets (3**%**).
- **63%** of medicines first approved as orphan drugs were awarded at least one post-approval indication.
- **Spotlight on Cancer:** Post-approval indications are especially common with oncology medicines and represent important advances for cancer patients:
    - **61%** of small molecule cancer medicines were awarded at least one post-approval indication.
    - **Nearly 40%** of post-approval indications awarded to small molecule cancer medicines were for new disease targets, typically a different type or subtype of cancer.
    - **Nearly half** of post-approval indications received were for a new age group or other expanded population.
    - **17%** of post-approval indications received were for earlier intervention in the progression of the cancer.
    - **41%** of post-approval indications were awarded seven or more years after initial approval.

Background

Small molecule medicines play a crucial role in the treatment of a wide range of diseases and conditions due to their unique characteristics. Their ability to reach therapeutic targets within cells and cross the blood-brain barrier make them indispensable in the treatment of many diseases—including cancer, neurological disorders, mental illnesses, infectious diseases, and many more. They can also be formulated in a variety of dosage forms—from tablets and topicals to inhalants and injections, potentially enabling more tailored administration to individual patient needs and decreasing barriers to patient adherence.

The IRA, which came into law in 2022, contains provisions that mandate the government set prices for specific medicines covered by Medicare. According to these provisions, the government can select eligible small molecule medicines for price setting as early as seven years after they were approved by the FDA, with the government set price coming into effect two years later.

This timeframe for government price setting under the IRA is considerably shorter than the current average timeframe of 13-14 years between a small molecule's initial drug approval and the launch of its first generic competitor.[1] The "effective patent life" is the result of intellectual property protections including patents and data exclusivities, which incentivize R&D investment in both the development of new drugs and the continued research of already approved drugs. Such incentives are needed because the development of a single new small molecule medicine is highly uncertain and can take an average of 10-15 years before initial FDA approval. In addition, further clinical research into a single new use of an already approved medicine can take an additional three to six years of costly phase III trials, with no guarantee of success.

This research focuses specifically on the latter type of investment—the additional "post-approval R&D" that companies conduct on a medicine after it is approved—and the potential impacts that the IRA could have on this important source of innovation.

Biopharmaceutical companies conduct post-approval R&D to evaluate the safety and efficacy of the medicine for new uses, including the treatment of different conditions, different stages of disease, or different patient populations. For example, a medicine approved to treat asthma in adults may be studied post-approval for safety and efficacy in children or post-approval R&D

[1] Grabowski H, Long G, Mortimer R, Bilginsoy M. Continuing trends in U.S. brand-name and generic drug competition. *Journal of Medical Economics*. 2021;24(1):908-917. doi:10.1080/13696998.2021.1952795

may demonstrate that the mechanisms of action for medicine to treat a rare disease could be relevant to multiple diseases. Post-approval R&D is vital to addressing unmet needs for patients, contributing to important advancements in the use of medicines and patient care, and is especially common in oncology, where expanded research on a medicine's safety and efficacy in different cancers or biomarker-positive subgroups is particularly important.

To add to the understanding of the role of post-approval R&D in the drug development life cycle and how the IRA might disrupt this process in the future, this research brief quantifies the frequency, timing, and type of post-approval advances awarded to small molecule medicines approved between 2006-2012. The findings suggest that policies like the IRA, which undermine the longstanding biopharmaceutical timelines that have incentivized continued R&D investment, could sharply reduce companies' investment in post-approval R&D, leading to fewer new medical advances to address patient needs.

Methods

For this analysis, we used data from the FDA to compile a list of all small molecule brand prescription medicines that received an initial FDA approval between January 1, 2006 and December 31, 2012.[2] We then analyzed the product labeling, FDA approval supplement categories, and approval types on the Drugs@FDA webpage[3] for each medicine to determine whether additional indications had been approved, and if so, the date when they were approved and included in the product labeling.

We defined a new indication, for simplicity of analysis, as a single FDA-approved change to a product's labeling. It is possible that an indication defined this way can represent multiple advances.

To characterize the types of advances for patients that these post-approval indications represented, we assigned each post-approval indication to one or more of the following categories, based on the information contained on the product label (categories are not mutually exclusive):

[2] Center for Drug Evaluation and Research. Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals. *FDA*. Published online March 21, 2023. Accessed May 9, 2023. https://www.fda.gov/drugs/drug-approvals-and-databases/compilation-cder-new-molecular-entity-nme-drug-and-new-biologic-approvals

[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

- *New disease target* – the medicine received approval to treat a new disease or organ system.
- *New genetic target* – the medicine received a new approval to treat a genetic subgroup of a disease that it was not previously indicated for.
- *Earlier disease intervention* – the medicine was previously approved to treat a condition after other treatments had failed (later line of therapy) but is now approved for use in an earlier stage of disease or earlier in the treatment process, such as expanding from metastatic-only to all breast cancer.
- *Standalone therapy* – the medicine was previously indicated in combination with other medicines for a particular condition but is now approved to be used to treat the condition on its own.
- *New combination therapy* – the medicine received a new indication for use in combination with another therapy it was not previously approved in combination with.
- *New age group* – the medicine received approval to treat a broader age range of patients than previously approved, such as expanding to treat a pediatric population.
- *Other population expansion* – the medicine received a post-approval indication to treat a different population defined by characteristics other than age, such as whether the patient has been previously treated for the condition or whether the patient possessed or lacked certain comorbidities.

We categorized medicines by therapeutic area based on the therapeutic area associated with a medicine's initial approval.

We generated descriptive statistics on this dataset to highlight the following:

- Number of medicines by number of post-approval indications, e.g., 0, 1-2, 3 or more.
- Number of medicines by timing of their post-approval indications, e.g., <5 years, 5-7 years, or 7 or more years after the medicine's initial approval.
- Number of post-approval indications by therapeutic area. For simplicity of analysis, therapeutic area was assigned based on the therapeutic area associated with the medicine's initial approval. Therapeutic areas are mutually exclusive, but indications designated as treating rare disease may overlap with other listed therapeutic areas. For this analysis, the term "rare disease" is based on orphan designation. For simplicity of analysis, post-approval *indications* are categorized as "rare" if the medicine's *initial* indication carries an orphan designation from the FDA. Thus, a post-approval indication for a non-rare (non-orphan) condition may be categorized as rare, and a post-approval

indication for a rare (orphan) condition may be categorized as non-rare, if the post-approval indication is for a different condition than the medicine's initial indication.

- Number of post-approval indications by type of advance. Types of advances are not mutually exclusive.
- Similar statistics focused specifically on oncology medicines, for which post-approval advances may be particularly important.

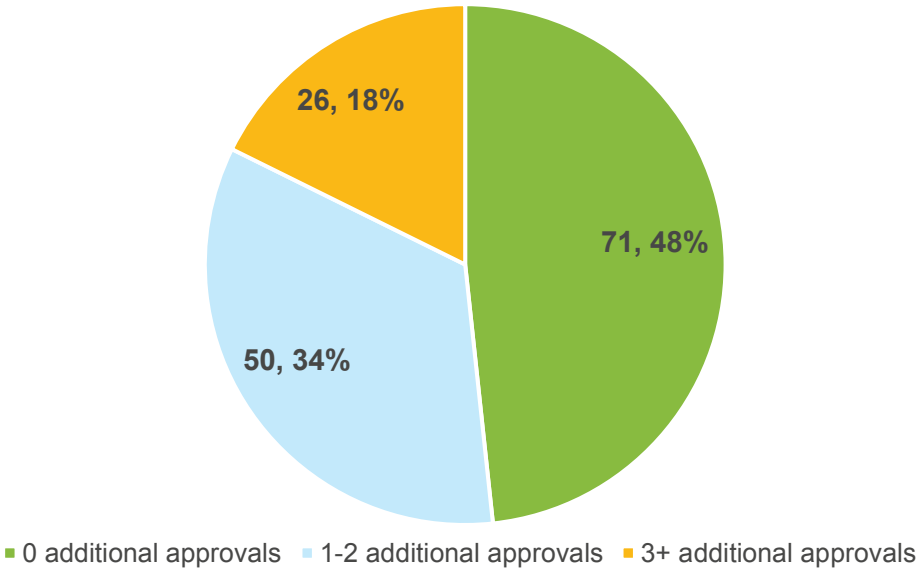
Results

From 2006-2012, a total of 147 small molecule drugs were approved by the FDA. These medicines subsequently received approval for 161 indications in addition to the original 147 indications. Post-approval indications therefore represented 52% of the 308 total indications for the cohort of medicines in this analysis. We note that this may understate the contribution of these post-approval indications because we define a new indication as a single FDA-approved change to a product's labeling, and it is possible that an indication defined this way can represent multiple advances.

Post-approval indications

Continued development of small molecule medicines after their initial approval is common. More than half of small molecule medicines approved from 2006-2012 were awarded at least one post-approval indication, and nearly 20% received three or more additional approvals (**Figure 1**).

Figure 1. **Medicines by number of post-approval indications, for small molecule medicines receiving initial FDA approval between 2006-2012 (n=147 small molecule medicines)**



Of the 161 post-approval indications developed for the small molecule medicines in the sample, 45% of were awarded seven years or more after initial approval, and more than 60% were awarded after five years (**Figure 2**). Moreover, post-approval indications were awarded steadily over many years after a medicine's initial approval and were most common a full decade after initial approval (**Figure 3**).

Figure 2. **Timing of post-approval indications, for small molecule medicines receiving initial FDA approval between 2006-2012 (n=161 post-approval indications)**

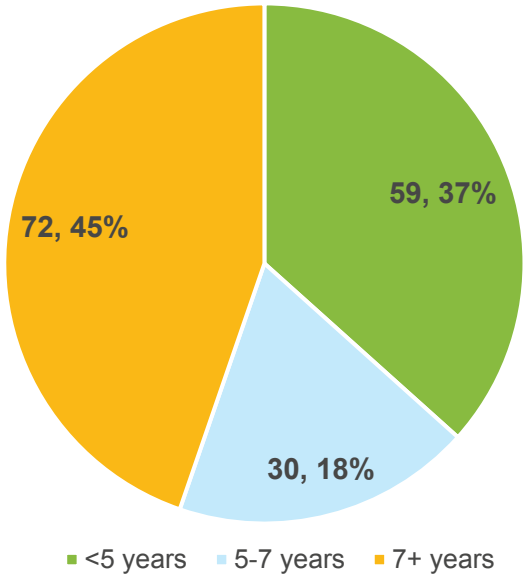
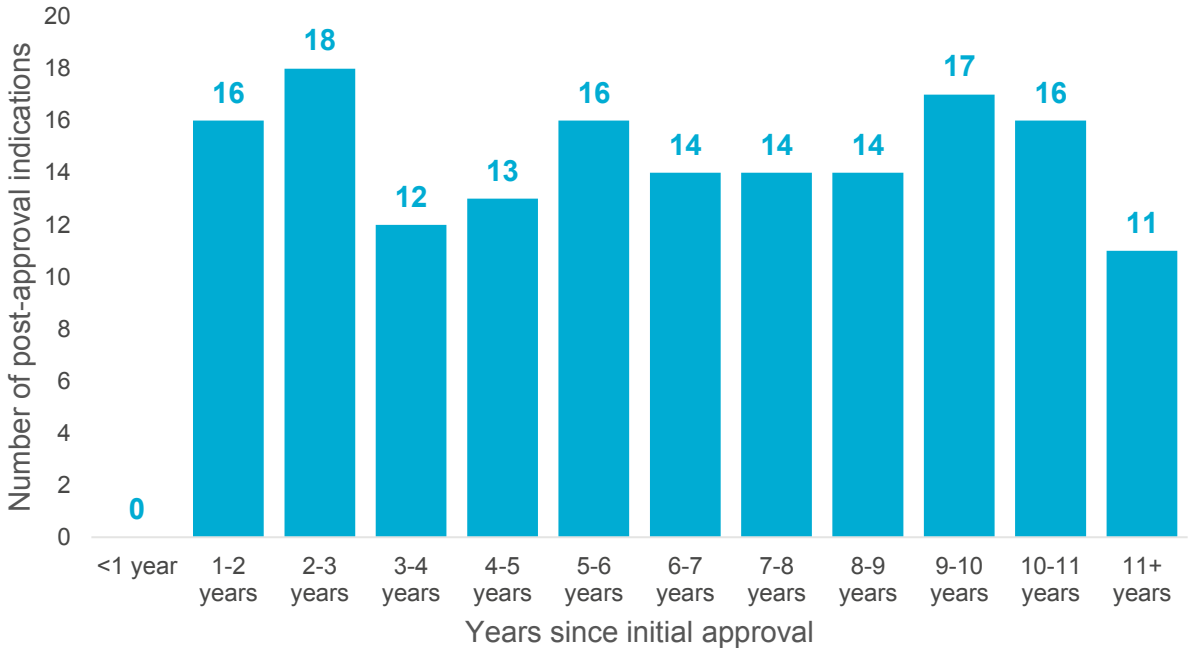


Figure 3. **Timing of post-approval indications for small molecule medicines receiving initial FDA approval between 2006-2012 (n=161 post-approval indications)**

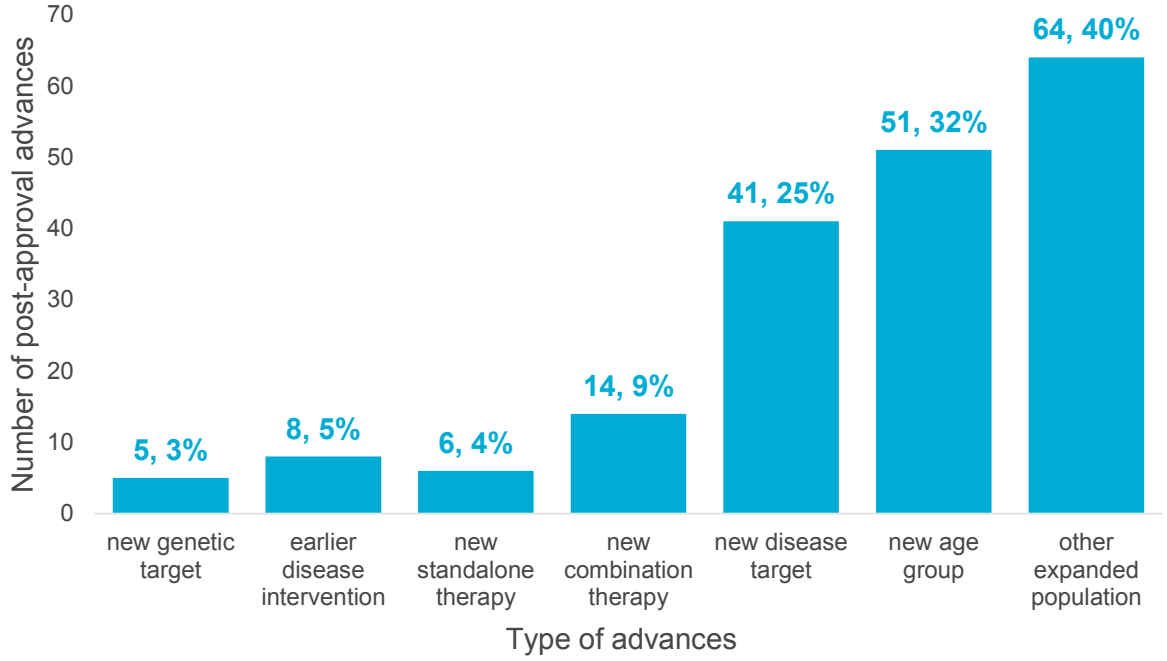


Post-approval innovation by type of treatment advance

Post-approval indications can represent a variety of different types of advances that expand the value of a medicine. These include expanding the use of the drug to different conditions, different stages of disease, or different patient populations (**see text box**).

A quarter of post-approval indications for small molecule medicines awarded between 2006-2012 were awarded for new disease targets (**Figure 4**). This could include different subtypes of a disease (such as cancer), or entirely different conditions from the condition the medicine was originally approved to treat. About a third (32%) of post-approval indications expanded the use of the drug to different age groups (for example, children), and 40% expanded the use to populations in ways unrelated to age, such as to patients with different comorbidities or patients with different treatment experience prior to taking the medicine.

Figure 4. **Type of treatment advances represented by post-approval indications, for small molecule medicines receiving initial FDA approval between 2006-2012 (n=161 post-approval indications)**



Examples of Post-approval Innovation

After receiving initial FDA approval for a medicine, a company often continues to develop the medicine to find new uses, expand treatment to more people, or to build evidence for how to use it more effectively. Below are some examples of ways companies have brought greater value to patients from their medicines through post-approval R&D.

New disease targets. Post-approval research can demonstrate that a medicine approved for one condition is also effective for another condition.

> ***Example:*** *A therapy indicated for the treatment of patients with schizophrenia receives an additional indication for treatment of patients with depressive episodes associated with bipolar disorder.*

New genetic targets. Post-approval research can allow the therapy to be targeted only to patients who will respond to the targeted therapy, avoiding exposure to ineffective therapies and delays in accessing effective therapies.

> ***Example:*** *A therapy for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) receives a post-approval indication for treatment biomarker-positive metastatic NSCLC as detected by an FDA-approved test.*

Earlier disease intervention. Post-approval research can enable patient access to a therapy at an earlier stage of their disease, providing access earlier and when the patient is less sick.

> ***Example:*** *A medicine approved for the treatment of patients with moderately to severely active ulcerative colitis who have had an inadequate response to other therapies receives an expanded indication for all patients with moderately to severely active ulcerative colitis.*

New standalone therapy. Post-approval research can help to reduce the number of medicines needed to treat a condition, avoiding associated adverse events, when efficacy of an adjunctive therapy is shown to be effective as a single treatment.

> ***Example:*** *A medicine indicated as adjunctive (supportive) therapy in the treatment of partial-onset seizures that receives a post-approval indication without other therapies for the treatment of partial-onset seizures.*

New combination therapy. Post-approval research can demonstrate improved efficacy and safety when a medicine is used in combination with one or more other medicines.

> ***Example:*** *A medicine indicated for the treatment of patients with multiple myeloma receives a post-approval indication in combination with two other approved medicines for the treatment of patients with multiple myeloma.*

New age group. Post-approval research on the safety and efficacy of a medicine for additional age populations, often for populations with high unmet need such as pediatric patients, broadens the number of patients who can benefit from a medicine based upon FDA-evaluated safety and efficacy in that population.

> ***Example:*** *A medicine for the treatment of moderate to severe plaque psoriasis in adult patients receives a post-approval indication for patients aged 6 years or older with moderate-to-severe plaque psoriasis.*

Other population expansion. Post-approval research into the safety and efficacy of a medicine for patients beyond the originally intended population or a subgroup of that population, for example, patients with different comorbidities, improves access and knowledge of the optimal use of that medicine for more patients.

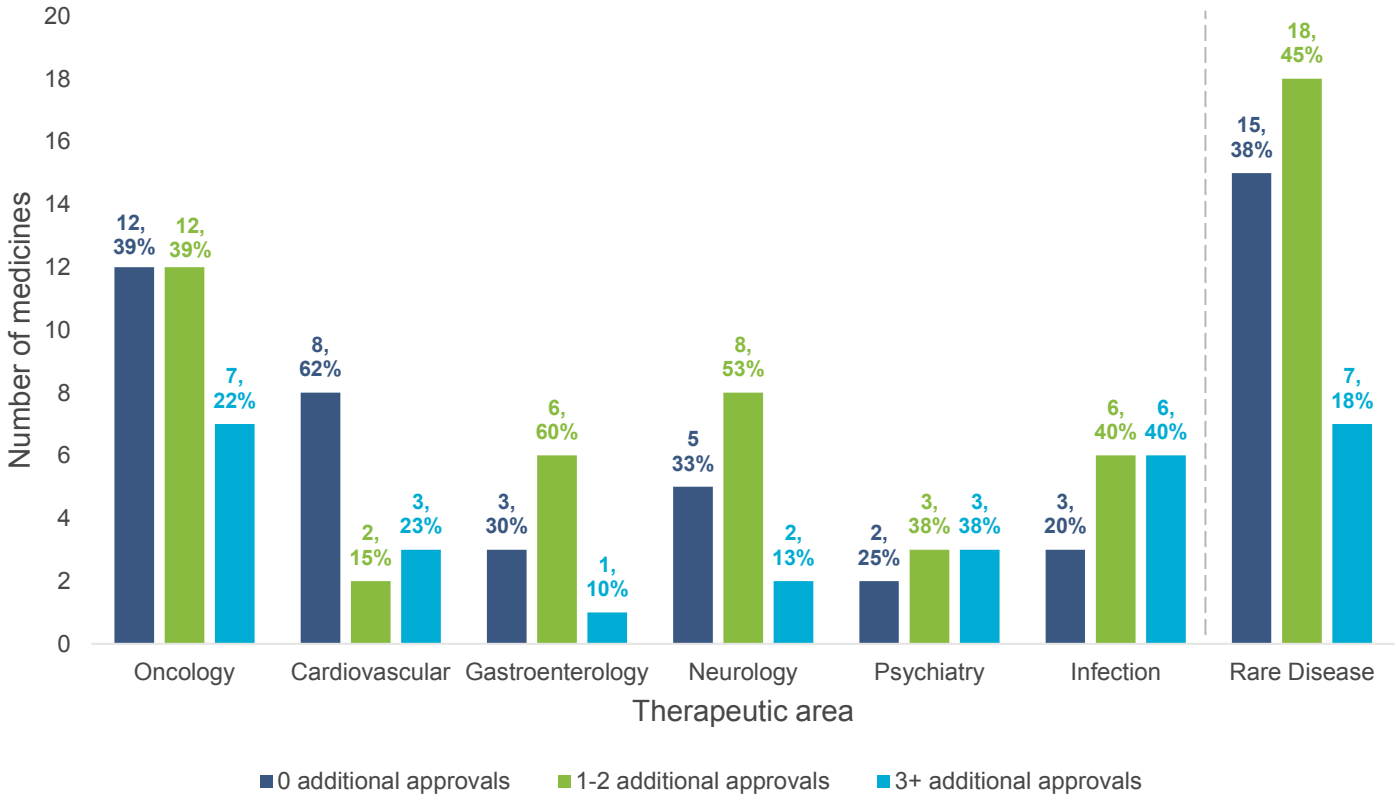
> ***Example:*** *A medicine indicated for patients newly diagnosed with HIV that receives a post-approval indication for HIV patients who have already been treated with other HIV regimens.*

Post-approval innovation by therapeutic area

As shown in **Figure 4**, post-approval indications for a medicine can be awarded in a different therapeutic area than the medicine's initial approval. For small molecule drugs approved between 2006 and 2012, 25% of post-approval indications were approved for a different disease or disease subtype than the initial approval.

Other notable patterns emerge when we look at post-approval indications by therapeutic class (**Figure 5**). Three quarters of psychiatric medicines and 80% of medicines for infectious diseases were awarded at least one post-approval indication. Additionally, more than 60% of medicines originally approved as orphan drugs were awarded at least one post-approval indication.

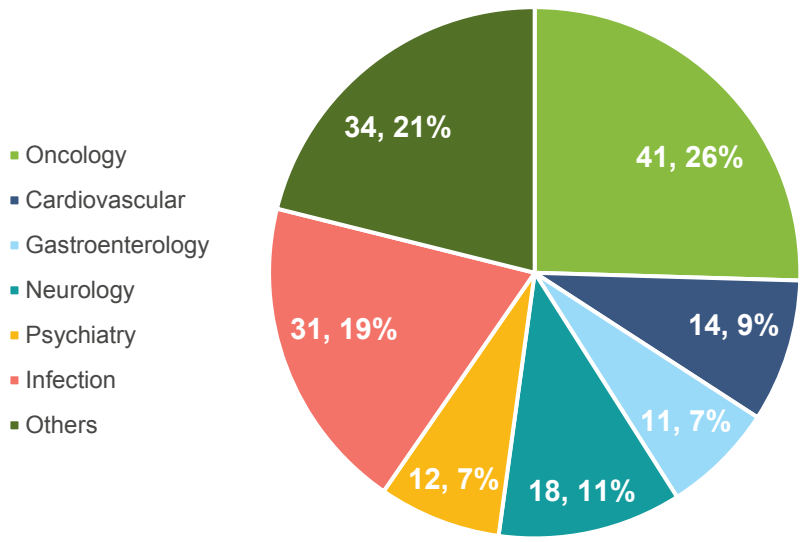
Figure 5. **Number of medicines with post-approval indications by select therapeutic area, for small molecule medicines receiving initial FDA approval between 2006-2012 (n=147 small molecule medicines)**



Note: Rare disease is not mutually exclusive from therapeutic areas listed.

The most common therapeutic areas for post-approval indications were oncology, infectious disease, and neurology (**Figure 6**).

Figure 6. **Number of post-approval indications by therapeutic area, for small molecule medicines receiving initial FDA approval between 2006-2012 (n=161 post-approval indications)**



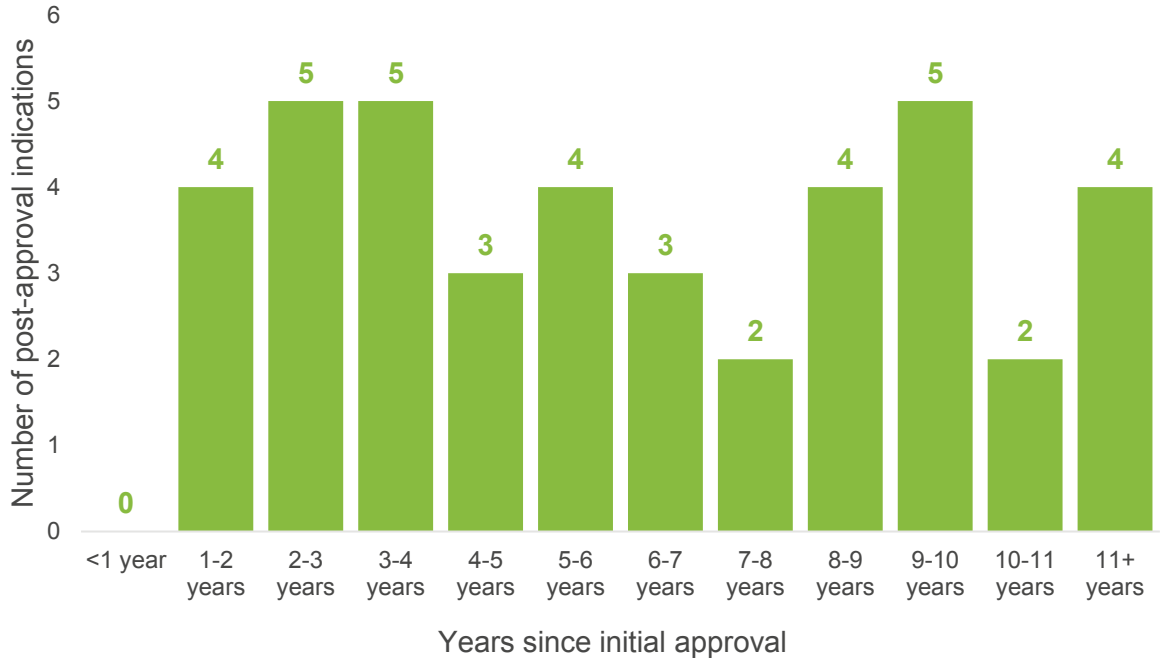
Note: Indications categorized by therapeutic area are based on the therapeutic area of the medicine's initial indication.

Spotlight on Cancer Medicines

Post-approval indications were especially common within the oncology medicines in our sample. Of the 31 small molecule oncology drugs approved from 2006 to 2012, 61% received at least one post-approval indication (**Figure 5**).

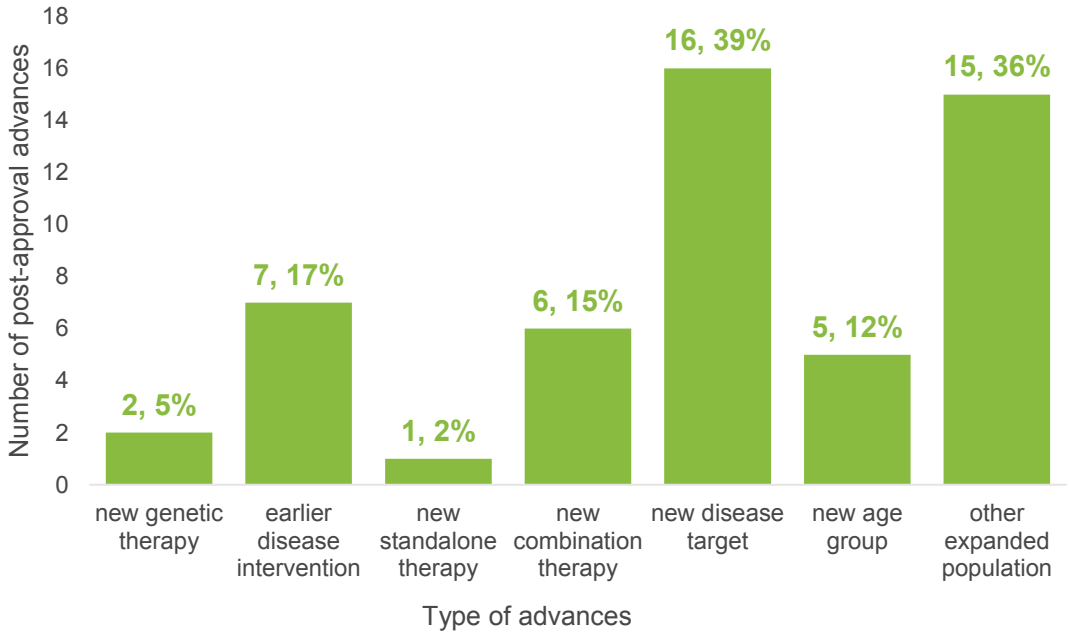
Notably, many of these post-approval indications were awarded late in a drug's life cycle. Of the 41 post-approval indications awarded to these cancer medicines, 41% were awarded seven years or more after the medicine's initial approval, and 59% were awarded five years or more after initial approval (**Figure 7)**. Moreover, post-approval indications for oncology medicines were awarded consistently for eleven or more years following initial approval.

***Figure 7*. Timing of all post-approval indications for oncology small molecule medicines receiving initial FDA approval between 2006-2012 (n=41 post-approval indications)**



The data further show that post-approval indications for small molecule cancer medicines represent important advances for cancer patients. Nearly 40% of these post-approval indications were awarded for new disease targets, generally a different type or subtype of cancer (**Figure 8**). Nearly half were either for a new age group, typically children, or for other expanded populations. Importantly, 17% were awarded for earlier intervention in the progression of the cancer.

Figure 8. **Type of advances represented by post-approval indications for oncology small molecule medicines receiving initial FDA approval between 2006-2012 (n=41 post-approval indications)**



Discussion

Our research shows that innovative biopharmaceutical companies often continue to invest in additional R&D after initial FDA approval to assess the safety and efficacy of approved medicines for a variety of new uses, including new patient populations, additional stages of disease, and different conditions. More than half of the medicines in our sample received one or more new indication on their labeling in the years that followed initial approval. Further, 63% of post-approval indications were awarded five or more years after initial approval. These new indications are significant medical advancements that offer a wide range of conditions and diverse patient populations new treatment options beyond the drugs' original studied use.

Notably, about 60% of oncology medicines and 63% of medicines originally approved as orphan drugs were awarded at least one post-approval indication. As more than 90% of rare diseases do not have a single FDA-approved treatment, and as many deadly cancers (including rare cancers) still lack adequate treatment, post-approval R&D is critical to expanding treatment options for these patients.[4]

[4] https://rarediseases.org/new-study-investigates-the-number-of-available-orphan-products-generics-and-biosimilars/

The IRA,[5] passed in 2022, contains provisions that require the government to establish prices for specific medicines covered by Medicare. According to these provisions, the government can select eligible small molecule medicines for price-setting at seven years after initial FDA approval, with the government set price going into effect two years later. This timeline is significantly shorter than the pre-IRA timeframe of 13-14 years (on average) that biopharmaceutical companies have relied on to both incentivize the large and uncertain investments in R&D required to develop a medicine and to earn revenues to fuel future R&D. These shorter timeframes mean many critical post-approval advancements may not be realized, significantly disrupting the R&D process.

The present study illustrates how newly established government policies can jeopardize the continuity of vital R&D initiatives after drugs are approval by mandating that drugs be selected for price regulation as early as seven years post-approval, a period that predates the realization of many innovations in our sample. Conducting R&D to meet unmet patient needs and further scientific progress requires substantial investment and time. Placing drugs under government price regulation at this point after their initial approval—which is particularly short for small molecule drugs under the IRA—undermines the motivation to invest in this essential R&D and puts the critical treatment advances they bring to patients at risk.

[5] Rep. Yarmuth JA [D K 3. H.R.5376 - 117th Congress (2021-2022): Inflation Reduction Act of 2022. Published August 16, 2022. http://www.congress.gov/