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The Inflation Reduction Act (IRA) and drug development for supplemental indications

December 2024 Brief

Is the IRA a real risk for supplemental indications?

The IRA of 2022's price negotiation provision for drugs continues to be a subject of debate in the healthcare community. In recent months, during the course of Tapestry healthcare initiatives, the topic of supplemental indication development arose as a potentially unintended consequence of the IRA's drug price program. In general, many industry leaders who spoke with Tapestry espoused nuanced views on the IRA and its implications for drug development, with some expressing confidence in their individual companies' ability to reap rewards from pharmaceutical innovation in the short term and others expressing deeper concerns. Considerations and concerns specific to supplemental indication development were especially prominent in discussions.

Researching approved medicines for supplemental indications has long been considered an efficient way to advance innovation for a broad range of patient populations. Even though there is *"still a fair amount of risk when you go into a new indication,"* developing a molecule and *"getting to know its safety profile and manufacturing needs"* before investing in additional uses helps *"de-risk development,"* as one industry executive explained. Therefore, many leaders are wondering not if, but how the industry might approach investing in supplemental indications for approved drugs given that the IRA "clock" starts at an initial indication's approval, thereby compressing the time horizon for potential rewards from any supplemental indication developed.

Against this backdrop, Tapestry explored views on supplemental indication pursuit in the post-IRA market, with a focus on capturing candid industry perspectives and insights as a complement to other emerging research on this topic.[i] The following briefing document provides takeaways from these conversations and potential next steps for consideration by the life sciences community and others.

Pharma is already rethinking risks and rewards for supplemental indication pursuit

Although many leaders in drug development believe there is still ample opportunity for well-differentiated innovation post-IRA, several underscored that the internal risk calculus specific to supplemental indication development is already being reassessed. Key takeaways that emerged from discussions on these topics are as follows:

- The IRA "clock" is already starting to inform decisions around supplemental indication pursuit that may not yet be fully apparent to the public. Small- and medium-sized oncology-focused company leaders in particular emphasized the level of concern and impact vis-à-vis supplemental indications to date.
- Justifying the costs of Phase 3 trials for supplemental indications will become more challenging over time. Importantly, supplemental indications most often receive FDA approval after a Phase 3 trial when compared with initial indications, which may receive approval earlier in development.[ii] Interviewees affirmed that drugmakers are likely to shift away from indication-sequencing strategies of the pre-IRA era and simply prioritize larger populations for an initial indication to obtain the greatest possible rewards on an asset's development.

"Phase 3 trial costs are a main driver of overall R&D cost. When you do it for another indication, you're working against the clock and you're going to get less return on a sizable Phase 3 investment. It's hard to justify that. We're already seeing post-IRA decisions on this happen."

- Interviewees affirmed that the IRA, coupled with increased market competition for high-priority targets, has created pressure for greater efficiency in development timelines in certain areas. Small molecule drugs in therapeutic areas that are relevant for Medicare populations and have historically employed "stepwise development"[iii] approaches for a variety of supplemental indications (e.g., oncology) are under the greatest IRA-related timeline constraints, they underscored. Thus, internal viewpoints from Tapestry discussions aligned with recent data-driven analysis on this specific point.[iv] Indeed, amendments to revise the small molecule disparity have been a recent focus of industry advocates and supporters.[v]

- Some emphasized that concerns about supplemental indication development are most acute when considering orphan drug designation (ODD) status. The IRA exempts orphan drugs from negotiation so long as the orphan drug targets a single indication–a provision that has also ushered in proposed amendments.[vi] Industry internal teams have already been rethinking advancing trials for some indications because of IRA implications linked to loss of ODD status. In parallel, other interviewees observed that ODD definitions are getting (and will continue to get) more creative–e.g., narrower biomarker-based target populations for ODD status. Such trends now may have important IRA implications.

"You're developing a drug for rare disease, which is hard enough. When you do the math for ODD, it may not make sense to do a trial for another indication because you don't have to give up orphan designation."

Post-IRA adaptations will emerge across the industry

New timeline constraints will change R&D trends and strategy for supplemental indications. Stakeholders described several of these and the implications for innovation across short- and long-term time horizons:

- Larger pharma companies are well-positioned to absorb post-IRA supplemental indication challenges, and some are already advancing "workarounds" such as parallel development of assets. Instead of sequencing first, second, and third indications for a single asset, they are *"developing multiple molecules against same target that are not differentiated."* Some might entail *"a single atom change so they can start the clock again."* Firms are employing such workarounds now, and some expect they may soon proliferate. Industry leaders underscored that such a trend is a business response to IRA constraints, is inefficient, and not ideally how drug development would work. Several underscored that small- and medium-sized firms will not be able to initiate such workarounds in pipelines.
- Many oncology drugs targeting early-stage cancers are supplemental indications; therefore, early-stage oncology drug development may be at particular risk in a post-IRA world. Traditionally, companies have initially developed assets for later-stage cancers and then *"walked back"* that asset to focus on supplemental indications for earlier-stage cancers. The latter typically takes longer and is more costly. The IRA may now further complicate such investment, some surmised.
- Over time, some leaders wondered if the landscape will simply yield more off-label utilization as developers back away from investing in supplemental indications. The IRA might undermine regulatory pathways for supplemental indication pursuit, especially if insurers rely on guidelines or compendiums as

evidence to support coverage for off-label treatment in the United States.[vii] Despite such speculation, several industry leaders responded that "off-label as a strategy" for supplemental indications will not likely play out given the need to market products in an era of increased competition, which developers cannot do for off-label indications. Additionally, because reimbursement authorities in many other countries outside the United States do not cover off-label treatments, trial sponsors are likely to embrace some kind of regulatory pathway–even if ex-US–for the supplemental indications they want to pursue.

Multistakeholder, candid dialogue is needed to address R&D in the post-IRA era

The time may be ripe to reconsider optimal ways to advance supplemental indications for existing medicines in light of unmet patient needs, regulatory requirements, and the post-IRA drug market. Given the sensitivity of these issues, it may be prudent to identify new avenues for relevant pre-competitive, multistakeholder discussions given that industry's approach for supplemental indication development may look distinct from pre-IRA paradigms. Stakeholders shared key areas that may require particular attention:

- Efforts to enable R&D efficiency, including trial design and use of surrogate endpoints, are already happening but will now be more important than ever, especially for supplemental indications. Stakeholders need to come together to better define evidence development and *"how quickly high-quality evidence can be pulled together in a time-compressed landscape,"* with appropriate regulatory rigor and safeguards in place.
- Creating greater efficiencies in early drug discovery and pre-clinical data is even more important now to ensure resources are spent as wisely as possible when moving forward with a Phase 1 trial.
- It may be prudent to brief regulators on the potential implications of parallel asset development for administrative procedures and filing/submission trends. Additionally, FDA and other stakeholders should advance thoughtful reflection and feedback opportunities on existing programs to ensure greater efficiency in submissions for supplemental indications—e.g., the Split Real Time Application Review (STAR) program and Real-Time Oncology Review (RTOR) initiative—to ensure that these programs are potentially optimized for a post-IRA world.
- Supplemental indication development should be of interest to the rare disease (and especially rare cancer) patient community; these are patient populations with indications that are, in the eyes of some, *"always going to be supplemental."* Such groups need to be more deeply engaged in the way forward for drug innovation.

Broadly, some noted that industry has largely shied away from talking about the nuances of IRA implications for R&D given its public focus on fighting the IRA's price provision in courts. However, as legislators, policymakers, and regulators continue to assess how best to cultivate a US life sciences ecosystem primed for rapid innovation in science and medicine while addressing issues of pricing and cost, it is important that industry and other diverse stakeholders lean into the complexities of what the IRA means for R&D in as neutral a fashion as possible. Supplemental indication development is one of the priority topics that should be thoughtfully discussed across the community as the IRA's implementation proceeds.

About this document

This document synthesizes views from confidential conversations with life sciences leaders conducted in mid-2024.

Endnotes

[i] David McIntosh, Margaux Hall, and Kyle Connors, "Transactional Implications of Inflation Reduction Act's Drug Pricing Provisions," Bloomberg Law, March 2023; Julie Patterson, James Motyka, and John Michael O'Brien, "Unintended Consequences of the Inflation Reduction Act: Clinical Development Toward Subsequent Indications," *The American* Journal of Managed Care 30, no. 2 (2024), 82-86; Henry Grabowski, Joseph A. DiMasi, and Genia Long, "Postapproval Innovation For Oncology Drugs And The Inflation Reduction Act," *Health Affairs* 43, no. 10 (2024), 1400–1409.

[ii] Initial and supplementary indication approval of new targeted cancer drugs by the FDA, EMA, Health Canada, and TGA | Investigational New Drugs (springer.com)

[iii] Suchita Shah, Jim Meyers, Mitch Kirby, and Lu Chen, "Navigating the Inflation Reduction Act's Impact on Drug Pricing and Innovation," Boston Consulting Group, September 24, 2023

[iv] Henry Grabowski, Joseph A. DiMasi, and Genia Long, "Postapproval Innovation For Oncology Drugs And The Inflation Reduction Act."

[v] "Murphy Introduces Legislation to Eliminate IRA "Pill Penalty" and Support Small Molecule Drug Innovation," news release, February 1, 2024.

[vi] Biotechnology Innovation Organization, "The Orphan Cures Act," accessed December 11, 2024.

[vii] Meera M. Dhodapkar, Joseph S. Ross, Reshma Ramachandran, "US Food and Drug Administration Review Time of Supplemental New Indication Approvals of Drugs and Biologics, 2017 to 2019," (research letter), *JAMA Network Open* 6, no. 6 (2023),e2318889.