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The Value of Follow-On Biopharma Innovation for Health Outcomes and Economic Growth

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Follow-on biopharmaceutical innovations deliver substantial health and economic benefits by improving the safety and efficacy of existing therapies, addressing unmet patient needs, expanding therapeutic applications, and enhancing adherence. Supportive policies are essential to sustain progress and ensure broad access to these medical advances.

KEY TAKEAWAYS

- Biopharmaceutical innovation represents cumulative progress: Each innovation builds on earlier ones. Follow-on innovations are key in this process, refining, optimizing, and adding to first-in-class innovations to improve efficacy, safety, and access.
- Accounting for a substantial share of innovations in key therapeutic areas, follow-on innovations create better formulations and dosage forms of existing therapies or broaden their therapeutic applications to new indications and patient populations.
- Follow-on innovations expand indications and drive patient-centric improvements, increasing treatment adherence by addressing challenges including side effects, complex treatment regimens, or difficult administration.
- Follow-on innovations also deliver economic and health-system benefits. By improving adherence and expanding treatment options, they reduce work absenteeism and hospitalizations, boost productivity, improve health-care quality, and lower costs.
- Follow-on innovations also expand treatment options and encourage competition, which can lower drug prices.
- Policy support is crucial to foster follow-on innovation. Policies such as the Best Pharmaceuticals for Children Act and the Orphan Drug Act encourage such innovations, addressing pediatric and rare disease treatment gaps.

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INTRODUCTION

Innovation, including in the biopharmaceutical industry, represents an inherently cumulative process, advancing through both radical leaps and incremental steps, wherein each advancement builds upon earlier discoveries. The vast existing literature on innovation typically distinguishes between two types of innovation: radical innovations (breakthroughs that make earlier technologies obsolete, fundamentally transforming industries and opening new avenues to explore) and incremental innovations (advances that build upon and extend existing knowledge, refining and optimizing technologies to improve performance or expand their applications and value).[1] Both types of innovation play a very important role in driving progress, often complementing each other to produce long-term technological and scientific advancements.[2]

In the biopharmaceutical industry, radical innovation is often exemplified by the discovery of "first-in-class" therapies—drugs with entirely novel mechanisms of action that address unmet medical needs, targeting previously unaddressed biological pathways. These therapies either tackle diseases for which no effective treatments currently exist or approach conditions in fundamentally new ways. Such breakthroughs are pivotal, not only in providing new hope for patients but also in establishing the foundation for subsequent waves of innovation.

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Follow-on innovations build upon this foundation by enhancing an original innovation's attributes. Such innovations may focus on improving efficacy and safety, reducing side effects, optimizing administration procedures, or expanding the use of an existing treatment to new therapeutic indications or patient groups, resulting in treatments that are not only more effective but also more applicable and user friendly for patients, increasing treatment adherence. Together, radical and follow-on innovations form a dynamic cycle that drives the evolution of health care and continually raises the standard of care. As this report shows, follow-on innovations produce significant health and economic benefits.

FOLLOW-ON BIOPHARMACEUTICAL INNOVATION

Follow-on biopharmaceutical innovations—often interchangeably referred to as incremental or continued innovations—are key to advancing health care. While the term "incremental innovation" can be perceived as implying lesser value compared with radical innovation, this does not do justice to the significant benefits that such innovations produce. This report will illustrate various types of follow-on innovations. Research on this topic tends to present two conceptions of the term: one that encompasses gradual enhancements to an existing drug compound, and another that refers to the development of additional drugs within an established drug class, such as drugs that possess similar mechanisms of action or emerge from post-approval research on approved drugs. This report encompasses both types and refers to them collectively as "follow-on innovations".[3]

Follow-on innovations on a particular drug can improve treatment adherence by offering enhanced efficacy and safety, simpler administration routes, and fewer side effects. From a patient's perspective, making a drug more tolerable may be more revolutionary than the discovery of the original drug itself, assuming it allows for better treatment adherence and increases quality of life. Better treatment adherence for patients with chronic illnesses can improve labor outcomes by reducing disease-related work absenteeism and produce savings for the health-care system through fewer emergency care and inpatient hospital visits.[4] As this report discusses, for both patients and society, follow-on innovations are key in transforming promising drugs into safer and more effective treatment options. The perspective (e.g., that of a patient, medical provider, health-care system, or society) taken to assess an innovation, and the time at which its value is evaluated, often determine what truly constitutes a transformative innovation. While patients and physicians regard both the user experience and the health benefits of these innovations as substantial improvements, conventional value assessment methodologies may undervalue some of these benefits.[5] Regulators have thus increasingly advocated for more patient-centric development of therapeutic solutions, emphasizing their importance from a public health perspective.[6]

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Beyond refining the properties of existing drugs, follow-on innovations can also extend the application of these therapies. This can include making the drug available to new patient populations, such as expanding adult-approved cancer therapies to pediatric patients through rigorous clinical trials, or demonstrating safety and efficacy in new therapeutic areas, such as using a cancer drug for a different type of cancer or an entirely different disease. Follow-on innovations can address accessibility challenges, such as by modifying formulations to improve heat stability for use in low-resource settings, or by developing novel delivery methods (e.g., oral instead of injectable formulations) for simpler and broader administration.

For example, new delivery methods such as pediatric chewable tablets can simplify medication regimens for children.[7] Similarly, transdermal patches can be a useful alternative to oral pills for elderly patients, allowing for easier administration, better bioavailability, and reduced dosages and side effects.[8] By overcoming potential challenges with original drugs and addressing diverse

patient needs, follow-on innovations can improve the utility of existing therapies while creating a foundation for future innovation.[9] Together, radical and follow-on biopharmaceutical innovations form a cycle that drives the evolution of health care and continually raises the standard of care.

A recent working paper shows that the overall productivity of biopharmaceutical innovation—accounting for both radical and follow-on innovations—increased by 30 percent between 1980 and 2009, when measured as the health impact of new drugs relative to research and development (R&D) spending.[10] This contrasts with R&D productivity metrics based solely on the number of new drugs approved per billion U.S. dollars spent on R&D, which decreased during that time.[11] The paper further argues that biopharmaceutical productivity should be evaluated through the health impact of drugs rather than purely the count of new molecular entities (NMEs) introduced, and defines health impact as composed of the number of people using the drugs, adherence (the share of patients taking the drugs as prescribed), and efficacy (the health benefit per prescription). Often overlooked by conventional analyses, follow-on innovation emerges as a key driver of the productivity increase identified in the paper, accounting for nearly half of the total health impact of pharmaceutical innovations in the 2000s.[12] The paper highlights a need to adopt a broader perspective on biopharmaceutical innovation, recognizing the value of both radical and follow-on advances. By measuring productivity through health impact, the study provides a more nuanced understanding of the contributions of follow-on innovation to improving health outcomes and enhancing the efficiency of R&D investment.[13]

Indeed, biopharmaceutical advancements should not be viewed solely on the basis of the chemical novelty of a medication, as drugs can provide significant health and economic benefits even if they are not NMEs. While U.S. Food and Drug Administration (FDA) approval designations (e.g., NMEs vs. non-NME new drugs) reflect the perspective of expert reviewers on molecular novelty and potential clinical advancement, these designations do not fully capture the potential health, economic, and societal values of these innovations (e.g., improved adherence from a simpler treatment regimen reduces hospitalizations, disease-related work absenteeism, or both) or their ultimate medical value in clinical practice. This distinction highlights two important facets of innovation: scientific or technological innovation and patient-centric innovation.

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It is important to note that some first-in-class drugs may not achieve widespread use in clinical practice and are often replaced by improved follow-on drugs. For example, while atorvastatin (Lipitor) was not the first statin—a type of medication used to treat high cholesterol levels—it became the most widely prescribed drug in its class due to its superior efficacy and safety profile. Atorvastatin showed greater potency to reduce cholesterol levels and had better overall cardiovascular outcomes compared with earlier statins, making it the drug of choice for many doctors and patients.[14] This suggests that there is value beyond the first-in-class paradigm, and that later entrants can become standards of care. It is also important to have a variety of statins available on the market, since there is considerable heterogeneity in the way patients respond to medications, with as few as 1 in 50 patients benefiting from one single statin drug.[15]

Importantly, follow-on innovations require significant investment in R&D, as they are not simply adjacent knowledge. An analysis by ATI Advisory—a health-care research and advisory services firm—of the R&D costs for the first 10 Medicare Part D drugs selected for price setting under the Inflation Reduction Act (IRA) finds that on average, 61 percent of R&D costs (spending on clinical studies) are incurred after a drug's first FDA approval. For six out of the eight drugs with data on clinical trial starts, most trials—ranging from 54 to 84 percent—started after approval. This indicates that post-approval R&D is prevalent and important to advancing medical knowledge.[16]

Additionally, between 2008 and 2018, 65 percent of oncology drugs went on to have at least one subsequent indication to another type of cancer post-approval.[17] If the argument is that post-approval research is trivial, this would suggest that most knowledge on the use of medicines can routinely be gathered from the initial approval. But in reality, a majority of clinical trials start after first FDA approval, and the gathering of evidence to observe how medicines actually work in real-world conditions, which can inform later trials, is important to the development of follow-on innovations—whether those are enhancements to an existing drug or potential uses in patients beyond the original indication.

In a recent study analyzing European Medicines Agency (EMA) approvals from 2011 to 2018, IQVIA researchers explored the value and scope of person-centered therapeutics, and showed that they account for substantial shares of innovation in key therapeutic areas. These therapeutics encompass follow-on drugs, drug reformulations, drug repositions, and combinations of drugs or drug/device pairings. Although they are not considered first-in-class, product extensions, or new post-approval indications, the study highlights the substantial value and benefits these innovations have provided to patients.[18]

Follow-on drugs are also prominent on the World Health Organization's (WHO's) Essential Drug List, which includes medicines that are deemed essential to address the public health needs of developing nations. According to a study from the Tufts Center for the Study of Drug Development, up to 63 percent of drugs on the list are follow-on drugs.[19]

TYPES OF FOLLOW-ON INNOVATION

Follow-on innovations encompass a wide range of improvements and adaptations that enhance existing therapies and address unmet patient needs. This section describes different types of follow-on innovation. Benefits resulting from post-approval R&D can include new uses or indications to treat different medical conditions and new patient populations; new formulations that enhance existing therapies; and new dosage forms that can improve patient adherence.[20] Indeed, as a Fraser Institute report notes:

> [T]he first-in-class medicine, the first or breakthrough drug in a new therapeutic class, is rarely optimal or best-in-class … the superiority of successive generations of some drugs attests to the benefits of this work. These efforts may also result in supplemental indications and the ability to treat unrelated conditions with the originator drug.[21]

New Uses or Indications

One type of follow-on innovation involves taking an existing drug and using it to treat a different condition—that is, new uses or indications. This approach is being increasingly used, as it builds on previous R&D investments and derisks clinical trials, as a drug's safety has already been established.[22] Drugs originally developed for one purpose can be adapted for different conditions by identifying additional pharmacological properties and validating them through clinical trials.

Drug development tends to initially focus on a single therapeutic indication, and early-stage clinical research prioritizes this to manage the risk of failure and for regulatory and logistical efficiency.[23] Moreover, unexpected drug properties and pharmacological effects applicable to new uses frequently often only emerge later, as secondary effects are revealed over time through additional research, data acquired from real-world use by large, diverse populations, and evolving scientific understanding—highlighting the iterative nature of biopharmaceutical innovation.[24] Scientific and technological advances—such as in the fields of genomics and artificial intelligence—have also led to the identification of new therapeutic targets. The discovery of such new targets that drugs can interact with offers existing drugs new therapeutic applications.[25]

Further, developing a new drug for even one indication is very expensive, costing up to billions of dollars, which further limits researchers' ability to investigate multiple drug uses early on.[26] Such follow-on R&D is not trivial, as many drug effects are unanticipated due to the complexity of human physiology, making additional uses unpredictable. Long-term studies are often needed to identify secondary effects of drugs.

A well-known example of a drug whose secondary—and most well-known—effect was discovered later is sildenafil (Viagra). Originally developed by Pfizer in the 1980s to treat the heart condition angina by relaxing the smooth muscles of the coronary arteries, it was repurposed in the 1990s after years of clinical observations about its vasodilatory effects to treat erectile dysfunction, and then again to treat pulmonary arterial hypertension (PAH) in 2005.[27]

Follow-on R&D can uncover new ways for existing drugs to address unmet medical needs in other indications, as more knowledge is accumulated about a drug through scientific advances, real-world use in the broader population, and rigorous clinical trials to demonstrate efficacy in new areas.

Other examples include cancer drugs that were subsequently used to treat nononcological conditions. Methotrexate, initially developed as a chemotherapy agent in the 1940s, later showed promise in the treatment of autoimmune conditions, such as rheumatoid arthritis and psoriasis due to its immunosuppressive properties.[28] The variety of uses of methotrexate have made it a cornerstone therapy in both oncology and autoimmune diseases, highlighting the versatility and importance of follow-on innovations to expand the clinical utility of existing drugs.

A third case is AZT (Zidouvudine), originally developed in the 1960s as a potential cancer treatment. When it failed to show efficacy, research on the drug was largely abandoned for decades. In the early 1980s, as the HIV/AIDS epidemic peaked, researchers revisited the drug and discovered its efficacy against the virus.[29] It was then repurposed, becoming the first effective antiretroviral therapy (ART) for HIV/AIDS to be approved by the FDA in 1987, giving hope to many patients with otherwise no treatment options. While AZT did have significant side effects, it laid the foundation for both ARTs and combination therapies, as AZT was later used

alongside other ART drugs to improve efficacy and reduce side effects and resistance.[30] The repurposing of AZT is a landmark case in pharmaceutical history, showing how a drug once considered a failure could revolutionize treatment of a completely different and lethal disease.

Follow-on R&D can uncover new ways for existing drugs to address unmet medical needs in other indications, as more knowledge is accumulated about a drug through scientific advances, real-world use in the broader population, and rigorous clinical trials to demonstrate efficacy in new areas. Developing drugs for novel indications offers several advantages, including reduced time, cost, and risk compared with developing entirely novel molecules and by being able to build on existing safety and pharmacokinetic data.[31] For such repurposed drugs, a study finds that FDA approval rates can be nearly 30 percent compared with less than 10 percent for NMEs.[32]

New Patient Populations

Another type of follow-on innovation involves exploring new patient populations. This entails adapting existing drugs to address the needs of new subsets of patients, such as children or the elderly, as well as individuals in diverse geographic regions. Patient heterogeneity often necessitates multiple therapeutic options, meaning there is value beyond first-in-class drugs, since tailoring treatments to different patient groups may allow those who were unable to take the drug in its original form to do so.

For instance, some drugs initially developed and approved for adult populations are reformulated and studied further to meet the specific physiological and dosing requirements of pediatric patients.[33] By turning adult-approved drugs into child-friendly dosage forms—such as liquid suspensions or chewable tablets—these therapies make administration easier and safer for children. One notable example is the development of dispersible amoxicillin tablets, which dissolve quickly in small amounts of water. According to WHO, pneumonia is the top infectious cause of death in children worldwide, with the highest death rates being in southern Asia and sub-Saharan Africa.[34] Initially produced as a standard antibiotic for adults—a solid, compact pill—the reformulation of amoxicillin into a dispersible tablet to treat pediatric pneumonia made administration simpler for children, providing the flexibility needed for pediatric dosing. WHO recommends dispersible tablets for children, as they are stable at room temperature, are easy to store and transport compared with bottles of amoxicillin liquid suspensions, and maintain efficacy in high-temperature environments, which makes them ideal for treating pediatric pneumonia in resource-limited settings that lack reliable refrigeration.[35]

By tailoring medicines to meet the unique challenges faced by children, older adults, and individuals in low-resource settings, the pharmaceutical industry can bridge critical gaps in access and effectiveness.

Another example is donepezil (Aricept), a treatment for Alzheimer's disease. Donepezil was originally developed and approved by the FDA as an oral tablet in 1996.[36] The tablets presented challenges for elderly patients who may have had difficulty swallowing or suffer from cognitive impairment, making treatment adherence challenging for patients and caretakers. To address these issues, orally disintegrating tablets (ODTs) of donepezil were later introduced. ODT as a drug delivery system was initially developed in the late 1970s as an alternative to tablets for geriatric patients.[37] ODTs dissolve on the tongue without the need for water, making them much

easier to administer to elderly patients. The FDA approved donepezil ODT in 2004, and later, in 2022, approved it as a transdermal patch delivering the medicine directly into a patient's skin, bypassing the digestive system and thus reducing gastrointestinal adverse effects and easing administration.[38] ODTs target the needs of an aging population with unique physiological and practical challenges, improving ease of use and adherence. Further, a study shows that caregivers of Alzheimer's disease patients on donepezil treatment are more satisfied with ODT than with tablets due to the former's enhanced ease of use.[39] Such adaptations show how tailoring medication forms to elderly patients can address barriers to treatment, ultimately improving health outcomes for older adults.

Addressing the needs of diverse populations—across different age groups and geographic regions—helps foster equitable access to essential medical treatments. By tailoring medicines to meet the unique challenges faced by children, older adults, and individuals in low-resource settings, the pharmaceutical industry can bridge critical gaps in access and effectiveness, extending the reach of modern medicine to underserved areas where environmental factors and limited health-care infrastructure often hinder treatment accessibility. These follow-on innovations exemplify the importance of patient-centric approaches, fostering inclusivity and addressing disparities in health-care access.

New Formulations

Another type of follow-on innovation consists of new formulations—how the various active and inactive compounds of the drug are combined to form the medicine—that offer significant therapeutic benefits. New formulations can play an important role in improving safety and efficacy and addressing side effects.

One example is bimatoprost (Lumigan), a treatment for glaucoma, an eye disease caused due to high eye pressure, which can lead to permanent vision loss or even blindness if left untreated. Lumigan, approved by the FDA in 2001, could slow disease progression by reducing eye pressure, but often caused severe red eye, which discouraged adherence. Scientists at Allergan, the maker of Lumigan, discovered a novel formulation with much fewer side effects. The drug was reformulated to minimize red eye, improving safety without compromising efficacy.[40]

New formulations can play an important role in improving safety and efficacy and addressing side effects.

The development of degludec (Tresiba), a diabetes treatment, is another example of how formulation improvements can improve efficacy and reduce side effects. Degludec is an ultralong-acting insulin that provides a stable glucose-lowering effect for more than 24 hours, which reduces fluctuations and the risk of hypoglycemia (low blood sugar) compared with traditional long-acting insulins such as glargine.[41] Glargine was approved by the FDA in 2000, and degludec followed in 2015 after significant R&D investment.[42] Degludec's extended duration and reduced side effects improved outcomes for patients with adherence difficulties.[43]

Similarly, later generations of beta-blockers—drugs used to manage cardiovascular conditions, primarily hypertension—have shown significant value by improving upon the safety and efficacy of earlier versions. First-generation nonselective beta-blockers, such as propranolol, were effective but had significant pulmonary side effects. Second-generation beta-1 selective agents,

known as "cardioselective" drugs, including metoprolol, bisoprolol, and atenolol, improved safety by targeting receptors primarily in the heart, reducing side effects and making them safer for patients with lung problems.[44] Third-generation beta-blockers, such as carvedilol and nebivolol, added vasodilating effects, which helped relax blood vessels, further enhancing their utility in treating high blood pressure. These advances have expanded treatment options for physicians and patients, addressing the heterogeneity of patient profiles and needs.

Another example of an impactful follow-on formulation innovation is the development of Genvoya (EVG/c/TAF/FTC), a once-daily, single-tablet regimen developed by Gilead to treat HIV infection, approved by the FDA in 2015.[45] Compared with previous drugs such as Stribild (EVG/c/TDF/FTC), Genvoya's formulation replaced TDF (tenofovir disoproxil fumarate) with TAF (tenofovir alafenamide) at a much lower dose. TAF is considered safer than TDF due to its lower dose, making it safer for the bones and kidneys.[46] Since Genvoya has similar efficacy with a better safety profile, it became the standard of care over Stribild in HIV treatment. The transition from TDF, first described in 1993, to TAF in the early 2000s, involved substantial advances in drug design and delivery, reflecting the cumulative nature of pharmaceutical innovation that builds on earlier innovations to create safer and more effective therapies for patients.[47] Follow-on formulation innovations such as these ensure that therapies continue to evolve, offering more tailored and effective solutions to patients over time.

New Dosage Forms

Another type of follow-on innovation entails the development of new dosage forms, which may involve different administration routes designed to increase patient adherence and improve treatment outcomes. Such innovations can make medications more convenient, comfortable, and effective for patients, addressing challenges such as fear of needles and the need for frequent dosing.

Improving patient adherence and addressing accessibility challenges are critical priorities in the development of new dosage forms. For example, converting injectable drugs to oral formulations can substantially reduce the burden on health-care providers and improve patient adherence through greater convenience. By tailoring and optimizing delivery mechanisms, follow-on innovations can address key barriers to consistent medication use and improve health and economic outcomes.[48]

For example, in a study of type 2 diabetes, 81.9 percent of participants preferred a once-daily oral treatment over a once-daily injectable, with 57.5 percent ranking the administration route as the most important factor for their preference.[49] Reasons for the oral preference included fear of injections or needles, fear of consequences of incorrect administration, fear of pain at the injection site, and enduring stigma around injectable medication use.[50] Further, a study comparing a once-daily oral tablet with a once-weekly injectable finds that 76.5 percent of participants preferred the once-daily oral and 23.5 percent preferred the once-weekly injectable.[51] Heterogeneity in patient preferences is another reason for the importance of different administration forms.

In PAH, an illness caused by the constriction of the arteries that carry blood from the heart to the lungs, medicine previously delivered intravenously or subcutaneously, which created complications for patients, was later developed as a pill and approved by the FDA in 2013. The pill form of the medicine, the first orally administered treatment available, offered patients a

more convenient and easier-to-tolerate method of delivery, promoting the heart muscle to relax and decrease blood pressure in patients with PAH.[52]

Further, extended-release therapies—which allow medications to be released slowly over time, reducing the frequency of dosing—can improve patient convenience and adherence. This is especially beneficial for managing chronic conditions such as diabetes and cardiovascular diseases. For example, extended-release metformin, which can be given once daily, simplify the dosing schedule for patients with type 2 diabetes, reducing the burden of multiple daily doses while maintaining effective glycemic control and reducing the risk of gastrointestinal side effects.[53] This also addresses forgetfulness, a common issue in adherence.[54]

As another example, in the treatment of depression, Prozac Weekly, an extended-release oral form of fluoxetine (Prozac) was developed to improve patient adherence and outcomes. By extending the dosing interval from daily to weekly, it reduces the burden of daily medication, which is particularly beneficial for patients with chronic conditions necessitating long-term therapy. A study finds that the efficacy of the once-weekly form is similar to that of the daily form, but patience adherence to the medication was higher (87.5 percent in patients receiving the once-weekly fluoxetine vs. 79.4 percent in patients receiving the daily medication).[55] A survey study also finds that once-weekly vs. daily dosing was more convenient for patients requiring long-term maintenance therapy for major depressive disorder.[56]

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Additionally, in Parkinson's disease, the introduction of controlled-release forms of levodopa/carbidopa—medications used to treat the condition—deliver a substantial improvement for patients with advanced disease. As the disease progresses, many patients experience symptoms that can no longer properly be controlled by standard oral therapy due to the medication's short half-life, which results in more motor and nonmotor symptoms (e.g., fatigue, anxiety) negatively affecting patients' quality of life. New forms of levodopa-carbidopa gel, administered through a pump directly into a patient's intestine, bypass absorption issues associated with oral therapies, improving efficacy and reducing disease symptoms, patients' quality of life, and caregiver burden.[57]

Further, innovations such as transdermal patches are also revolutionizing drug delivery to improve adherence and reduce side effects. Patches for hormone therapy, for example, offer a noninvasive, steady delivery of hormones, providing consistent relief with fewer gastrointestinal side effects.[58] Such dosage-form innovations reflect a commitment to patient-centered care that extends beyond simplifying treatment regimens. By addressing challenges such as forgetfulness, logistical constraints, and side effects, follow-on innovations contribute to improved health outcomes and greater health-care equity.[59]

ECONOMIC BENEFITS OF FOLLOW-ON INNOVATION

The previous section discusses different types of follow-on innovation and their health benefits for patients. This section describes the economic benefits of follow-on innovation.

In addition to providing patients with increased therapeutic options, the emergence of multiple follow-on drugs in a therapeutic class can offer societal benefits by driving price competition, reducing costs for employers and taxpayers.[60] If follow-on innovations were truly trivial, as some critics falsely contend, payers and pharmacy benefit managers (PBMs)—who manage medicine coverage and access in the United States—would have little incentive to offer reimbursement and coverage beyond the previously approved medicine.

Moreover, follow-on drugs to an original drug compete with the earlier version, which might often already be available as a generic. These competitive market dynamics ensure that the United States benefits from the broadest access to novel drugs while also maintaining extensive availability of cheaper generic drugs. Access to novel therapies has greatly expanded, while the generic share of retail prescriptions has risen from 18.6 percent in 1984 to 90 percent in 2021.[61]

Additionally, improved adherence—which can stem from enhanced formulations or dosage forms—can also generate considerable economic benefits. Increased adherence can improve labor outcomes by reducing illness-related absenteeism and lower health-care costs by decreasing hospital stays and complications from untreated chronic conditions.[62]

A study evaluating the impact of medication adherence on health-care utilization and costs for several chronic conditions finds that high adherence was associated with lower disease-related medical costs for diabetes and hypercholesterolemia, resulting in a net reduction in overall health-care costs. Further, patients with diabetes, hypertension, hypercholesterolemia, and congestive heart failure with high adherence had significantly lower hospitalization rates.[63]

A review study published by the Integrated Benefits Institute also finds a positive relationship between medication adherence and short-term disability outcomes, particularly for patients with diabetes. In the United States, an estimated 38.4 million people, accounting for 11.6 percent of the population, have diabetes. This includes 29.7 million diagnosed cases and 8.7 million undiagnosed cases.[64] The study suggests that employers could mitigate costly productivity losses by increasing adherence rates for employees with chronic conditions.[65] Other studies also show that adherence can reduce hospitalizations, emergency room visits, and provider office visits, generating savings for health-care systems.[66]

A study by the Organization for Economic Cooperation and Development (OECD) reports that poor medication adherence can result in severe health complications and increased health-care utilization. For the three-most-prevalent chronic conditions—diabetes, hypertension, and hyperlipidemia—the OECD paper notes that every additional dollar spent on medications for patients with high adherence can generate between $3 and $13 in savings on emergency department visits and inpatient hospitalizations. Improving adherence is critical, because failure to take medications is a very common problem.[67] Among patients with diabetes, hypertension, and hyperlipidemia, 4 to 31 percent do not fill their first prescription, and of those who do, only 50 to 70 percent take their medications consistently.[68] Addressing this nonadherence challenge by creating more convenient and accessible follow-on innovations can result in improved health

outcomes, improved worker productivity, and health-care system savings.[69] The health savings from increasing adherence could be significant. For instance, one study finds, "The estimated average annual cost of prescription drug-related morbidity and mortality resulting from nonoptimized medication therapy was $528.4 billion in 2016 US dollars," with a range of $495.3 billion to $672.7 billion.[70] To put the potential of savings in perspective, these amounts substantially exceed the $435 billion the United States has spent on all branded medicines in 2023.[71]

The skepticism about the significance of post-approval R&D often arises out of concerns about intellectual property protection.

Novel formulations of existing drugs, such as extended-release versions, can also increase patient options and encourage competition. For example, the development of extended-release metformin has allowed manufacturers to launch a premium-priced alternative to the generic immediate-release version of the medication, catering to certain subsets of patients.[72] Follow-on therapeutic alternatives compete with the original versions of the drugs, giving providers and patients more options and driving down drug prices.[73]

MISCONCEPTIONS RELATED TO FOLLOW-ON INNOVATION

This section describes some of the core misconceptions about follow-on innovation that underlie a sometimes-dismissive attitude toward such advances.

1. Follow-On Innovation Is Trivial and Does Not Provide Meaningful Benefits to Patients

One misconception is that post-approval R&D, key to the development of follow-on innovations, is duplicative or trivial. This report provides different examples highlighting how significant follow-on research, as well as scientific and technological advances, are needed to identify drug applications for new indications and patient groups, and to developed enhanced formulations and dosage forms.

The skepticism about the significance of post-approval R&D often arises out of concerns about intellectual property protection. Patents on follow-on innovation are sometimes referred to as "secondary" patents, implying that the underlying inventions are less deserving of patent protection than those in "primary" patents—that is, those coverings a drug's active ingredient. It should be noted, however, that follow-on innovation patents are subject to the same rigorous legal standards and patent examination process as "primary" patents. Further, it is important to note that having patents does not mean that the market must adopt follow-on drugs if they do not confer value for providers and patients—if they are adopted, it is due to the derived value of the innovation in satisfying unmet need. If not, the original drugs can continue to service the market.

In 2015, the United Nations Development Programme (UNDP) issued a working paper intended to provide guidelines for how patent examiners should examine secondary patent claims in a way that would "protect public health and promote access to medicines."[74] The guidelines deemed many follow-on innovations as unworthy of patent protection, including "pharmaceutical compositions (formulations); claims over the dose of a drug; combinations of known drugs … and new medical uses of a known drug."[75] In the United States, lawmakers have also introduced

several bills in recent years framed as addressing "evergreening," "patent thicket" and "product hopping" concerns that could have harmful impacts on follow-on innovation. Examples include the Reforming Evergreening and Manipulation that Extends Drug Years (REMEDY) Act, introduced in July 2024, and the Terminating the Extension of Rights Misappropriated (TERM) Act in 2019, the Affordable Prescriptions for Patients Act of 2023, A Bill to Address Patent Thickets, introduced in 2024, and the Medication Affordability and Patent Integrity Act. Research cited in this report and studies by other scholars find that credible evidence for such claims continues to be very limited.[76] An article published in *Biotechnology Law Report* amplifies this report's findings on the importance of follow-on patents, explaining why the ultimate patient benefits of such patents are similar to, or in some cases even exceed, those of primary patents.[77]

For example, recall the HIV treatment AZT. In this case, a secondary patent enabled the investment needed to bring this lifesaving drug to market. AZT was developed in 1964 as a potential anticancer treatment, so by the time researchers began to explore its potential to combat HIV in the 1980s, a primary patent on the compound itself was no longer possible. Drug developer Burroughs-Wellcome secured a method-of-use patent (categorized as a secondary patent by the guidelines) to use AZT to treat HIV. This patent provided the necessary incentives to translate early promising research into a safe and effective breakthrough drug for HIV patients.[78]

The difference between the original and improved formulations [of Lumigan] is "the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment."

UNDP guidelines also advise against the patenting of new formulations, as they "confront an objection of lack of inventive step."[79] But as this report shows, new formulations can provide significant health and economic benefits, and patents are key to incentivizing the necessary R&D. Recall, for example, the example of Lumigan, used to treat glaucoma. The original formulation caused severe red eye, leading patients to discontinue treatment. Patent protection spurred further research into this drug, leading scientists to develop an improved formulation with fewer side effects. As noted by the U.S. Court of Appeals for the Federal Circuit, the difference between the original and improved formulations is "the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment."[80] It is therefore critical for such follow-on innovations to be incentivized by the patent system to improve human health.[81] While it is commonly recognized that the patent system promotes competition by facilitating the introduction of generic or biosimilar versions of original compounds after patent expiration, the role of IP rights as a catalyst for innovation and market competition during the term of patent exclusivity is often misunderstood. Many overlook its function in incentivizing the development of new products in the first place, which leads to more investment and competition in the market and ultimately increases the availability of affordable generic medicines.

2. Pharmaceutical Companies Can Manipulate the Marketplace by Switching Patients to New Drugs With Trivial Improvements, Effectively Extending Market Exclusivity

Another misconception about follow-on innovations is that pharmaceutical companies can manipulate the marketplace, switching patients to new drugs with small improvements to extend market exclusivity. This argument ignores the driving forces of prescribing and utilization management in the U.S. market—such as the critical clinical judgment that medical providers exercise on behalf of patients, the guidelines of U.S. medical societies, the preferences of health plan sponsors and the PBMs that place these therapies on their formularies. In sum, it disregards the overall health and economic value these therapies provide to the entire health-care system given their continued coverage and utilization.

Patients, doctors, and payers determine the value that medicines provide to patients. If drugs—including improved versions of existing drugs or otherwise additions to a first-in-class drug in a class—provide meaningful benefits to patients, those improvements will translate into market success. If not, doctors can prescribe, and patients can use, the original drug, including generic versions available after patent expiry. To the extent that novel entries in a drug class offer limited differentiation, payers and PBMs use various utilization control tools to drive price competition across the entire class.

In some cases, certain subsets of patients—rather than the entire patient population—will benefit from a follow-on innovation, such as a different dosing regimen or an alternative delivery method. In such situations, it is neither the case that the entire market should switch to the follow-on drug nor that the subset of patients that values the follow-on benefit should not be able to access it because follow-on R&D innovation has been disincentivized. Utilization management tools such as prior authorization and step edits can be calibrated to support the appropriate clinical management that enables physicians to provide these therapies to the subpopulations with the greatest benefit.

Patents on follow-on innovations do not extend the patent life of an original drug. Generic versions of an original drug are free to launch upon expiry of the original patent—and they readily do so.

An example discussed in this report is insulin. Different types of insulin exist—such as rapid-acting and long-acting insulins—that address the diverse needs of diabetic patients based on their glucose management requirements and lifestyles.[82] Long-acting insulins (e.g., insulin glargine) provide a steady release of insulin over 24 hours, reducing the number of daily injections. This is particularly beneficial for patients who prefer simpler regimens or have difficulties managing frequent doses. Rapid-acting insulins (e.g., insulin lispro) are designed to mimic the body's natural insulin response during meals, which is vital for patients who require precise glucose control.[83] Not all patients with diabetes need, or prefer, the same insulin formulation. Patients with predictable meal schedules may benefit from long-acting insulins, while patients with irregular mealtimes or frequent glucose spikes may prefer rapid-acting insulins. These innovations do not require the entire market to switch to a single type of insulin. Instead, they ensure that subpopulations can access the formulation that best meets their specific needs.[84]

3. Follow-On Innovation, and Related Patents, Function to Keep Generics off the Market and Extend Patent Exclusivity

Another misconception about follow-on innovation is that its patents function to keep generics off the market and extend patent exclusivity. However, patents on follow-on innovations do not extend the patent life of an original drug. Generic versions of an original drug are free to launch upon expiry of the original patent—and they readily do so.

A recent study by the United States Patent and Trademark Office on drug exclusivity periods explores this issue by examining the market exclusivity of 25 New Drug Applications (NDAs) approved by the FDA between 2005 and 2018.[85] It found a range "from about 3 to about 16 years" of market exclusivity for the therapies examined before generics entered the market.[86] The study also explores whether follow-on innovation, which produces additional patents, results in extended market exclusivity periods for the original drug beyond the expiration of the earlier patent, finding that it does not.

According to the study:

> In some of the cases analyzed, the data indicates that a generic competitor drug was approved and launched, while later patents directed to follow-on innovation and listed in the Orange Book were still in force…In other cases, later patents may have claims directed only to specific aspects of the NDA holder's drug product, and may not block a generic from launching a competing product once the earlier patents have expired.[87]

POLICIES RELATED TO FOLLOW-ON INNOVATION

By presenting several examples and quantitative data from different studies, this report discusses the significant value of follow-on innovation for health and economic outcomes. Thus, it is critical for public policies to support such innovations.

Examples of U.S. policies that have encouraged follow-on innovation include the Best Pharmaceuticals for Children Act (BPCA) and the Orphan Drug Act (ODA). The BPCA, originally enacted in 2002, encourages pharmaceutical companies to conduct pediatric studies through various incentives. The act aims to address the historical lack of pediatric-specific drug safety and efficacy data, a key gap in health care. The act "requires that the National Institutes of Health (NIH), in consultation with the FDA and experts in pediatric research, develop and publish a priority list of needs in pediatric therapeutics; establish a program for pediatric drug development studies of primarily off-patent medications; and submit clinical trial findings to the FDA for drug label change consideration."[88] This act has been crucial in promoting R&D into the unique pharmacological needs of children.

According to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), since the BPCA's enactment, over 150 drugs have been included in the BPCA's Clinical Program through different clinical trial designs. Out of these drugs, the NIH has funded 51 clinical trials and submitted 27 Clinical Study Reports to the FDA for label change considerations, resulting in 20 drug label updates to date for the drugs to be made available to pediatric populations.[89] Key outcomes of the act include increased pediatric data and expanded treatment options for children due to incentives for follow-on innovation that explore pediatric

uses of existing therapies. The BPCA has driven significant progress in pediatric drug research, addressing gaps in knowledge and improving health outcomes in children. By focusing on real-world needs and incentivizing innovation, it ensures that children, along with adults, benefit from pharmaceutical innovation.

Another policy that supports follow-on innovation is the ODA of 1983, which sought to incentivize the development of treatments for rare diseases, which are those that typically affect fewer than 200,000 people in the United States. There are approximately 7,000 rare diseases, the majority of which are genetic in nature and which in total affect between 25 million and 30 million Americans, although approximately 95 percent have no effective treatment.[90] Rare diseases often lack sufficient market incentives for R&D due to their small patient populations, making the ODA a crucial driver of innovation. To incentivize R&D of drugs for such diseases, Congress created an orphan drug tax credit (ODTC) equal to 50 percent of qualified clinical trial costs and also offered a seven-year period of orphan drug exclusivity.[91]

Examples of U.S. policies that have encouraged follow-on innovation include the Best Pharmaceuticals for Children Act (BPCA) and the Orphan Drug Act (ODA).

The policy has spurred ground-breaking research into rare diseases by providing incentives in the form of market exclusivity and financial incentives for R&D, including for follow-on innovation such as exploring new uses and indications of existing drugs. According to a recent IQVIA report, as of March 2023, 6,506 orphan drug designations had been granted by the FDA, of which 1,144 have led to orphan-designated drug approvals.[92] Most orphan drugs target conditions in oncology, followed by neurology, infectious diseases, and hematology.[93] A 2015 study by the National Organization for Rare Disorders found that at least one-third fewer new orphan drugs would have been developed to treat rare diseases over the preceding 30 years had the act not been implemented.[94] Unfortunately, the 2017 Tax Cuts and Jobs Act halved the ODTC to just 25 percent.[95]

In addition to supportive policies such as the BPCA and the ODA, public private partnerships (PPPs) can also encourage the development of follow-on innovations. For instance, the Discovering New Therapeutic Uses of Existing Molecules initiative by NIH'S National Center for Advancing Translational Sciences is a PPP that was launched in 2012 to explore the repurposing of drugs to new indications. It provides academic researchers the opportunity to access pharmaceutical industry data and explore new ways to treat diseases, helping accelerate research collaborations.[96]

Beyond these specific policies, core patent law principles and rules that encourage follow-on innovation (e.g., continuation applications and terminal disclaimer practice) should be preserved. Policymakers should carefully consider patent-related policy proposals to ensure that the "problem to be solved" is supported by credible data and evidence, and that the policy does not adversely impact the ability of pharmaceutical companies to develop follow-on innovations.

While policies such as the BPCA and the ODA have supported follow-on innovation, others, such as the IRA, risk harming such R&D. A recent USC Schaeffer Center white paper notes that in addition to the IRA's negative impact on new drug (NME) approvals, decreased pharmaceutical company revenues from the IRA can also lead to less follow-on innovation. This could reduce

incentives for the development of drugs targeting diseases that disproportionately impact the elderly on Medicare, including cancer, Alzheimer's disease, and heart conditions. The white paper also argues that the IRA could reduce the discovery of new uses and indications for existing drugs, since price negotiations would start 9 or 13 years after drug approval (for small molecule drugs and biologics, respectively), even if new indications are identified.[97]

The IRA also presents risks to orphan drug innovation. While orphan drugs with a single indication are exempt from IRA price setting, this exemption does not apply to those with multiple indications, disincentivizing follow-on research even though orphan drugs often prove effective against multiple rare diseases. The proposed Orphan Cures Act seeks to fix this by amending the IRA to ensure that orphan drugs treating one or more rare diseases are excluded from price setting.[98]

Follow-on innovation requires significant R&D investment, and due to its positive health and economic benefits, as discussed in this report, it is important to encourage such R&D through policies such as the BPCA and the ODA and the establishment of PPPs. Policies should support the development of best-in-class drugs, recognizing value beyond that of first-in-class drugs and acknowledging the enhanced safety, efficacy, and convenience that follow-on innovations can provide. PPPs, such as the NIH's Discovering New Therapeutic Uses of Existing Molecules, are also important for accelerating the development of treatments for different indications to address unmet medical needs. Further, it is essential to avoid policy disincentives—such as those in the IRA—that could harm follow-on innovation pipelines.

CONCLUSION

Follow-on innovation plays a critical role in advancing public health and supporting economic growth, and policies should foster continued investment in post-approval R&D. To better understand and assess the value of follow-on innovation, it is essential to have a more comprehensive approach to conceptualizing and measuring biopharmaceutical innovation in the first place—one that incorporates not only the scientific and technological perspective (i.e., the novelty of a drug based on whether it is an NME) but also the perspectives of patients, caregivers, payors, and employers.

Policies should support the development of best-in-class drugs, recognizing value beyond that of first-in-class drugs and acknowledging the enhanced safety, efficacy, and convenience that follow-on innovations can provide.

Doing so reveals that follow-on innovations produce significant positive impacts on public health, the overall health-care system, and the economy, as discussed in this report. From a patient perspective, follow-on innovation can have substantial benefits due to treatments that are better suited to their specific needs, treatments that generally have greater effectiveness and improved safety/tolerability, or both.[99] Such benefits can improve quality of life and treatment adherence, which in turn can reduce caregiver burden, decrease disease-related work absenteeism, and lead to enhanced productivity. From a payor perspective, increased competition from follow-on innovations can generate more patient choices and lower drug prices. From a public health perspective, improved adherence can lead to reduced mortality and a longer life expectancy, and for the health-care system, follow-on innovations can increase system efficiency through reduced

health-care utilization due to improved adherence, longer dosing intervals, and simplified monitoring, among others. Lastly, for communities across the United States, R&D investment in post-approval research can produce high-quality jobs, improve labor productivity, and generate economic growth. Supportive policies, including the BPCA and the ODA, can help incentivize valuable follow-on innovation.

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